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CARDIOVASCULAR DRUGS INDUCED HYPOGLYCEMIA – MECHANISM AND MANAGEMENT

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ABSTRACT

Drug-induced Hypoglycemia may lead to significant consequences including severe Hypoglycemia, coma, and death. Hypoglycemia symptoms can occur when blood glucose is <70 mg/dl, and the Whipple triad help to confirm the diagnosis of Hypoglycemia. Cardiovascular drugs that cause Hypoglycemia may include ACE Inhibitors, Non-Selective Beta-Blockers, Quinidine And Disopyramide can induce Hypoglycemia through multiple mechanism, including changes in peripheral insulin sensitivity, glucose uptake secretion of insulin from pancreas as well as mask autonomic hypoglycemic symptoms the symptoms of Hypoglycemia varies greatly neurogenic or autonomic symptoms includes tremors, palpitation, anxiety, due to catecholamine mediated autonomic effects and sweating, hunger, tingling due to acetylcholine mediated autonomic effects, neuroglycopenic symptoms such as irritability, drowsiness, blurred vision, difficulty with speech, confusion, changes in behaviour as a result of brain neuronal glucose deprivation risk factors for drug-induced Hypoglycemia includes advanced age, concomitant use of more than one drug that can induce Hypoglycemia and malnutrition hepatic dysfunction and renal dysfunction, Hypoglycemia should be clinically diagnosed prior to treatment and it should differentiate between mild-moderate versus severe signs and symptoms because treatment based on level of severity patients who are conscious should receive a fast-acting carbohydrate such as glucose or simple carbohydrates or fruit juice, intravenous dextrose or intramuscular glycogen is administered to unresponsive patients. Patients receiving medication known to cause Hypoglycemia or high-risk patients should be educated regarding the associated signs and symptoms, consistent intake of meals, and snacks, and demonstration of self-monitoring of blood glucose.

KEYWORDS: Hypoglycemia, Cardiovascular Drugs, Mechanism, Management.

INTRODUCTION

Hypoglycemia is a Greek word that means under sweet the blood in 1992, Hypoglycemia was first discovered by James Collip when Collip was working on purifying the insulin. He rejected insulin in rabbits and realized the reduction in blood glucose levels. Collip discovered that with an injection of large doses of insulin, the rabbit got into a coma and died.

Individuals with diabetes show weakened counterregulatory reactions to Hypoglycemia and/or experience Hypoglycemia unawareness, a measured glucose level <70 mg/dl [3.9 mmol/l] is considered clinically important [free of the severity of acute hypoglycemic symptoms].[1] The diagnosis of Hypoglycemia is usually done in patients without diabetes when venous plasma glucose is <3 mmol/l [55 mg/dl] and is supported by the presence of Whipple's triad.[2] Evaluation and management of Hypoglycemia only in patients in whom Whipple's triad in a set of three - symptoms, signs, or both consistent with Hypoglycemia, a low plasma glucose concentration, and resolution of those signs and symptoms after the plasma glucose concentration is raised.[3]

Level 1 Hypoglycemia is characterized as a measurable glucose concentration <70 mg/dl [3.9 mmol/l], but ≥54 mg/dl [3.0 mmol/l] that can make an individual aware to take action. Glucose levels <70mg/dl [3.9 mmol/l] are clinically significant, free of the severity of acute symptoms level 2 Hypoglycemia is characterized as a measurable glucose concentration <54 mg/dl [3.0 mmol/l] that needs quick activity level 3. Hypoglycemia is a severe event characterized by altered mental and/or physical status requiring support.[4]

CLASSIFICATION

The classification of Hypoglycemia in diabetes.

1. Severe Hypoglycemia: severe Hypoglycemia is an event in the need for the assistance of another person to

actively administer carbohydrates, glucagon, or take other remedial actions. Plasma glucose concentrations may not be accessible during an event, but rather neurological recuperation following the arrival of plasma glucose to normal is considered sufficient proof that the event was induced by a low plasma glucose concentration.

2. Documented Symptomatic Hypoglycemia: Documented symptomatic Hypoglycemia is an event during which typical symptoms of Hypoglycemia are followed by a measured plasma glucose concentration of ≤70 mg/dl [≤3.9 mmol/l].

3. Asymptomatic Hypoglycemia: asymptomatic Hypoglycemia is an event not followed by typical symptoms of Hypoglycemia but rather with a measured plasma glucose concentration of ≤70 mg/dl [≤3.9 mmol/l].

4. Probable Symptomatic Hypoglycemia: probable symptomatic Hypoglycemia is an event during which symptoms typical of Hypoglycemia are not followed by a plasma glucose determination, but rather was probably caused by a plasma glucose concentration ≤70 mg/dl [≤3.9 mmol/l].

5. Pseudo-Hypoglycemia. Pseudo-Hypoglycemia is an event during which the individual with diabetes reports any of the typical symptoms of Hypoglycemia with a measured plasma glucose concentration of >70 mg/dl [>3.9 mmol/l] yet moving towards the level.[5]

Insulin-related Hypoglycemia and errors are clinically huge reasons for ed visits and hospitalizations for long periods, especially among elderly patients with diabetes. Reducing ed visits for adverse events related to injectable antidiabetic agents has been perceived as a national priority for working on the well-being of Americans in new healthy individuals as a 2020 goal.[6]

ETIOLOGY OF HYPOGLYCEMIA

Table 1: Patients With Diabetes.

