Review Article

Literature review: drug and alcohol-induced hypoglycaemia

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Objective: Narrative literature review of medication and alcohol related hypoglycaemia.

Background: Drugs and alcohol are the commonest causes of hypoglycaemia and account for a significant number of emergency department attendances and hospital admissions.

Methods: Hypoglycaemia risk with various drug classes and alcohol is discussed along with underlying mechanisms, characteristics and caveats around the diagnosis and management.

Conclusions: Hypoglycaemia is most common with insulin treatment in type 1 diabetes but insulin in type 2 diabetes, sulphonylureas, other anti-hyperglycaemic medications and medications from other classes like beta-blockers, angiotensin converting enzyme inhibitors, fibrates, psychotropic medications, anti-malarial drugs, antibiotics, anti-arrhythmic drugs, non-steroidal anti-inflammatory agents, and a few other classes of medications may also increase hypoglycaemia risk. The risk, depending on the drug class, may be as monotherapy or when used in combination with anti-hyperglycaemic medications and may either be in the therapeutic doses or only in overdose. Alcohol has profound effects on glucose metabolism. However, the incidence of alcohol-induced hypoglycaemia in healthy individuals with good glycogen reserve is low. Glycogenolysis plays an initial role in the defence against alcohol-induced hypoglycaemia and gluconeogenesis takes over later on to prevent profound hypoglycaemia. There are inconstancies in the literature about the role of counter-regulatory hormones in alcohol-induced hypoglycaemia.

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Drugs and alcohol are the commonest cause of hypoglycaemia in adults (1,2). Up to 20% of adverse drug-related hospital admissions are hypoglycaemia related (3) and has been reported to account for up to 1.7% of hospital admissions (4). The commonest drugs causing hypoglycaemia are anti-diabetic drugs but it is also frequently reported with beta-blockers, antibiotics, anti-arrhythmic medications, anti-malarial medications and analgesics (5). Mechanisms for hypoglycaemia include one or more stimulation of insulin release, reduction of insulin clearance, alteration of insulin sensitivity, interference with glucose metabolism and modulation of effect of anti-diabetic medications.

The harmful effects of alcohol, including alcohol-induced hypoglycaemia (AIH), are well known. Yet alcohol is a part of many lives. AIH was first described approximately 80 years ago by Brown and Harvey in 1941 (6). During the following decades, this phenomenon has been extensively investigated to improve our understanding of the effect of alcohol on glucose metabolism. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/jlpm-21-16).

Anti-hyperglycaemic agents

Sulphonylureas

Sulphonylureas have been used since the 1950s and are one of the most commonly used oral anti-hyperglycaemic medication groups in the treatment of type 2 diabetes worldwide. They act by binding to the sulphonylurea receptors in the pancreatic β-cell membrane leading to the closure of adenosine triphosphate-sensitive potassium channels, which in turn leads to the opening of calcium channels leading to insulin release. This continues till there is ongoing drug stimulation and β cells remain functional even when blood glucose levels are below the normal threshold for glucose-stimulated insulin release (approximately 5 mmol/L) (5). First-generation sulphonylureas (tolbutamide, chlorpropamide, tolazamide, and acetohexamide) are rarely used nowadays. The more potent second-generation sulphonylureas (glibenclamide or glyburide, gliclazide, glipizide, glimepiride and gliquidone) are more widely prescribed (5,7). Chlorpropamide, glibenclamide, and glimepiride are classed as long-acting while gliclazide, tolbutamide and gliquidone are short-acting (7,8).

Hypoglycaemia is the commonest reported side effect with sulfonylurea use and generally tends to occur more frequently with long-acting agents (8). In a recent model-based meta-analysis by Maloney *et al.* comparing hypoglycaemia risk across six non-insulin drug classes, the relative hypoglycaemia risk increase versus placebo was highest with sulphonylureas compared to the other classes (9). Risk factors for hypoglycaemia with sulphonylureas include high medication dose, missed meals, prolonged physical activity, elderly patients, renal failure, liver dysfunction, duration of treatment, simultaneous use of insulins and β blockers, multiple drug interactions and genetic susceptibility with low CYP2C9 activity (10,11). A meta-analysis by Schopman *et al.* demonstrated that hypoglycaemia with glucose ≤3.1 or ≤2.8 mmol/L was experienced by 10.1% and 5.9% of patients with any sulfonylurea treatment. Severe hypoglycaemia requiring third-party assistance occurred in 0.8% of patients (12). The hypoglycaemia risk also varies between agents within the sulphonylurea group. The relative hypoglycaemia risk increase versus placebo was lower with gliclazide at 3.6, compared to glimepiride (8.9), glibenclamide (10.2) and glipizide (13.9) (9). The risk of hypoglycaemia appears to be lower with sustained-release sulphonylurea preparations, as demonstrated by the GUIDE study, a double-blind randomised controlled trial and the EASYDia study, a real-world study (13,14).

