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Review

Drugs and hyperglycemia: A practical guide

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ABSTRACT

Drug-induced diabetes is one of the factors contributing to the increasing incidence of diabetes worldwide. This review considers the frequency, pathogenesis and treatment of drug-induced diabetes. Drugs that induce diabetes include hormonal therapy, especially glucocorticoids and androgen blockers, cardiovascular drugs, especially statins, beta-blockers and diuretics, antipsychotics, especially clozapine, olanzapine and quetiapine, antiretrovirals (protease inhibitors and non-reverse transcriptase inhibitors − NRTIs) and other drugs (mechanistic target of rapamycin inhibitors −mTORs, post organ transplantation drugs, tyrosine kinase inhibitors and interferon-alpha). Abnormalities of the distal gluco-regulatory pathways of hyperglycemia involve decreased insulin secretion and frequent insulin resistance, whereas the proximal defects are unknown, thus limiting targeted treatment.

Drug-induced diabetes is potentially reversible and the risk is underestimated. There is little information on its long-term effects on microvascular complications as clinical trials have not been long enough and neither have they focused on these factors.

Overall management includes awareness of a drug's diabetogenic potential, underlying diabetes risk, benefits and risks of continuing vs discontinuing the drug, plus a consideration of drug duration and dose. While diabetes and its severity can be identified and controlled, the likelihood of *future diabetes complications* frequently cannot. This, balanced against the predicted benefit of the drug, results in clinical uncertainty.

Empirical approaches to drug-related hyperglycemia include decreasing the dose or selecting an alternative treatment, if possible. In the absence of drug-specific evidence, treatment of drug-induced hyperglycemia and diabetes is similar to comprehensive standard diabetes care, including lifestyle modifications, oral/injectable antidiabetic agents and insulin. Important clinical considerations include surveillance of glucose before and during treatment and, in some cases, institution of diabetes preventive measures like lifestyle modification and early treatment. Future research is needed to elucidate pathophysiology and optimal targeted treatment for drug-induced diabetes and its long-term complications.

1. Introduction

A broad range of commonly prescribed medications can lead to hyperglycemia or new onset diabetes (NOD). The true incidence and prevalence of drug induced diabetes is not known due to short duration of diabetes and lack of systematic ascertainment of both diabetes and its long term complications. Diabetes is diagnosed by fasting blood glucose≥ 126 mg/dl, random or 2 h post prandial blood glucose ≥200 mg/dl or a hemoglobin A1C ≥ 6.5% (HbA1c). This paper reviews the recent literature on drug induced hyperglycemia and NOD.

Drug induced diabetes is clinically important and underreported in clinical studies. Risks for developing drug induced diabetes include dose and duration of treatment and usual risk factors like age, family history of diabetes and BMI. The severity of hyperglycemia is variable and marked hyperglycemia may be a feature of therapy with glucocorticoids, somatostatin analogues, androgen deprivation, antipsychotics, interferon, older anti-retroviral agents and mTOR inhibitors. The distal glucoregulatory pathways (insulin secretion and insulin action) are impaired in diabetes and the proximal pathways are poorly understood, likely drug-specific, and this is a hindrance to the development of targeted treatment. Different drugs within a class may differ in diabetogenic potential as with statins and antipsychotics. Drug

Abbreviations: BMI, Body Mass Index; mTOR, Mechanistic target of Rapamycin; NOD, New onset diabetes; HbA1c, Hemoglobin A1c; ADT, Androgen Deprivation Therapy; GLP-1, Glucagon Like peptide; CVD, Cardiovascular disease; HIV, Human Immunodeficiency Virus; LDL, Low density Lipoprotein; HAART, Highly Active Antiretroviral therapy; CCR5 C-C, Chemokine receptor type 5; ART, Antiretroviral therapy; NRTI, Nucleoside Reverse Transcriptase Inhibitor

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induced diabetes is usually type 2 and typically resolves upon drug discontinuation. An exception to this fact is Interferon which is associated with type 1 diabetes. The true incidence of drug induced diabetes and its relationship to long-term diabetic micro and macrovascular complications is unknown which contributes to clinical uncertainty.

Critical in the approach to drug induced diabetes is an awareness of the diabetogenic potential of different drugs and diagnosis through early institution of blood glucose surveillance. The development of diabetes or worsening of glucose control should trigger reassessment of the drug. Lifestyle modifications, weight reduction and careful selection of drugs based on the patient's metabolic risk assessment and the appropriate use of antidiabetic medications is required. Importantly, the benefit usually outweighs the risk as the immediate hyperglycemia can usually be effectively treated.

2. Drug classes associated with hyperglycemia and diabetes

2.1. Androgen deprivation therapy (ADT)

These are used for prostate cancer treatment and are associated with increased diabetes (28%) and cardiovascular disease [1]. ADT lowers testosterone level to and creates an insulin resistant state which worsens glucose control. In studies while the average HbA1C increase was only 0.14% nearly 20% (vs.12% controls) had an increase HbA1c of > 1% [2]. Management includes reconsidering the benefit of ADT and use of standard diabetes treatment.