S.NO	IN PATIENTS WITH DIABETES		
1.	Missed, delayed, or inadequate meal.[7]	8.	Errors in insulin dose [schedule/administration].[16]
2.	Chronic alcohol use.[8]	9.	Unusual exercising.[17]
3.	Hypoglycemia unawareness.[9]	10.	Burns.[18]
4.	Hepatic, renal, and cardiac failure.[10]	11.	Decreased renal insulin clearance in renal failure patients.[19]
5.	Lack of nutritious food.[11]	12.	Reactive Hypoglycemia.[20]
6.	Weight loss.[12]	13.	Trauma.[21]
7.	Factitious disorder.[13]	14.	Sepsis [including malaria].[22]
8.	Errors in oral anti-diabetic agents.[14,15]		

Table 2: Patients Without Diabetes.

S.NO	IN PATIENTS WITHOUT DIABETES	
1.	Critical illness	Heart failure.[24] Renal[25], hepatic[26], and Malnutrition.[27]
2.	Congenital disorders	Glycogen storage disease.[28] Congenital hypopituitarism.[29]
3.	Endogenous hyperinsulinism	A. Insulinoma.[30] B. Functional β-cell disorder. Non-insulinoma pancreatogenous Hypoglycemia.[31] Post gastric bypass Hypoglycemia.[32] C. Insulin autoimmune Hypoglycemia. Antibody to insulin.[33] Antibody to the insulin receptor.[34] D. Insulin secretagogue[35]
4.	Exogenous hyperinsulinism	Accidental, surreptitious, or malicious. [Hypoglycemia].[36]
5.	Drugs	E.g., Non-selective beta-blockers.[37]
6.	Hormone deficiency	Growth hormone.[38]

PATHOPHYSIOLOGY

GLUCOSE HEMOSTASIS

Carbohydrates are one of the four significant classes of organic molecules in the living systems that assist in energy production, long-term storing of energy, the formation of nucleic acids [ribose and deoxyribose], and the detoxification process. They also function as signaling, recognition, and adhesion molecules.[39] Glucose can be produced from three sources: fat, proteins via gluconeogenesis; and liver, and muscle via glycogenolysis.[40] The liver has a role in maintaining glucose homeostasis. It is therefore not expected that insulin can control hepatic glucose production [HGP] through numerous mechanisms.[41]

The mammalian brain relies upon glucose as its primary source of energy. In the adult brain, neurons have the highest energy demand, requiring constant delivery of glucose from the blood. In humans, the brain represents roughly 2% of the body weight, yet consumes roughly 20% of glucose-determined energy, making it the primary consumer of glucose [approximately 5.6 mg glucose per 100 g of human brain tissue per minute]. Glucose metabolism fuels physiological brain function through the generation of ATP, the establishment of neuronal and non-neuronal cellular maintenance, and the generation of neurotransmitters.[42] Among the 14 currently identified members of the facilitative glucose transporter family, only GLUT2, GLUT5, GLUT7, GLUT9, AND GLUT12 are known to exist within the small intestine.[43]

In the small intestines and kidneys, glucose is effectively absorbed against its concentration gradient. The transport of glucose is based on the chemical gradient of Na +, which is maintained by the action of Na + /k+ - ATPase with the hydrolysis of ATP. The first Na + - dependent glucose transporter [cotransporter] was discovered, SGLT1.[44]

The major cellular mechanism for the removal of an exogenous glucose load is insulin-stimulated glucose transport into skeletal muscle. Skeletal muscles store glucose as glycogen and oxidize it to deliver energy following the transport step. The vital glucose transporter protein that intercedes this uptake is one isoform [gene name, SLC2A4; protein name: GLUT4] of a group of sugar transporter proteins containing 12-transmembrane domains. The GLUT4 is a glucose transporter thus a significant mediator of glucose expulsion from the circulation and a key regulator of entire body glucose homeostasis.[45]

Gastrointestinal absorption of glucose is connected in a way to the retention of sodium ions.[46] Glucose transport from the lumen across the apical membrane of the epithelial cell happens against a concentration gradient and, requires a functioning transport process. The proximal tubule's early convoluted segment [S1] reabsorbs around 90% of the separated renal glucose. This is achieved by the high-capacity, low-affinity SGLT2 transporter. The excess 10% of the filtered glucose is reabsorbed by the high-affinity, low-capacity sglt1 transporter in the proximal tubule's distal straight segment [S3]. Both SGLT1 and SGLT2 coupled glucose transport to the sodium gradient and the sodium electrochemical gradient generated by active sodium transport gives the energy required for glucose transport.[47]

The rate-limiting step towards muscle glucose use is the transmembrane transport of glucose interceded by glucose transporter [GLUT], which is expressed principally in skeletal muscle heart, and adipose tissue, GLUT4 mediates glucose transport stimulated by insulin and contraction/exercise.[48] A central role for GLUT4 in entire body metabolism is strongly supported by a variety of genetically engineered mouse models where expression of the transporter is either improved or removed in muscle or adipose tissue or both.[49]

Glycolysis is the pathway of a breakdown of glucose into pyruvate/lactate following glucose uptake by cells and glucose phosphorylation.[50] Glycolysis additionally gives the substrates for energy production through the formation of ATP as well as substrates for storage pathways of glycogenesis and lipogenesis 450 the pentose phosphate pathway [PPP], also known as the pentose phosphate shunt, is an important part of glucose metabolism.[51]

