Hypoglycemia induced by beta blockers

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Abstract - Hypoglycemia is often defined by a plasma glucose concentration below 70 mg/dL; however, signs and symptoms may not occur until plasma glucose concentrations drop below 55 mg/dL. Patients with type 1 diabetes in this group are at three times greater risk of developing hypoglycemia during treatment compared to patients with type 2 diabetes. Beta blockers are a class of drug that are mainly given to treat cardiovascular conditions . In the study we summarized the pharmacological actions of beta blockers that leads to the masking of hypoglycemic conditions, as well as their related complications, and alternative treatment options available of beta blockers ,with epidemiological evidences.

IndexTerms – International diabetes federation (IDF), Type 2 Diabetes Mellitus (T2DM), Adverse Events (AEs), Cardiovascular System (CVS), Calcium Channel Blockers (CCB), Angiotensin-2 Receptor Blocker (ARB), Renin-angiotensin system (RAS), Angiotensin Converting Enzyme (ACE), Congestive Heart Failure (CHF).

I. INTRODUCTION

Hypoglycemia is often defined by a plasma glucose concentration below 70 mg/dL; however, signs and symptoms may not occur until plasma glucose concentrations drop below 55 mg/dL. Patients with diabetes who are taking medication for their condition are most likely to experience hypoglycemia. Patients with type 1 diabetes in this group are at three times greater risk of developing hypoglycemia during treatment compared to patients with type 2 diabetes[1]. International Diabetes Federation describes "Hypoglycemia is a common and serious complication of diabetes, particularly affecting people with diabetes on insulin treatment. It is characterized by abnormally low blood sugar levels, which can lead to cognitive impairment and in some severe cases, seizures, loss of consciousness, coma, and even death"[2]. Low blood glucose levels can vary from person to person. The preceding are symptoms and signs of low blood sugar, ranging from milder, more prevalent indicators to the most severe: experiencing trepidation or anxiety, Profusely sweating, chilly, and clammy Petulance or irritability, confusion, Hunger, Nausea, skin color fading out (pallor), Sleepy, distorted or damaged eyesight[3]. However, potential consequences of hypoglycemia include higher levels of circulating inflammatory markers, vascular adhesion molecules, and indicators of thrombosis and platelet activation all increase the risk of cardiovascular disease. Alterations in cardiac electrical function are also linked to insulin-induced hypoglycemia, which may play a role in the occurrence of severe arrhythmias[4]. Hypoglycemia in diabetes is associated with increased morbidity and constitutes a barrier to glycemic control. Therefore great effort must be invested in patient education on hypoglycemia prevention and management. In non-critically ill hospitalized patients, the prevalence of hypoglycemia is thought to be 4.2% of all blood glucose measures or 3.5% of patient days. Even more frequently occurs hypoglycemia in hospitalized patients receiving insulin. Among hospitalized diabetic patients, insulin doses, inappropriate scheduling of insulin doses, low body mass index, impaired renal function, dietary changes, or concomitant drugs like steroids, and beta blockers are all contributory factors to hypoglycemia episode. India, which ranks second in terms of diabetic population in the world, with more than 72 million people living with T2DM in 2017, the problem of hypoglycemia, appears to be a neglected entity[5]. Beta blockers are the class of drugs that are primarily indicated in the management of cardiovascular disorders. For the treatment of tachycardia, hypertension, myocardial infarction, congestive heart failure, cardiac arrhythmias, hyperthyroidism, essential tremor, aortic dissection, portal hypertension, glaucoma, migraine prophylaxis, and other disorders, beta-blockers are indicated and have FDA approval. Furthermore, they are employed in the management of uncommon diseases such as long QT syndrome and hypertrophic obstructive cardiomyopathy. Some individuals may experience hypoglycemia as a result of taking beta blockers because either they worsen an existing episode or they prolong the duration it takes for them to recover. Fairly known pharmacological action of beta blockers that can induce hypoglycaemia is Beta 1 receptor is G-protein coupled receptor which convey through Gs alpha subunit, by signaling these subunits, a cyclic AMP-dependent pathway is proposed through adenylyl cyclase, that potentiates the receptor's function. Selective stimulation of beta-1 receptors in the heart ,leads to increased atrioventricular, sinoatrial nodal and ventricular muscular contraction, which increases heart rate (tachycardia) and contractility, The stroke volume and cardiac output will also increase when heart rate and contractility increases. Beta 1 receptors also induces renin secretion which causes increase in blood pressure[6].