In cases of unexplained hypoglycaemia in non-diabetics, inadvertent sulphonylurea use should be considered, especially in children and the elderly. Sulphonylureas have also been used deliberately to induce factitious hypoglycaemia, hypoglycaemia with criminal intent and in suicide attempts (15). The laboratory picture would be of low plasma glucose with inappropriately non-suppressed insulin with non-suppressed C-peptide and appropriate insulin to C-peptide ratio (16). A urine sulphonylurea screen could be helpful in these cases and may alleviate suspicion of an insulinoma (15). The clinical team should be wary of recurrent hypoglycaemia after correction of the presenting episode of hypoglycaemia, especially with longer-acting sulphonylureas and long-acting insulins (15). Glucagon is best avoided in insulin secretagogue (sulphonylurea and glinide) induced hypoglycaemia, especially in patients with suspicion of depleted hepatic glycogen stores, because glucagon can exacerbate hypoglycaemia by further stimulating insulin release (15,17).

Insulin

Due to the availability of rapid-acting and long-acting insulin analogues, much has changed regards insulin treatment of type 1, type 2 and gestational diabetes during the previous two decades and much has been written about insulin-induced hypoglycaemia.

The action profile of rapid-acting insulin analogues (insulins lispro, aspart and glulisine) better match meal-related glycaemic excursion. In type 1 diabetic patients, short-acting insulin analogues cause less total hypoglycaemic episodes, less severe hypoglycaemia, less nocturnal hypoglycaemia despite achieving better post-prandial glucose and better HbA1c compared to regular human insulin (18). The evidence in hypoglycaemia reduction with rapid-acting insulin analogues in type 2 diabetes mellitus is questionable and weak, in part due to differing study designs and overall low frequency of severe hypoglycaemia in type 2 diabetes (19).

Neutral Protamine Hagedorn (NPH) insulin has a pronounced peak and relatively variable absorption compared to the newer long or ultra-long-acting insulin analogues like detemir, glargine and degludec (20). In type 2 diabetes mellitus, data around differences in hypoglycaemia rates with newer longer-acting insulin analogues, when compared with NPH insulin, are

inconsistent. In a meta-analysis, detemir or glargine did not reduce the risk of hypoglycaemia related emergency department visits or hospital admissions and did not lead to improved glycaemic control in patients with type 2 diabetes mellitus (21). A recent Cochrane meta-analysis of randomized controlled trials (RCTs) found comparable HbA1c reduction with detemir, glargine and NPH insulins but reduced hypoglycaemia frequency with analogues and reduced hypoglycaemia severity with detemir. However, the absolute risk reduction was small (22). In type 1 diabetes, nevertheless, insulins glargine and detemir have been shown to reduce nocturnal hypoglycaemia episodes while also achieving HbA1c reduction. However, severe hypoglycaemia was note significantly reduced (23). Insulin degludec, the newest long-acting insulin analogue, has been shown to cause fewer or similar overall hypoglycaemic episodes while reducing nocturnal hypoglycaemic episodes compared to insulin glargine and detemir (24). The newer 300 U/mL glargine insulin has been shown to achieve HbA1c reduction despite no change in hypoglycaemia frequency or weight gain in type 1 diabetes and may reduce nocturnal hypoglycaemia compared to 100 U/mL glargine insulin (24,25). Insulin glargine or detemir did not reduce the frequency of hypoglycaemia in pregestational and gestational diabetes in a recent small sample size study (26).

Continuous glucose monitoring (CGM) (27,28), as well as flash glucose monitoring, have been shown to reduce the frequency of hypoglycaemia in diabetic people on insulin (29,30). Real-time CGM has been shown to reduce severe hypoglycaemia in type 1 diabetes patients with impaired hypoglycaemia awareness (28,31).

Exogenous insulin administration may be used with suicidal or homicidal intention. Also, any proven hypoglycaemia can be used in defence against a criminal charge (32). Hypoglycaemia due to overdose of long-acting insulins could be prolonged or recurrent. Extended intravenous glucose infusion and close monitoring may be required in such cases (15). Prolonged hypoglycaemia episodes have been reported in intentional or unintentional overdose with insulins degludec, glargine and detemir (33-36). Prolonged hypoglycaemia requiring intravenous dextrose for 13 days has also been reported in mega doses with regular human insulin and isophane insulin (37).