As fasting progressed, the glycogen supply was exhausted and new glucose synthesis, or gluconeogenesis, turned into the predominant process contributing to glucose production. Under fasting conditions, the liver plays a significant part in producing glucose as fuel for different tissues, such as the brain muscles, red blood cells and. At first, the pancreatic hormone glucagon increases the cascade of kinase action [stated below in detail] that releases glucose from the stored glycogen via glycogenolysis.[52] gluconeogenesis in humans and nonruminants comprises the synthesis of glucose and glycogen from lactate, pyruvate, glycerol, and certain amino acids. The liver is the principal site of gluconeogenesis with the kidney turning into a vital site in the course of hunger and acidosis. Adipose and other tissues contain some of the enzymes of gluconeogenesis but their function appears to be related to glycogenesis or the replenishment of citric acid cycle intermediates.[53]

Insulin plays a central role in the fuel homeostasis of the whole body the impairment of insulin secretion in islets from type-2 diabetic donors connects with a strong [> 70%] decrease of the mRNA levels for key exocytotic proteins like synaptotagmin-5, syntaxin-1, snap-25 and vamp-2 [Ostenson et al. 2006].[54] One of insulin's essential physiologic functions is storing ingested glucose for future use. The insulin released during carbohydrate ingestion does so by potentiating the effect of glucose to increase both liver and muscle glucose uptake.[55] Insulin signaling binding of insulin to its receptors results in phosphorylation of specific intracellular proteins that are thought to act as transducers of the hormone signal, insulin plays an important role in the regulation of skeletal muscle protein turnover in vivo. It promotes protein deposition each with the aid of the inhibition of proteolysis and stimulation of protein synthesis.[56] In normal physiology, Insulin secretion occurs from the β-cell of the islets of Langerhans in the pancreas. The secretory responses of this cell are well understood by separately examining glucose stimulation and non-glucose stimulation. Glucose stimulation of the b cell: in

a normal man, glucose stimulation of the b cell results directly in insulin secretion.[57]

The secreted insulin consists of 51 amino acids with a molecular weight of 5.8 kDa. However, the insulin gene encodes a 110-amino acid precursor recognized as preproinsulin. Insulin biosynthesis is controlled by multiple factors, glucose metabolism is the most important physiological event.[58] Increased blood glucose levels stimulate insulin gene transcription and insulin secretion. Insulin gene transcription is controlled by a 340 bp promoter region upstream of the transcription start site of the insulin gene.[59] Proinsulin biosynthesis in islets of Langerhans occurs at a rate that is slower than the rate at which the insulin is been released when the islets are stimulated. Thus, to ensure adequate supplies of insulin for release, the islet relies on a biosynthetic process which is continually active β-cells of islets of Langerhans react to excessive glucose concentrations and anticipated excessive rates of insulin release by transcriptional and post-transcriptional effects to stimulate proinsulin biosynthesis.[60] The insulin response to glucose is so severely inhibited by somatostatin in humans that glucose tolerance is greatly reduced. Somatostatin completely abolished both the first and the second phases of glucose-induced insulin release. Thus, the mechanisms underlying somatostatin's inhibitory activity are unclear and require further examination.[61]

Glucagon is an essential hormone regulating glucose homeostasis and acts as a counterregulatory hormone to insulin. Glucagon for the most part raises circulating glucose levels by stimulating hepatic glucose production via increased glycogenolysis and gluconeogenesis in the fasting state [Cherrington et al., 1978].[62] Glucagon stimulates insulin secretion from islet β-cells although its physiologic significance is not yet clear. As a mechanism of this action, it had been generally accepted that insulin secretion is stimulated by glucagon directly through its receptor on the β-cell.[64]

During hypoglycemic pressure, glucagon secretion increases and insulin secretion decreases. Early anatomic examination demonstrated that parasympathetic nerves innervate the pancreatic islets, an issue, that recommends extensive cholinergic innervation. The postganglionic parasympathetic nerves are predominantly cholinergic, parasympathetic nerves can influence islet function because electrical activation of the vague stimulates the secretion of both insulin and glucagon.[64] High serum cortisol levels are significantly associated with decreased ß-cell function, even in the physiological cortisol range, t higher serum cortisol levels are a risk factor for future incidence of diabetes.[65]

The ability of catecholamines to elevate the blood glucose con¬ centration has led to the concept that one of the more important metabolic functions of the sympathetic nervous system is to maintain an adequate glucose supply to peripheral tissues.[66] The role of the sympathetic nervous system is that of producing an increase in blood glucose, and the effects appear to be mediated principally by epinephrine. Interference with the integrity of the sympathetic nervous system by cordotomy or by adrenal denervation results in an impaired recovery from insulin-induced Hypoglycemia. Lack of change in glucose-mediated insulin secretion following vagotomy indicates that the vague has little if any impact of glucose loading on insulin secretion the current investigations do not, thus supporting the concept that vagal hyperactivity is responsible for reactive Hypoglycemia.[67]

Normal responses to a drop in plasma glucose levels follow a specific hierarchy in order to prevent the onset of hypoglycemia. Initial increases in the release of counterregulatory hormones [glucagon, epinephrine, GH, and cortisol] occur at about 70 mg/dl [4 mm]. [ACTH]] and a concomitant increase in the discharge of autonomic nervous system neurotransmitters norepinephrine and acetylcholine[68] Insulin signaling binding of insulin to its receptors results in the 0phosphorylation of specific intracellular proteins that are thought to act as transducers of the hormone signal, insulin plays an important role in the regulation of skeletal muscle protein turnover in vivo. It promotes protein deposition both by the inhibition of proteolysis and stimulation of protein synthesis.[69]