2.2. Somatostatin analogues (SA)

SA's are primarily used for acromegaly and Cushing's disease. A new, potent SA, pasireotide, compared to Octreotide/Lanreotide, tripled NOD and has been associated with hyperglycemia and diabetes in up to 30% of patients [3]. SA's cause inhibition of insulin and glucagon secretion and thereby diabetes. It is reversible upon discontinuation of pasireotide and standard treatment is effective in controlling diabetes. Incretin-based anti-diabetic agents may *prevent* hyperglycemia and inform future approaches to glycemic management [4]. Active surveillance is recommended.

2.3. Glucocorticoids

There are multiple uses of glucocorticoids including rheumatologic disorders, asthma, COPD, lymphomas etc.This class is associated with fasting and especially post prandial hyperglycemia depending on dose and duration of treatment, presence of co-morbidities and diabetes risk factors like age, obesity and family history of diabetes. It is estimated that almost 64% of hospitalized patients may have glucocorticoid associated hyperglycemia and diabetes and this can occur with the oral, injectable or the inhaled route [5]. The mechanism reflects decreased insulin secretion and action, increased hepatic gluconeogenesis and lipolysis. Management includes use of the lowest effective dose whenever possible. Hyperglycemia can often be severe, may require insulin and is reversible with glucocorticoid discontinuation. Metformin, sulfonylureas, glucagon like peptide-1 (GLP-1) agonists and insulin used as a 3-part insulin regimen (basal, bolus and correction dose) is effective [6].

2.4. Mechanistic target of rapamycin inhibitors (mTORi's)

Temsirolimus and Everolimus inhibit tumor proliferation and angiogenesis and are used to treat cancer. A meta-analysis of mTORi's has shown that their use is associated with 5.3% incidence of high grade hyperglycemia (blood sugars > 250 mg/dl) [7]. In clinical trials, the rates of hyperglycemia and NOD ranged from 10 to 50%. The mechanism includes decreased insulin secretion and action. Management includes life style modification and weight reduction with standard diabetes medications.

2.5. Immunosuppressants

Sirolimus and Tacrolimus are used as immunosuppressants after renal transplantation. Post-transplantation hyperglycemia and NOD is common with a frequency of 15–30% and is immunosuppressant specific. NOD or impaired fasting glucose was greater with tacrolimus compared to cyclosporine treatment (33.6 vs 26.0% respectively); Sirolimus is also an independent risk factor for NOD [8]. Management of NOD after transplantation includes individualized immunosuppressant selection based on immunological risk, early blood glucose surveillance when the risk of diabetes is greatest and initiation of standard anti-diabetes treatment [9]. Medication should be adjusted based on renal function and considerations of drug-drug interactions.

2.6. Tyrosine kinase inhibitors (TKI's)

Imatinib and Nilotinib are new cancer treatments and are associated with both hyperglycemia and hypoglycemia. Hyperglycemia was common with nilotinib and imatinib (20%–36%) and is due to insulin resistance [10]. Prior to and during treatment, blood glucose surveillance and patient awareness of symptoms of hyper and hypoglycemia are important aspects of standard glycemic management.

2.7. Diuretics and beta-blockers

These agents are used to treat hypertension, myocardial infarction, chronic angina, systolic heart failure, atrial and ventricular arrhythmias. However, long-term use of beta-blockers or thiazide diuretics increased NOD with a relative risk of 1.20–1.32 in prospective cohorts [11]. Metoprolol reduces heart rate and cardiac output leading to peripheral vasoconstriction and increased insulin resistance. In contrast, carvedilol, a vasodilating beta blocker showed positive or neutral effects on glycemic control and insulin sensitivity suggesting this agent may be preferable in hypertension with or without diabetes [12]. Chlorthalidone was associated with an 11% incidence of diabetes at 4 years versus 9.3% and 7.8% for amlodipine and lisinopril respectively [13]. However, chlorthalidone was superior in preventing heart failure and stroke. It induces potassium depletion mediated decrease in insulin secretion and sensitivity, which is dose dependent. Correction of hypokalemia may reverse hyperglycemia. Management includes lifestyle modification and when feasible use carvedilol over metoprolol.

2.8. Statins

Statins are used for primary and secondary prevention of cardiovascular disease and are known to cause a 9–12% increase in diabetes with an absolute risk of 10–20 per 10,000 per year in primary prevention trials [14]. Diabetes risk is associated with dose and duration of statin use and other diabetes risk factors including BMI. Diabetes develops early in the course of statin use and may be stable over time. Statins interfere with *many* glucoregulatory pathways resulting in decreased insulin secretion and action. The more potent lipid-lowering statins (atorvastatin, rosuvastatin, simvastatin) are more diabetogenic than less potent ones (pravastatin) [14]. Interestingly, Low density lipoprotein (LDL) cholesterol lowering genetic variants were associated with higher plasma glucose suggesting inherent metabolic links [15]. Statins decrease macrovascular events and this greatly outweighs increased diabetes risk or its associated vascular events. It is not known if statins decrease microvascular complications of diabetes [16]. Management includes statin dose reduction if feasible and standard anti-diabetes medications.

2.9. Antipsychotics

Antipsychotics, both first and second generation, amplify an already 3–4 fold increase in diabetes in schizophrenia. Diabetes contributes to