The biochemical picture in exogenous insulin-induced hypoglycaemia would be low plasma glucose, low serum C-peptide due to suppression of endogenous insulin release and elevated serum insulin (32). However, caution is required as not all insulin assays detect all the insulin analogues (38). Serum insulin result from assays which do not detect or under-recover the injected insulin would be lower than the "true" circulating insulin concentration at the time. While investigating suspected exogenous insulin-related hypoglycaemia, therefore, it is essential to know recovery of the insulin in question with the available assay or, preferably, to measure insulin by one of the assays which detects most analogues (38).

Metformin

Metformin, first used in diabetes in the 1950s, is the most commonly used oral anti-hyperglycaemic medication in type 2 diabetes across the world. Metformin neither stimulates insulin secretion nor modulates the glucose counter-regulatory pathways and therefore does not usually cause hypoglycaemia in monotherapy (39). Its blood glucose-lowering effect is a consequence of inhibition of hepatic glucose production, and sensitisation of peripheral tissues (muscle and fat) to the effect of both endogenous and exogenous insulin (39). In a recent model-based meta-analysis, the rate of hypoglycaemia was generally low with metformin, although this was comparatively higher compared to DPP-4 inhibitors, SGLT2 inhibitors and thiazolidinediones (9). Combination therapy with insulin and sulphonylureas can increase the hypoglycaemia risk. In patients on metformin, the addition of insulin was associated with a higher risk of the first hypoglycaemic episode than the addition of sulfonylurea (40).

Alpha-glucosidase inhibitors

Alpha-glucosidase inhibitors such as acarbose, miglitol and voglibose, inhibit maltase, sucrase and other disaccharide hydrolases in the brush border membrane of the small intestine and as such, improve postprandial hyperglycaemia by delaying carbohydrate absorption (41). Since they are not involved in the insulin secretion pathway, they do not cause hypoglycaemia in monotherapy. There was no difference between acarbose and placebo in terms of hypoglycaemia risk in the UKPDS trial (42) and even in elderly patients who are generally more prone to hypoglycaemia (43). However, combination therapy can be associated with hypoglycaemia, especially with sulphonylureas or insulin (44). Since these drugs do not affect monosaccharides, hypoglycaemia in patients on α-glucosidase inhibitors should be treated with a monosaccharide such as glucose, grape juice or honey. Glucagon is an alternative for severe

hypoglycaemia (44).

Thiazolidinediones

Thiazolidinediones activate peroxisome proliferator-activated receptor gamma and act as insulin-sensitizers. The effect is a reduction in blood glucose levels with minimal risk of hypoglycaemia (45). Pioglitazone is the only thiazolidinedione prescribed in clinical practice nowadays. The risk of hypoglycaemia with pioglitazone was very low in a recent model-based meta-analysis (9), lower than sulfonylureas in TOSCA.IT randomized controlled trial (46) and lower than metformin in a retrospective cohort study by Leonard *et al.* (47).

Meglitinides

Meglitinides, nateglinide and repaglinide, promote insulin release from pancreatic beta cells by interacting with the ATP-sensitive potassium channels. In contrast to sulphonylureas, meglitinides bind to a different part of the sulfonylurea receptor and this interaction is weaker than that of a sulphonylurea. This translates into a shorter duration of action and a higher blood glucose threshold before meglitinides induce insulin secretion (48). They, therefore, cause hypoglycaemia relatively less frequently than sulphonylureas (49,50). Repaglinide was more frequently associated with hypoglycaemia than nateglinide in a randomized controlled trial perhaps because it is more potent and it achieved greater HbA1c reduction than nateglinide (51). The risk of hypoglycaemia with meglitinides increases in the presence of renal failure, inadequate carbohydrate intake, and various drug interactions which increase the serum meglitinide level. For this reason, repaglinide should not be taken with gemfibrozil and its dose may need to be reduced with concurrent use of medications like ketoconazole, itraconazole, rifampicin, carbamazepine, montelukast, and deferasirox (52). Like other diabetes medications, combination therapy tends to increase the hypoglycaemia risk with meglitinides (53).

Dipeptidyl peptidase-4 (DPP-4) inhibitors

DPP-4 inhibitors, also known as gliptins, inhibit the protease DPP-4 that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Thus, by prolonging the activity of incretins, DPP-4 inhibitors increase postprandial glucose-dependent insulin secretion and decrease glucagon secretion. Vildagliptin, sitagliptin, saxagliptin, linagliptin, and alogliptin are all DPP-4 inhibitors (54).