The abnormalities in glucose metabolism that occur with aging and the high prevalence of glucose intolerance in the elderly population may be caused by age-related insulin secretory malfunction.[70]

RISK FACTORS

AGE

The occurrence of hypoglycemic events is extremely normal in older patients with diabetes in our observation and found no relationship between specific comorbidities and Hypoglycemia. The outcome was inconsistent with most previous studies focused on specific comorbidities such as depression, dementia, CVD, stroke, cancer, history of falls, hypertension, liver cirrhosis, or renal diseases.[71] Hypoglycemia in older people [>75 years] with diabetes is common, its acknowledgment can be challenging at times, making a diagnosis in this age group unsure. Due to the increased likelihood of developing hypoglycemia's negative effects in older adults with diabetes prevalence of multiple comorbidities, undernutrition, and polypharmacy compared with younger people is thought to develop as a result of abnormalities in molecular, cellular, and physiological levels.[72]

The high frequency of hypoglycemic episodes in older adults with poor glycemic control and larger studies are needed to determine the relationship between the frequency of hypoglycemia and various insulin regimens and groups of oral medicines. In a recent retrospective

analysis, munshi and colleagues have shown that older patients with diabetes who have simpler diabetic regimens are with decreased frequency of self-reported Hypoglycemia.[73] Although polypharmacy is thought to increase the risk of Hypoglycemia, this theory has not been addressed epidemiologically.[74] A combination of worsened insulin secretion and increased insulin resistance. Adiposity, sarcopenia (decreased muscle mass), and physical inactivity are thought to be a combination of factors that contribute to insulin resistance that is associated with aging.[75] Multiple severe hypoglycemic episodes increased the risk of severe hypoglycemic episodes in patients with comorbid depression may be due to poor self-care or psychobiologic changes associated with depression. Comorbid depression in an adult population with diabetes was associated with an increased risk of time to a hypoglycemic episode requiring an ER visit or hospitalization. Weight loss may result from the increased risk of macrovascular, microvascular, and dementia in people with diabetes who also have significant depression.[76]

MALNUTRITION

The term 'malnutrition' has no universally accepted definition. It has been used to describe a deficiency, excess, or imbalance of a wide range of nutrients, resulting in a measurable adverse effect on body composition, function, and clinical outcome.[77] One of the conditions associated with dysglycemia is malnutrition. Reasons for this imbalance may include the patient's age socioeconomic status, and comorbidities Many TPN recipients, especially those getting it during surgery, have varying degrees of malnutrition, therefore careful monitoring of glucose metabolism is necessary to prevent reactive hypoglycemia linked to malnutrition.[78]

HYPOGLYCEMIC DRUGS

The annual rates ofhypoxiaycameraa requiring third-party assistance in the home or workplace among persons with diabetes who are receiving hypoglycemic agents are not known, although these rates have been reported to be as high as 59% for persons receiving insulin in a large health maintenance organization based on survey results these studies have led to a consensus among major American and European diabetes professional societies to recommend individualized target goals for persons with diabetes who are older or who have significant acute or chronic medical, neurological, or mental comorbid conditions that put them at higher risk for Hypoglycemia.[79]

The risk of Hypoglycemia increases with increases in treatment intensification in reducing hba1Hypoglycemia is associated with a wide range of adverse clinical outcomes in the advanced trial, Hypoglycemia was associated with increased hazards of disease entities of the respiratory system, gastrointestinal system, and dermatologic systems, although the details were not specified fear and avoidance of Hypoglycemia may promote defensive eating resulting in weight gain or obesity.[80]

The use of most sulfonylurea derivatives is accompanied by the development of severe Hypoglycemia. Glibenclamide in smaller doses exhibits a stronger hypoglycemic effects advantage over metformin over drugs that stimulate insulin secretion in the absence of pronounced hypoglycemic reactions.[81] tight glucose control did not significantly reduce hospital mortality but significantly increased the risk of Hypoglycemia. Hypoglycemia was not independently associated with increased risk of death, and released mortality could not be excluded with severe Hypoglycemia [BG of 1.2 mmol/l] and in patients admitted with BG of 10 mmol/l the standard cut-off to define Hypoglycemia [2.2 mmol/l] might not be the threshold for deleterious adverse effects.[82]

Reduced Hypoglycemia, during this experiment, a significant difference in body weight was seen between the insulin detemir group and the NPH group. When combined with a rapid-acting analog like is, a basal-bolus insulin regimen with insulin detemir may provide tighter glucose control than that feasible with NPH insulin.[83]

SIGNS AND SYMPTOMS

The physiological defenses against falling plasma glucose concentrations include decreased pancreatic islet β cell insulin secretion, increased pancreatic islet α cell glucagon secretion; and, absent the latter, increased adrenomedullary epinephrine secretion.[84] Clinical Hypoglycemia is a plasma glucose concentration low enough to cause symptoms and signs, including impairment of brain function. The clinical manifestations of Hypoglycemia are nonspecific symptoms of Hypoglycemia are categorized as neuroglia panic and neurogenic or autonomic.[85]