Beta 2 adrenergic receptors are present in various tissues, such as smooth muscle, skeletal muscle and myocardium, these receptors are stimulated through catecholamines, norepinephrine and epinephrine. In the cardiovascular system (CVS), the beta receptors stimulation causes increased cardiac muscle contraction, cardiac output and heart rate.

Nonselective beta-blockers should potentially increase the incidence of hypoglycaemic episodes since they are more likely to impair liver glycogenolysis and gluconeogenesis through the beta 2-receptor[7].

The corporeal changes also occur during hypoglycemia as a result of the autonomic nervous system's stimulation give rise to neurogenic symptoms, these symptoms include sweating, hunger, tingling (expressed through cholinergic system) and tremulousness, increased

heart rate, and nervousness (expressed through adrenergic system). Hypoglycemic symptoms such as a tachycardia and tremor can be masked by Beta-blockers ,because they inhibit the effects of norepinephrine, resulting in decreased heart rate and reduced tremor. Hunger, irritability, and confusion may be concealed as well along with masking of these hypoglycemic symptoms, beta-blockers also modify glycogenolysis and gluconeogenesis leading to slow recovery of blood glucose levels[8].

II. Associated complications of hypoglycemia with beta blockers

Masking of hypoglycemic symptoms for prolong time associated with use of beta blockers can lead to severe hypoglycemia and can cause hypoglycemic induced conditions. As cases of beta-blocker-induced hypoglycemia have been reported in healthy individuals during exercise and postoperatively, both of which are conditions that are associated with increased secretion of counter-regulatory hormones, this issue is also relevant because the risk of hypoglycemia is not only restricted to patients of extreme ages. Additionally, there is decreased adrenaline counter-regulation, which reduces sympathetically driven glycogenolysis and gluconeogenesis and inhibits the removal of glucose by insulin-dependent tissues. Additionally, because beta-blockers may have stimulatory effects on pancreatic beta cells, babies born to mothers who take them are more likely to experience hypoglycaemic episodes. Cases of neonatal hyperinsulinemic hypoglycemia in children born to mothers who take these medications have been documented. Thus, Beta receptors are also responsible for lactate formation in skeletal muscle and, therefore muscle glycogenolysis. Beta receptors activation also induces lipolysis in adipose tissue, which indirectly increases blood-glucose level by providing glycerol as a substrate for gluconeogenesis[9]. Numerous investigations shown that nonselective beta-blockers are more frequently than selective ones linked to the risk of hypoglycemia. Beta-blockers may be able to conceal hypoglycemic symptoms. Tremor and palpitations are among the catecholamine-mediated neurogenic hypoglycemic symptoms which is masked by this class of drugs. Additionally, hunger, trembling, agitation, and bewilderment could be masked as well. But in people using beta-blockers, sweating is still visible and could be the only telltale sign of hypoglycaemia[10].By sympathetic and parasympathetic nerve cell bodies located in the medulla of the central nervous system, the autonomic nervous system is subconsciously controlled. The sympathetic nervous system's following mechanisms release catecholamines, specifically norepinephrine and epinephrine. Both mechanisms involve sympathetic nerve cell bodies, which are found in the intermediolateral cell column (IMLCC) of the spinal cord (T1–L3). These cell bodies have preganglionic nerve axons that release acetylcholine in the sympathetic ganglion, which then activates nicotinic (or "ionotropic") receptors to start an action potential on the postganglionic sympathetic nerve axon, or directly act on the adrenal gland to secrete epinephrine (80%) and norepinephrine (20%) into the circulation. In almost all circumstances, the postganglionic sympathetic nerve fibre will release norepinephrine at various target organs, such as smooth and cardiac muscle, in order to activate various adrenergic