Since their action is glucose-dependent, the risk of hypoglycaemia is nearly 10-fold lower compared to sulphonylureas. This was consistently observed in both RCTs (irrespective of the DPP-4 inhibitor or sulphonylurea used) and observational studies (55). In combination therapy with metformin, pioglitazone, SGLT2 inhibitors or insulin, there appears to be no higher risk of hypoglycaemia, compared to monotherapy with these individual antidiabetics. In contrast, their addition to sulphonylureas may lead to more frequent hypoglycaemia compared to sulphonylurea monotherapy (55).

GLP-1 receptor agonists

GLP-1 receptor agonists provide pharmacologic levels of GLP-1 which leads to an increase in postprandial glucose-dependent insulin secretion, decrease in glucagon secretion, delay in gastric emptying and increase in satiety (56). Exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide and semaglutide are all drugs within this class (57). They are administered via the subcutaneous route. Semaglutide is also available in an oral formulation (58).

Due to their glucose-dependent mechanism of action, the risk of hypoglycaemia is low for the GLP-1 receptor agonist monotherapy. However, in combination with sulphonylureas or insulin, GLP-1 receptor agonists may increase the risk of hypoglycaemia (56,57). A recent model-based meta-analysis has shown that hypoglycaemia risk for GLP-1 analogues is slightly more than the DPP-4 inhibitors (9).

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors

SGLT-2 inhibitors, also known as gliflozins, are the newest class of oral anti-hyperglycaemic agents which include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (59). SGLT-2 inhibitors reduce renal tubular glucose reabsorption by blocking SGLT2 transporter proteins in the proximal convoluted tubule of the kidneys, and therefore reducing blood glucose without stimulating insulin release (59). This insulin-independent mechanism leads to improved glycaemic control, with a limited risk of hypoglycaemia. This was confirmed in three large prospective cardiovascular outcome trials, where the risk of hypoglycaemia was similar in the SGLT-2 inhibitor and

placebo groups (60). In a recent model-based meta-analysis by Maloney *et al.*, the hypoglycaemia risk for SGLT-2 inhibitors was generally very low and comparable to DPP-4 inhibitors and pioglitazone (9). In a meta-analysis, canagliflozin had a higher risk of hypoglycaemia compared to empagliflozin and dapagliflozin but the highest dose of canagliflozin also achieved greater HbA1c reduction compared to the highest doses of the rest two agents (61). In combination therapy with sulphonylureas or insulin, the hypoglycaemia risk is higher and a reduction of the dose of the insulin secretagogue or exogenous insulin may be required (60).

Pramlintide

Pramlintide, an analogue of the pancreatic hormone amylin, is administered subcutaneously and works by slowing gastric emptying, reducing glucagon release, and increasing satiety and is approved in the United States (62). Pramlintide in combination with insulin can increase the incidence of severe hypoglycaemia and the risk is particularly higher when initiating therapy (62).

Non-anti-hyperglycaemic medications

Beta-blockers

In healthy nondiabetic individuals, the risk of hypoglycaemia due to beta-blockers is minimal (63). However, beta-blockers, especially the non-selective ones, can cause severe hypoglycaemia in people with diabetes (63,64) and non-diabetic patients with chronic renal failure (65), liver diseases, poor nutrition and prolonged fasting and strenuous exercise (63,66). Beta-blockers could increase insulin release, reduce hypoglycaemia awareness and interfere with the response to hypoglycaemia by altering glucagon release, glycogenolysis, lipolysis and gluconeogenesis (63). At the same time, non-selective beta-blockers could worsen insulin resistance and increase the requirement of antidiabetic medications further increasing the risk (63). Selective beta-blocker should be chosen as far as possible if a diabetic patient requires beta-blockade (5,67).

Non-steroidal anti-inflammatory agents and analgesics

The effect of salicylates on glucose metabolism may be due to increased insulin release, reduced insulin clearance, increased insulin sensitivity and reduced gluconeogenesis (68-70). In the past, high dose salicylates were trialled as anti-hyperglycaemic agents (71). Salicylate induced symptomatic hypoglycaemia is rare in non-diabetic adults but salicylates, including topical preparations, are the leading cause of drug-induced hypoglycaemia in children (72,73). A few other non-steroidal anti-inflammatory drugs (NSAIDs) may also potentiate the hypoglycaemic effect of anti-diabetic agents. Such has been reported with ibuprofen, nimesulide, fenclofenac, piroxicam, indomethacin, phenylbutazone and azapropazone (5).