Symptoms of Hypoglycemia are classified as neuroglia panic, the result of central nervous system glucose deprivation, and neurogenic.[86] Increased sympathetic activity in response to Hypoglycemia is the increase in plasma epinephrine and norepinephrine concentrations. Awareness of Hypoglycemia is primarily caused by the perception of neurogenic symptoms. In diabetes, the development of autonomic dysfunction can result in an impaired adrenergic response, with resultant loss of warning symptoms. This phenomenon is known as 'Hypoglycemia unawareness drugs are the most common cause of Hypoglycemia. Alcohol is perhaps the next most common cause of drug-induced Hypoglycemia and acts predominantly by inhibiting gluconeogenesis.[87]

Symptoms of Hypoglycemia are divided into those directly attributable to glucose deprivation of the CNS [neuroglycopenic symptoms] and those attributable to the autonomic nervous system activation triggered by Hypoglycemia [neurogenic or autonomic symptoms, that

patients, use both neuroglycopenic and neurogenic symptoms to recognize developing Hypoglycemia symptoms of Hypoglycemia could include the adrenergic neurogenic symptoms of shaky/tremulous, heart pounding, and nervous; the cholinergic neurogenic symptoms of sweaty, hungry, and tingling [as well as "blood sugar low"]; and the neuroglycopenic symptoms of warm, weak, difficulty thinking, and tired/drowsy.[88]

Increased sympathetic activity in response to Hypoglycemia is the increase in plasma epinephrine and norepinephrine concentrations.[89] The adrenergic symptom response to Hypoglycemia in IDDM and control subjects is more closely related to the epinephrine response than to the peripheral MSNA response. Age, duration, and hba1 were not significant symptom predictors although both the epinephrine and MSNA responses to Hypoglycemia increased as glycemic control worsened.[90] Sympathetic neural responses to Hypoglycemia, like adrenomedullary responses, are reduced after recent Hypoglycemia.[91]

Hypoglycemia deprives the brain of the constant supply of glucose needed for energy. Such low levels of blood glucose are sensed by the ventromedial hypothalamus Hypoglycemia-associated autonomic failure may also result from intense physical activity Hypoglycemia adversely alters mood. Recurrent Hypoglycemia elevates anxiety, depression, and anergia. Such changes in emotion are usually correlated with lower self-reported energy and self-efficacy, which can impair cognitive performance diabetes education can provide patients with options that reduce fear and discourage choices that provide a rationale for poor glycemic control.[92]

It is unknown whether idiopathic reactive hypoglycemia and diabetes are related. Patients with reactive Hypoglycemia have been described as emotionally labile persons who complain of mild indications of hypoglycemia along with signs of autonomic dysregulation such as fatigue, dizziness, jitteriness, palpitations, and perspiration.[93] Altered hippocampal cholinergic receptors and decreased GABA receptor expression in hypoglycemic and diabetic rats suggest an involvement of these two systems in the pathophysiology of the neuronal damage associated with Hypoglycemia and Hyperglycemia in diabetes.[94]

For this reason, a number of hormonal and physiological factors work together to closely control glucose homeostasis. responses to the sympathoadrenal response include activation of the adrenal medulla to secrete release of norepinephrine and epinephrine as well as the sympathetic nervous system's activation of norepinephrine and acetylcholine. Cholinergic symptoms such as sweating, hunger, and paresthesias are mediated by acetylcholine from sympathetic postganglionic neurons. Both are largely mediated by sympathetic neural, rather than adrenomedullary, activation.[95] During acute insulin-induced in healthy individuals with hypoglycemia, symptoms can be seen at plasma glucose levels of approximately 60 mg per decilitre as measured in arterialized venous blood, and impairment of brain function has occurred at approximately 50 mg per decilitre [2.8 mmol per liter].[96]

DIAGNOSIS

The identification of a hypoglycemia disease necessitates strong clinical suspicion, careful consideration of the patient for the presence of mediating drugs or predisposing illness, and, when indicated, methodical evaluation based on well-defined diagnostic criteria.[97] Clinically significant Hypoglycemia is characterized by Whipple's triad: 1. symptoms of neuroglycopenia, 2. simultaneous blood glucose lower than 40 mg/dl [2.2 mmol/l], and 3. relief of symptoms with the administration of glucose. This blood glucose cut-off corresponds to plasma glucose of 45 mg/dl [2.5 mmol/l] a hypoglycemic disorder when a fingerstick capillary blood glucose result is low, this should be suspected. However, most reflectance glucometers in home and hospital use have poor precision at blood glucose values of less than 60 mg/dl [3.3 mmol/l].[98]

To describe the level of consciousness in patients with traumatic brain injury, the Glasgow Coma Scale (GCS) was created. It gauges the patients' best verbal, motor, and visual responses and categorizes their degree of consciousness as light (score of 14–15), moderate (score of 9–13), or severe (score of 3–8). Neuroglycopenic symptoms are frequently present in hypoglycemia individuals. Because the brain's glucose supply is insufficient, hypoglycemia patients' GCS scores are predicted to be low.[99] Glasgow coma scale: spontaneous, eye-opening Four to speak 3 to hurt 2 none the best response was an oriented five confused conversation. 3 unintelligible sounds, 4 offensive words 2 none 1 best motor reaction: follows instructions 6 pinpoints discomfort 5 flexion [normal withdrawal] Unusual flexion number four [decorticate] Extending by three [decelerate] 2 none-1.[100] Clinical Whipple's triad—symptoms, signs, or both consistent with hypoglycemia, a low measured plasma glucose concentration, and remission of those symptoms and indications after the plasma glucose concentration is raised—is the most effective method for proving hypoglycemia. The two most typical symptoms of hypoglycemia are pallor and diaphoresis [caused by adrenergic cutaneous vasoconstriction and cholinergic activation of sweat glands, respectively].[101]