receptors (such as alpha-1, alpha-2, beta-1, and beta-2) required for the acute stress response. This release of norepinephrine occurs outside of the adrenal glands. While most organs innervated by the sympathetic nervous system confirm to this, but sweat glands do not.Instead of norepinephrine, sympathetic postganglionic nerve axons emit acetylcholine. The sweat gland's nicotinic receptors (ionotropic receptors), which are necessary to regulate body temperature because it is likely to rise during a fight-or-flight reaction, are activated by the released acetylcholine. Because of this, beta-blockers can still prevent tachycardia and tremors but are unable to prevent sweating, thus it masks crucial symptoms that diabetes patients use to identify hypoglycemic episodes[11]. B-blockers can worsen an existing hypoglycemic episode or prolong the recovery process in some people, which might lead to or exacerbate hypoglycemia. Prescribers should work to prevent these adverse events (AEs) through appropriate counselling because the severity of the increased hypoglycaemic risk is greater in extreme ages and because the prevalence of patients with diabetes as a comorbid condition is rising, which has led to global increasing trends in hypoglycaemia and hypoglycaemia-related mortality[12]. Different beta-blockers may block sodium or potassium channels, which will lengthen the QRS and QTc intervals, respectively. Beta-blockers that block sodium channels are believed to have "membrane stabilising activity" that increases toxicity when taken in excess[13]. Today, the pathophysiology of the negative effects of severe hypoglycemia in people with diabetes mellitus is well understood. Catecholamine levels rise while using the hyperinsulinemic-hypoglycemic clamp technique. The ECG consequently displays variations in ventricular depolarization as well as silent ST-segment depression, T wave anomalies, and so on. Two common patterns of hypoglycemia are the lengthening of the QT interval and the arrhythmogenic impact[14]. In numerous investigations, it has been discovered that diabetic individuals who have severe hypoglycemia have significantly raised systolic and diastolic blood pressure. This can result in hypertensive emergencies such stroke, acute coronary syndrome, and aortic dissection. In addition, severe hypoglycemia frequently results in hypokalemia, which can cause deadly arrhythmias. Severe hypoglycemia has also been associated with hypokalemia, probably as a result of the fact that potassium is driven into the cell during hypoglycemia not only by catecholamine production but also by hyperinsulinemia. By using beta-blockers beforehand to prevent hypokalemia during extreme hypoglycemia, the risk of deadly arrhythmias may be reduced[15].Consuming drugs or alcohol can result in hypoglycemia, especially when combined with beta-blockers and glucose-lowering medications since it slows down the process of glucose counterregulation. These causes of hypoglycemia might be more significant for some patient populations because they have a higher risk of developing hypoglycemia. Old age is one of these risk factors for hypoglycemia. Increased susceptibility to medicines and weakened counterregulation may contribute to an increased risk of hypoglycemia in aged patients[16].

III. Treatment Alternatives of Beta Blockers

Beta-blockers inhibit the effects of nor-epinephrine, which causes a slowing of your heart rate and a reduction in tremor, so they can conceal hypoglycemia symptoms such a rapid heartbeat and tremors.

Selective Beta Blockers Vs Non-Selective Beta Blockers

The use of beta-blockers may help diabetic patients avoid harmful effects including severe hypokalemia, hypertension and during severe hypoglycemia[17].

When hospitalised patients who don't need basal insulin take beta blockers, their chances of developing hypoglycemia increase; these chances are higher with selective beta blockers than with non-selective beta blockers. Selective beta blocker users or non-users have an increased risk of hypoglycemia-related mortality, but non-selective beta blocker users do not.

Non-selective beta blockers can be preferred over selective beta blockers[18].