Paracetamol can cause hypoglycaemia in therapeutic doses in children and in overdose in adults (74). Hepatic necrosis due to overdose may be the reason (75). Of the opioid analgesics, hypoglycaemia has been reported with dextropropoxyphene, especially with renal failure and haemodialysis, and with tramadol (76,77). Proposed mechanisms are insulin release and increased hepatic insulin sensitivity (76,78).

Antibiotics

Many fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin and moxifloxacin) are known to cause hypoglycaemia (79,80) and the risk is higher in renal failure, with advancing age and in patients on diabetic medications, especially sulfonylureas or meglitinides (81,82). Hypoglycaemia is believed to occur due to the effect of fluoroquinolones on pancreatic beta-cell ATP-sensitive potassium channel leading to the release of insulin (83).

In a recent study based on data from the United States Food and Drug Administration adverse event reporting system, the highest hypoglycaemia reporting odds ratio amongst the antibiotics was with cefditoren which is a cephalosporin group antibiotic (82). It is believed to be secondary to hypocarnitinemia induced by pivalic acid moiety in cefditoren and the same has been reported with cefcapene pivoxil (84).

Clarithromycin has been implicated in many hypoglycaemia cases and the risk is particularly high in patients on repaglinide because clarithromycin increases repaglinide concentration by inhibiting its metabolism by CYP3A4 (82,85,86). Clarithromycin can also increase the concentration of sulfonylureas by inhibiting p-glycoprotein in the intestinal wall and predispose to hypoglycaemia (87,88).

There have been a few reported cases of hypoglycaemia associated with tetracyclines (tetracycline, oxytetracycline and doxycycline) in diabetic as well as non-diabetic patients (89,90) and the mechanism seems an improvement in

insulin sensitivity (91).

Cotrimoxazole (trimethoprim and sulfamethoxazole) has been implicated in multiple published reports of drug-induced hypoglycaemia. Sulfamethoxazole, due to structural similarity with a sulphonylurea, can cause insulin release and hypoglycaemia especially at extremes of ages and in renal failure, and diazoxide can be used to reduce insulin release if hypoglycaemia is severe and protracted (92,93). Trimethoprim and sulphonamides can also increase the concentration of sulfonylurea and repaglinide by inhibition of CYP2C8 and CYP2C9 and sulphonamides can displace protein-bound sulfonylureas leading to an increase in effective serum concentration and action (5).

Tigecycline, ertapenem and linezolid have also been reported to cause hypoglycaemia (82,94).

Antimalarial medications

Quine can frequently cause hypoglycaemia and the risk is especially high in pregnant women, children, patients with renal failure and patient with poor nutrition (95). Patients treated with intravenous quinine should be monitored for hypoglycaemia (96). Increased glucose consumption by plasmodium parasite and activation of voltage-sensitive calcium channels in pancreatic beta cells by quinine leading to insulin release, either alone or in combination, could result in hypoglycaemia (97). Somatostatin analogue octreotide antagonises quinine's effect on the beta cells and could be useful in quinine induced profound hyperinsulinaemic hypoglycaemia (98). Hypoglycaemia has also been reported with chloroquine, hydroxychloroquine, mefloquine and sulfadoxine-pyrimethamine (99-102).

Antiarrhythmics

Like quinine, quinidine and quinidine like agent disopyramide could induce hypoglycaemia by triggering insulin release from pancreatic beta cells by inhibition of ATP-sensitive potassium channels (97,103). Hypoglycaemia is more common in extremes of ages, and in patients with hepatic and renal failure (104,105). Due to a summative effect on the beta cells and the greater risk of hypoglycaemia, disopyramide should not be used in combination with sulphonylureas (106).

Psychotropic medications

Selective serotonin reuptake inhibitors (fluoxetine, sertraline) and other medications acting on the serotonin pathway like nefazodone are known to cause hypoglycaemia in therapeutic doses (107-109). Tricyclic antidepressants (doxepin, imipramine, nortriptyline) and tetracyclic antidepressant maprotiline can also cause hypoglycaemia in therapeutic doses (109). Citalopram and Venlafaxine are known to cause hypoglycaemia in overdose (110,111). Monoamine oxidase inhibitors (selegiline, rasagiline) are used in the treatment of Parkinson's disease and can also cause hypoglycaemia even in non-diabetic persons (112,113).

Of the antipsychotics, hypoglycaemia in therapeutic doses has been reported with haloperidol, risperidone and quetiapine in non-diabetic patients. Increased insulin secretion has been proposed as the mechanism (114-117).