CARDIOVASCULAR DRUGS CAUSING HYPOGLYCEMIA

ACE INHIBITORS

Hypertension, congestive heart failure, and myocardial infarction are common among patients with diabetes mellitus. The majority of these illnesses require lengthy medication treatments. A complicating factor in the treatment is the adverse effect on glucose metabolism of many drugs such as thiazide diuretics and beta-blocking

agents. The introduction of angiotensin-converting enzyme [ACE] inhibitors was welcomed as an improvement in the treatment of congestive heart failure and hypertension among diabetic patients. The use of ACE inhibitors in this trial was independently associated with an increase of 2-4 times in risk of hospital admission because of Hypoglycemia among individuals who had taken oral or injectable insulin for at least a year. The association between ace-inhibitor use and Hypoglycemia could be biased if ace inhibitors were preferentially prescribed to patients already at an increased risk of Hypoglycemia.[102]

Drug-induced Hypoglycemia may occur with therapeutic drug use in patients with diabetes mellitus, deliberate or accidental overdoses, drug interactions, inappropriate drug dispensing, and drug-induced hepatotoxicity and nephrotoxicity. Drug-induced Hypoglycemia is markedly increased in the presence of liver and renal diseases which are often compounded by poor nutrition. Ace inhibitors improve insulin resistance and glycaemic control in patients with or without diabetes mellitus and may lead to hypoglycemic episodes requiring a reduction in the dosage of hypoglycaemic agents was assumed that angiotensin ii had diabetogenic effects like other counterregulatory hormones.[103]

After the publication of incidental observations in the mid-1980s, which suggested that there was an, in conclusion, our study confirms that ace inhibitor therapy is associated with hospital admission for severe Hypoglycemia in diabetic patients. Improvement in glucose tolerance after treatment with an ace inhibitor, anecdotal reports from diabetic clinics described a reduction in insulin requirements. ACE inhibitors undoubtedly have advantages over other antihypertensive drugs in the treatment of diabetic patients with heart failure and microalbuminuria.[104]

Ace inhibitors increase blood flow in skeletal muscle by several mechanisms. These include a decrease in the concentration of angiotensin ii, a potent vasoconstrictor, and an increase in bradykinin, which has vasodilating and insulin-like properties.[105]

The overall pattern of results does not suggest that concomitant use of ACE in users of insulin secretagogues or metformin is associated with an increased rate of serious Hypoglycemia summary, concomitant use of ACE is overall was not associated with elevated rates of serious Hypoglycemia in users of insulin secretagogues possibly excluding those on glimepiride. Further research is warranted to understand any underlying mechanisms.[106]

NON-SELECTIVE BETA-BLOCKERS

The first reason usually given by physicians for withholding beta-blocker therapy is that these agents obscure the warning symptoms of Hypoglycemia, a dangerous complication of diabetes treatment blunting hypoglycemic awareness is much less of a concern with the use of more cardioselective agents such as atenolol and metoprolol nonselective beta-blockade during an acute episode of Hypoglycemia may also delay the physiological correction of Hypoglycemia in addition to lowering blood pressure, beta blockers have anti-anginal, anti-ischemic, and anti-arrhythmic properties, and are thought to be especially effective in the prevention of morbidity and mortality from coronary heart disease physicians remain concerned about the possibility of adverse surrogate endpoints, there are newer beta-blockers [e.g., acebutolol, labetalol, or carvedilol] that could be considered.[107]

Hyperinsulinemia Hypoglycemia may develop when the drug is used alone or in combination with other hypoglycemic owing to nonselective beta-adrenoceptor antagonists such as propranolol has been reported and may have a fatal outcome.' Beta-blockade is associated with the suppression of insulin secretion, and the release of counterregulatory hormones, including adrenaline, growth hormone, and cortisol, is generally increased. Some studies have noted no effect on the incidence and severity of symptoms of Hypoglycemia, whereas others have found moderate to marked attenuation. Angiotensin-converting enzyme inhibitors are associated with the onset of Hypoglycemia following their use, occurring with a greater frequency than can be accounted for by chance alone but only when the agents are taken in association with antidiabetic drugs.[108]

Propranolol has a half-life of four to six hours, which may be longer in infants and small children.[109] The adrenergic nervous system is one of many neural and hormonal factors that influence the secretion of insulin and glucagon and, ultimately, the regulation of glucose metabolism in the body f3-adrenergic stimulation causes a release of insulin from the β-cells [or b-cells] of the islet of Langerhans. Adrenergic stimulation of the b cells inhibits insulin secretion. A-adrenergic stimulation also causes lipolysis in adipose tissue, which can help gluconeogenesis produce glycerol, which in turn can indirectly boost blood sugar levels. A. Propranolol has been reported to increase the uptake of glucose into skeletal muscle cells but atenolol reportedly does not exhibit this effect.[110]

Among users of antihypertensive drugs, the rate of serious Hypoglycemia events per 100 person-years ß-blockers offers several advantages in the treatment of hypertension or heart disease among persons with diabetes. As reviewed by Tse and Kendall,7 the cardioprotective effects of ß-blockers following myocardial infarction in persons with diabetes equal to or exceed those in nondiabetic subjects.[111] B2-adrenergic receptors seem to have an important role in stimulating hepatic glucose production in humans.[2] Whereas nonselective β-adrenergic agonists have been shown to cause Hypoglycemia[3], β1-adrenergic selective antagonists have not been shown to influence glucose

metabolism [the lack of reported cases of Hypoglycemia associated with the administration of β1-selective-adrenergic antagonists suggests that Hypoglycemia-related solely to drug effect is rare.[112] Insulin resistance is a recognized feature of beta-blocker drug therapy and results in an exaggerated release in insulin in response to a given glucose load, not all patients taking beta blockers are prone to Hypoglycemia and further studies are required to determine at which site propranolol acts in patients with liver disease.[113]

QUINIDINE

Quinidine is a well-established anti-arrhythmic drug used to treat both ventricular and supraventricular arrhythmias, and also has powerful antimalarial activity [fletcher, 1925; sanders &dawson, 1932]. However, because of its potentially greater cardiotoxic effects, the use of quinidine in the treatment of plasmodium falciparum infections has hitherto been limited to situations where quinine is unavailable both quinine and quinidine are known to stimulate insulin secretion at therapeutic blood concentrations[Phillips et al., 1986; white et al., 1983] leading to Hypoglycemia, in stress and disease situations, there could be substantial changes in these parameters [such an adrenaline-mediated decrease in tissue sensitivity to insulin] which, in turn, might change the insulin response to the cinchona alkaloids and hence the risk of Hypoglycemia. Insulin secretion stimulated by quinine is determined by the plasma concentration of the drug and the ambient plasma glucose concentration. Quinidine is a much less potent stimulus to insulin release at the same tissue concentration, but glucose also amplifies the beta cell response to this drug.[114]

For more than 300 years, cinchona bark and the alkaloids that can be derived from it have been employed. Parenteral quinidine, lately rediscovered in industrialized nations for both its antiarrhythmic and antimalarial effect, is often given to severely ill patients in whom Hypoglycemia might be obscured by an underlying disease. Quinidine is more likely to cause Hypoglycemia in children,2' pregnant women,24, and those with renal failure. Quinidine may cause or aggravate Hypoglycemia.[115]

DISOPYRAMIDE

Disopyramide is a group I antiarrhythmic drug with electrophysiologic properties quite similar to those of quinidine first case of Hypoglycemia secondary to disopyramide administration was published in 1980 the mechanisms of disopyramide-induced Hypoglycemia remain unclear [Strathman et al., 1983]. Several hypotheses have been proposed based on inadequate production and/or excessive utilization of glucose.[116]

Disopyramide, a class I antiarrhythmic drug, has been widely used not only for the treatment of arrhythmias but also for the prevention of neutrally mediated syncope. It has been reported to cause sporadic fasting Hypoglycemia the therapeutic concentration of disopyramide inhibits ATP-sensitive potassium channels in cardiac cells and pancreatic β-cells and therefore causes over secretion of insulin.[117]

Disopyramide has both antiarrhythmic and hypoglycemic properties. It is presently among the most prevalent. causes of no antidiabetic drug-induced Hypoglycemia.[118]

Hypoglycemia is recognized, though recently infrequently reported side-effect [reviewed by cacoub et al., particularly as other anti-arrhythmic agents are now more frequently used. The risk of Hypoglycemia is greater if there is pre-existing chronic renal failure, advanced age, malnutrition, or when disopyramide is used in combination with certain antibiotics. There is only one other report in the documentation of a type 2 diabetic patient whose insulin needs fell from 41 to 21 u per day following commencement of disopyramide [3insulin requirements returned to the original dose when disopyramide was withdrawn. This is surprising, as the principal mechanism of Hypoglycemia is thought to be the stimulation of insulin secretion.[119]

During episodes of Hypoglycemia, secretion of the four counterregulatory hormones, glucagon, epinephrine, cortisol, and growth hormone, occurs. in addition, norepinephrine is released directly from sympathetic neurons. Hypoglycemia following disopyramide administration is uncommon although Hypoglycemia is an infrequent occurrence in patients treated with disopyramide, this adverse effect is clinically important and potentially life-threatening.[120]

Table 3: Mechanism Of Drugs Causing Hypoglycemia

S.NO	DRUGS	MECHANISM
1	ACE INHIBITORS	Increase peripheral insulin sensitivity
2.	NON-SELECTIVE β-BLOCKERS	Mask signs and symptoms of Hypoglycemia and increase peripheral glucose uptake
3.	QUINIDINE	Increase pancreatic insulin secretion
4.	DISOPYRAMIDE	Increase insulin secretion

MANAGEMENT

By discussing hypoglycemia's warning signs and symptoms with patients and nursing personnel, severe hypoglycemic episodes may be avoided. When a patient has a hypoglycemic episode, the level of awareness, respiratory and circulatory state, and capillary blood sugar levels must all be assessed at the bedside. blood glucose test results, the existence of iv access, time and amount of insulin doses, and NPO status or last food and amount of intake, before discharge, patients should receive education in the form of verbal instructions, written materials, and referral for the outpatient follow-up to avoid further events.[121]