Other medications

Angiotensin-converting enzyme (ACE) inhibitors are known to increase hypoglycaemia risk in patients on anti-hyperglycaemic medications which is believed to be due to improved insulin sensitivity (118,119). Angiotensin II receptor blockers (ARBs) are generally not believed to increase hypoglycaemia (119,120).

Fibrates (fenofibrate and gemfibrozil) do not cause hypoglycaemia as monotherapy but increase hypoglycaemia risk in diabetic patients on sulphonylurea, metformin and thiazolidinedione (121-123). The risk is higher in combination with glimepiride. The mechanism is believed to be due to the peroxisome proliferator-activated receptor α agonist effect indirectly affecting glucose metabolism (124) or due to inhibition of organic anion transporter polypeptides leading to reduced hepatic uptake and clearance of sulphonylureas (121). The increased hypoglycaemia risk has not been observed with statins (121).

Pentamidine was previously widely used in the prevention and treatment of *pneumocystis jirovecii* pneumonia in immunocompromised patients and it is used in the treatment of African trypanosomiasis, leishmaniasis, Balamuthia infections and babesiosis. Pentamidine is believed to be toxic to pancreatic beta cells and could lead to insulin release and hypoglycaemia when the beta cells are destroyed, which could lead to diabetes as a result (125,126).

Of the newer biologics, immune checkpoint inhibitors could induce hypoglycaemia which is usually secondary to endocrinopathy (127). Hypoglycaemia has also been reported with etanercept and was believed to be secondary to increased insulin sensitivity (128).

Tyrosine kinase inhibitors (imatinib, erlotinib) are used in the treatment of cancers and may increase hypoglycaemia risk in a subset of patients (129,130).

Varenicline is used in smoking cessation. It can improve insulin sensitivity and has been reported to induce severe hypoglycaemia in a patient on insulin (131).

Alcohol

Epidemiology

The true incidence of AIH has been elusive. AIH is more common in malnourished, binge drinker, children after accidental ingestion (132), diabetic on insulin or oral drug, Addison disease, pituitary deficiency and hyperthyroidism. In a study conducted by Sporer *et al.*, out of 378 non-diabetic intoxicated patients only 1% of the patients had severe hypoglycaemia. Furthermore, they could not find any correlation between AIH and epidemiological factors such as age, sex and race and concluded that it is a rare phenomenon for normal healthy subjects (133). Less than one per cent of people with alcohol intoxication who presented to an American emergency department were hypoglycaemic (134). Based on a case series report done in Uganda, socioeconomic factors may play an important role. In middle- and low-income countries the incidence may be higher compared to the developed countries where the prevalence of chronic malnutrition is negligible. Other factors such as type of alcohol consumed or genetic factors may also play a role (135). However, alcohol is particularly known to exacerbate insulin and sulfonylurea induced hypoglycaemia (2).

Alcohol metabolism

Alcohol is metabolised in the liver by alcohol dehydrogenase to acetaldehyde. During this process, nicotinamide adenine dinucleotide (NAD) is reduced to NADH. The resultant product from the first step, acetaldehyde, is converted to acetate by aldehyde dehydrogenase. This second step in alcohol metabolism also reduces NAD to NADH resulting in the net decrease of NAD/NADH ratio in the liver. This shift in the hepatic redox state has a significant impact on hepatic alcohol metabolism and gluconeogenesis since both of these metabolic processes depend on the NAD/NADH ratio. After the conversion of acetaldehyde to acetate, the acetate leaves the liver to be metabolised in extrahepatic tissues such as skeletal muscles (136).

Acute alcohol intoxication

Ingestion of excessive amount of alcohol within a short period of time could result in heterogeneous clinical manifestations affecting different bodily systems such as cardiovascular, respiratory, gastrointestinal, neurological and metabolic alterations (137). The effect of alcohol leading to various metabolic alterations can be dose dependent. Although the lethal dose of alcohol can vary between different individuals, blood alcohol concentration >300 mg/dL could produce profound effect on respiratory and cardiovascular systems and concentration >500 mg/dL could lead to disastrous effects on the cardiovascular and respiratory systems leading to death. Factors such as individual body weight and tolerance to alcohol, the amount ingested, the percentage of alcohol in the beverage and the period of alcohol ingestion play crucial roles in the development of acute alcohol intoxication. In addition, other factors such as age, sex, pre-existing medical conditions and the use of other drugs in addition to alcohol also influence the final outcome of alcohol intoxication (137).

Pathophysiology and presentation of AIH

Hepatic auto-regulation and neurohumoral mechanisms play a role in glucose counter-regulatory mechanism to prevent hypoglycaemia and during hypoglycaemia.

Role of hepatic auto-regulation

Hepatic autoregulation primarily includes glycogenolysis and gluconeogenesis (138). The effect of alcohol on plasma glucose level depends on the amount of alcohol consumed and the underlying nutritional status of an individual. It has been shown that alcohol rarely leads to hypoglycaemia within 8–12 hours (overnight fast) in a normal healthy person with normal glycogen reserve (139,140). Acute alcohol intake after fasting for 3 to 4 days, however, could induce severe and prolonged hypoglycaemia in otherwise healthy individuals (140,141). Individuals with diabetes, impaired liver function and poor nutrition are at higher risk (142).

Alcohol does not inhibit glycogenosis or the release of glucose from the pre-existing glycogen stores. Alcohol stimulates glycogenolysis and could contribute to hyperglycaemia in the fed state (143).

One of the major contributory factors leading to the development of hypoglycaemia in subjects who consumed alcohol is its inhibitory effect on gluconeogenesis (144). Gluconeogenesis requires a certain NAD/NADH ratio

along its pathway to produce glucose. The rise in NADH from alcohol metabolism in the liver can have a profound effect on the actions of certain dehydrogenases required during the metabolic process of gluconeogenesis. The initial step in gluconeogenesis is the conversion of lactate to pyruvate. However, an increased NADH level can strongly inhibit this step. Furthermore, reduced NAD/NADH ratio also has a profound effect on the conversion of malate to oxaloacetate which is another important step in gluconeogenesis. Hepatic gluconeogenesis may be decreased up to 45% after consumption of a moderate amount of alcohol (144). In the absence of gluconeogenesis, hypoglycaemia can occur 8-10 hour later, after the glycogen storage has been used up. Glycogenolysis accounts for 85% of initial hepatic glucose output but once the hypoglycaemia is established gluconeogenesis progressively takes over the overall hepatic glucose output to prevent a greater degree of hypoglycaemia (145).

In addition to impaired hepatic auto-regulation, moderate alcohol intake can lead to reactive hypoglycaemia when it is consumed together with a simple carbohydrate-rich meal or drink like gin and tonic (146). This is thought to be due to an exaggerated insulin response to carbohydrate and depends on the nature of carbohydrate (147). This is further supported by experimental studies which did not show an increase in insulin or C-peptide in alcohol-related hypoglycaemia of other mechanisms (140,148).

AIH may also lead to the development of alcoholic ketoacidosis (149). Due to the impairment of hepatic gluconeogenesis, counter-regulatory neurohormonal mechanisms are activated promoting free fatty acid release from triglycerides stored in the adipose tissues. Furthermore, alcohol may directly activate lipolysis increasing the fatty acid supply to the liver. A portion of these available free fatty acids is diverted into the ketogenesis pathway resulting in the increasing concentrations of acetoacetate acid and beta-hydroxybutyrate (150,151). Besides, hepatic redox shift allows pyruvate to be converted into lactate by enzyme lactate dehydrogenase leading to increase blood lactate levels during alcohol consumption. Elevation of plasma lactate level usually accompanies alcoholic ketoacidosis raising the anion gap further (152-154).

Counter regulatory hormonal response to AIH

An important area of interest in AIH is whether alcohol can blunt counterregulatory hormonal response. There is extensive literature surrounding this subject over the last 50 years. The role of glucagon, growth hormone, cortisol and the role of alpha- and beta-adrenergic responses to adrenaline and noradrenaline were reported in various studies. These neuro-humeral mechanisms influence glucose metabolism by acting upon glucose production and glucose utilisation. The synergistic action of glucagon, growth hormone and catecholamines generate profound insulin resistance compared to that of the action of individual hormone (155,156).

Glucagon is generally believed to be the major humoral factor responsible for glucose production in the event of hypoglycaemia (157). Epinephrine can reduce glucose clearance by as much as 30% and can also increase glucose production transiently for 90 minutes (158). Whereas cortisol reduces insulin sensitivity in hepatic as well as extrahepatic tissues to create a state of insulin resistance (159).