Management may be difficult as there are no established treatment guidelines, multiple treatment methods may be needed [iv bolus dextrose, glucagon, dextrose containing IVF, food/juice], and frequent reassessments are required.[122]

Patients should always have a rapidly available source of glucose with them to treat Hypoglycemia at the first sign of low glucose. Hypoglycemia [plasma glucose < 70 mg/dl], including asymptomatic Hypoglycemia and most episodes of mild to moderate symptomatic Hypoglycemia, is effectively self-treated by ingestion of some form of glucose. While pure glucose is desired, any kind of carbohydrate that contains glucose will raise plasma glucose. The "rule of 15" is an effective remedy. regimen when patients are able to self-treat. Typically, 15 g of carbohydrates [rapidly absorbing forms of glucose such as glucose gel, sugar-containing soda, or glucose tablets] should raise blood glucose by 50 mg/dl in 15 minutes.[123]

The “rule of 15” or the “15-15 rule” is commonly followed in the treatment of Hypoglycemia. It is a general starting point that includes the intake of 15 g of carbohydrates followed by a retest of blood glucose in 15 minutes. Within 15 minutes, 15 g of carbohydrates will raise the plasma glucose to about 75 mg/dl [Unger, 2013].[124] For people unable to consume oral glucose because of unconsciousness, seizures, or altered mental status, emergency personnel can administer a peripheral or central iv solution containing dextrose. Dextrose in water at a 50% concentration is the dose usually administered to adults, while a 25% concentration is usually administered to children dextrose at 50% and Due to their hyperosmolarity characteristics, which can result in tissue necrosis, 25% are severely necrotic. if the iv line becomes infiltrated;65 therefore, they must only be administered via a patent iv line.[125]

Somatostatin is generally ineffective in the treatment of Hypoglycemia. Glucagon is a major hormone released in response to Hypoglycemia, it stimulates hepatic glucose production by the breakdown of glycogen and by induction of gluconeogenesis.[126]

The first-line treatment for severe hypoglycemia in diabetic patients is glucagon, which is the main counter-regulatory hormone to insulin. Glucagon should only be administered if the patient is unconscious or unresponsive and unable to consume oral glucose. Glucagon should be taken either IM or SC at a dose of 1 mg, reconstituted in 1 ml of sterile water, to adults and children who weigh more than 55 lb (or older than 6 to 8 years of age if their weight is unknown). Only half the amount [0.5 ml] should be given to kids who weigh less than 55 lb, or who are less than 6 to 8 years old if their weight is unknown. Following reconstitution, glucagon should be delivered, and any leftover medication should be discarded.[127]

PREVENTION

The physiological mechanisms that prevent Hypoglycemia during prolonged fasting are not known these mechanisms have been clarified under other conditions, these data define the physiological systems that guard against hypoglycemia in people who fast for three days. They indicate that Reduced insulin secretion alone may not prevent hypoglycemia during fasting, therefore glucagon plays a primary counterregulatory role, and catecholamines are not normally critical but compensate and become critical when glucagon is deficient in humans. Progressive Hypoglycemia develops during fasting when both glucagon and epinephrine are deficient and insulin is present.[128]

In terms of drug-induced Hypoglycemia, Seltzer found that only 1418 cases were reported in the literature between 1940 and 1989, which is likely an underestimate of the 164 drugs associated with Hypoglycemia.[129]

Plasma glucose concentrations fell progressively to hypoglycemic levels during exercise when decrements in insulin and increments in glucagon were prevented and catecholamine actions were antagonized simultaneously. This was the result of both the absence of an increase in glucose production and an exaggerated initial increase in Glucose production and an exaggerated initial increase in glucose utilization during exercise.[130]

It is preferable to prevent rather than treat drug-induced Hypoglycemia. One of the most important ways to prevent Hypoglycemia is to educate the patient. Thomson et al. showed that 88% of patients taking oral antidiabetic drugs and 32% of insulin-treated patients denied any knowledge of Hypoglycemia. Teaching patients how to recognize, treat and prevent Hypoglycemia is essential. Furthermore, patients should be educated about Hypoglycemia risk factors, The removal or adjustment of the doses of the offending drug is mandatory.[131]

Health care providers should be vigilant to such potential errors, especially in cases of unexplained Hypoglycemia Cases of Hypoglycemia without an obvious cause should alert healthcare providers to the possibility of inadvertent

OHA use. Missing this etiology could lead to unnecessary investigation and prolonged hospitalization as well as considerable morbidity and even mortality. There can be a considerable financial impact from Hypoglycemia caused by medication dispensing errors. Hypoglycemia due to the inadvertent use of OHAs is recognized to be a dangerous but preventable condition.[132]

CONCLUSION

Prolonged Hypoglycemia can potentially cause acute brain damage and drugs induced Hypoglycemia can be prevented or minimized with an evaluation of the offending medication for adjustment in dosage and length of therapy and awareness of the problem and judicious use of the suspected drugs.

Patients should be further advised to inform each of their healthcare professionals about all medication use, including non-prescription medications and dietary supplements, management may be difficult as there are no established treatment guidelines, multiple treatment methods may be needed and frequency reassessments are required.

As well, the rule of 15 or the 15-15 rule is commonly followed in the treatment of hypoglycemia. it is preferable to prevent rather than treat drug-induced hypoglycemia, one of the most important ways to prevent hypoglycemia is to educate the patients.

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