Data surrounding the effect of alcohol on the counterregulatory hormones in the event of acute hypoglycaemia is extensive and sometimes contradictory. Avogaro *et al.* suggested that alcohol intake impairs glucose counter regulations during insulin-induced hypoglycaemia in type 1 diabetes and prevents spontaneous recovery from hypoglycaemia. During their study, an increase in glucagon response was found together with low cortisol and growth hormone levels (160). Bolli *et al.* also found defective glucose counter-response after subcutaneous insulin in type 2 diabetes patients (161). However, Rasmussen *et al.* did not find the same conclusion in their type 2 diabetes patients during insulin-induced hypoglycaemia after alcohol ingestion (162). Kerr *et al.* reported a smaller rise in serum growth hormone level during moderate hypoglycaemia (2.8 mmol/L) after mild alcohol intoxication (45–50 mg/dL) in persons with type 1 diabetes. Their study did not find a difference in other counter-regulatory hormones such as cortisol, glucagon, adrenaline and noradrenaline (163). This was further supported by Turner *et al.* who demonstrated that even though evening and overnight blood glucose levels were no different, fasting blood sugar and postprandial blood sugar the next morning were lower in type 1 diabetes patients who ingested alcohol in the evening before and the difference were attributable to reduced nocturnal growth hormone levels while insulin and other counterregulatory hormone levels were not different (164). Kolaczynski *et al.* found that serum growth hormone, cortisol and glucagon responses were reduced during insulin-induced hypoglycaemia after moderate alcohol ingestion. This study also suggested that insulin resistance caused by ethanol contribute to faster recovery from hypoglycaemia despite reduced counter-regulatory hormone response (165).

Even though the action of growth hormone and cortisol is important to defend against hypoglycaemia their effects take several hours and so these hormones may not play a role in the body initial compensatory response to hypoglycaemia (157).

Acute effects of alcohol on the other endocrine hormones

Acute effects of alcohol on other endocrine hormones have been reported in various studies. Leppäluoto *et al.* studied the effect of alcohol on pituitary function in healthy male volunteers and found no changes in plasma adrenocorticotropin (ACTH) concentrations during a period of 15 hours after the ingestion of alcohol but found lower luteinizing hormone (LH) levels in subjects who received alcohol (166). Ylikahri *et al.* investigated the acute impact of alcohol on the anterior pituitary hormones and concluded that acute alcohol ingestion had no significant impact on the basal concentrations of T3, T4, thyroid-stimulating hormone (TSH), LH and testosterone (167).

Acute effect of alcohol in patients with non-insulin treated diabetes

Alcohol induced hypoglycemia is a common complication in insulin treated diabetes. Christiansen *et al.* studied the acute effect of moderate ethanol intake in non-insulin dependent type 2 diabetes and found similar serum glucose, insulin, free fatty acid and triacylglycerol responses when compared to water. They did not observe any excess hypoglycaemia risk (168). Significantly less alcohol tolerance has been reported in chlorpropamide treated type 2 diabetics and the effect may extend to other sulphonylureas (169).

Alcohol induced hypoglycaemia and H2 blockers

The interaction between certain H2 blockers cimetidine, ranitidine and famotidine and alcohol was studied by Czyzyk *et al.* Hypoglycemia following alcohol ingestion was significantly enhanced by all H2-receptor antagonists but was most noticeable after famotidine. Only ranitidine significantly increased mean blood ethanol concentration and none of the drugs modified blood acetaldehyde concentration. Therefore, it was suggested that enhancement of alcohol induced hypoglycemia by H2 receptor antagonists is not entirely dependent on the increase of ethanol absorption from gastrointestinal tract, but rather represents an effect of these drugs on glucose metabolism (170). H2 receptor antagonists can reduce class 4 alcohol dehydrogenase activity in gastric mucosa thereby reducing first pass metabolism of alcohol in stomach and increasing blood alcohol level (171). Proton pump inhibitors may be preferable treatment modality in this patient group.

Prevention of alcohol induced hypoglycaemia

Hypoglycaemia is a major burden to the healthcare systems across the world. Intact awareness of hypoglycaemia is crucial to recognising and treating hypoglycaemia which can be impaired during acute alcohol intoxication. The risk is higher with the presence of other factors such as increasing age, presence of diabetes, underlying comorbidities and exercise. It is important to minimise the risk of developing significant hypoglycaemia due to alcohol by educating people that alcohol can reduce awareness of hypoglycemia and needfulness of close blood sugar monitoring following alcohol consumption in diabetes especially when they are treated with medications such as insulin or sulphonylurea. It is advisable not to drink excessive amount of alcohol on an empty stomach or during prolong period of starvation. It is better to avoid participating in strenuous physical activities after consumption of significant amount of alcohol. To this date, the main strategy to prevent alcohol induced hypoglycemia has been structured education.

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