Hypertension

Millions of people with high blood pressure die as a result of strokes, heart attacks, and other diseases. This situation could have been avoided with proper treatment. Researchers have experimented with various medications to treat high blood pressure. Beta-blockers are not as effective as other classes of medications in preventing deaths, strokes, and heart attacks, such as diuretics, calcium channel blockers, and renin-angiotensin system inhibitors[19]. The most commonly prescribed diuretics for hypertension are thiazide diuretics. Drugs include chlorothiazide, chlorthalidone, hydrochlorothiazide etc[20]. CCBs, in particular, have been one of the most widely used classes of antihypertensive agents in the last 20 years, owing to their effectiveness in lowering blood pressure levels, good tolerability, and abundant evidence on lowering the cardiovascular and renal consequences of hypertension. Drugs include amlodipine, diltiazem, nifedipine, verapamil etc[21]. In the treatment of hypertension, renin-angiotensin system (RAS) inhibitors, particularly angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs), are commonly used[22].

Tachycardia

Tachycardia is characterised by an abnormally fast heartbeat, with the heart beating more than 100 times per minute at rest. Tachycardia is classified into three types: sinus, supra-ventricular, and ventricular. All three types of this heart rhythm problem are caused by deviations from the normal sequence of the heart's electrical impulses[23].

In most supra-ventricular and ventricular tachycardias, amiodarone and sotalol are effective. Amiodarone exhibits electro-physiologic properties that are consistent with each type of anti-arrhythmic drug. It is a sodium channel blocker with relatively fast on-off kinetics, a non-selective beta-blocker, a potassium channel blocker, and a mild calcium antagonist.

In sinus tachycardias, beta-blockers are rarely effective and have numerous side effects. Ivabradine is a promising new drug that works by inhibiting the "funny" (If) current, resulting in a decrease in heart rate and an improvement in symptoms and quality of life.

Ivabradine belongs to the class of drugs known as hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers. It works by slowing the heart rate, allowing the heart to pump more blood throughout the body with each beat[24].

Congestive Heart Failure

According to current treatment guidelines, strategies include quitting smoking and controlling hypertension, diabetes, and dyslipidemia. In individuals with various vascular risk factors, angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor blockers [ARBs]) should be strongly considered for anti-hypertensive medication[25].

To promote effective diuresis, thiazides or the thiazide-like diuretic metolazone might be used with a loop diuretic. Thiazides may be recommended over loop diuretics in patients with just minor fluid retention and high blood pressure due to their longer lasting anti-hypertensive effects[26].

Nitrates and hydralazine were initially combined in the treatment of CHF. Nitrates are principally venodilators that reduce preload.

Hydralazine is a direct vasodilator that works primarily on arterial smooth muscle to reduce SVR and enhance stroke volume and cardiac output.

The combination of nitrates and hydralazine improves the composite endpoint of mortality, hospitalizations for HF, and quality of life[27].

Akathisia

Akathisia is defined as an inability to remain still. It is a neuropsychiatric syndrome that is associated with psychomotor restlessness. The individual with akathisia will generally experience an intense sensation of unease or an inner restlessness that usually involves the lower extremities[28].

A variety of drugs have been reported to be beneficial, although without much evidence. Anti-cholinergic medications (such as biperiden, trihexyphenidyl, and benztropine) and serotonin 5-HT2A antagonists (such as mianserin, mirtazapine, and cyproheptadine) are examples. Success has also been reported with vitamin B6, n-acetylcysteine, and tetrabenazine. Clonidine has been advised on occasion, and there has been one instance of tardive akathisia responding to clonidine. Dopamine agonists such as bromocriptine and amantadine have been attempted on rare occasions. Lastly, piracetam, buspirone, and opiates have been proposed to be useful in cases of more severe akathisia[29].

Atrial Fibrillation

Atrial fibrillation (AF) is a rhythm that originates in the atrium. Because of the high rates of morbidity, disability, and death associated with AF, it is the most prevalent persistent cardiac arrhythmia in clinical practice. The treatment of atrial fibrillation (AF) has become a hot topic in the field of cardiovascular medicine. More evidence and advances in medical technology have recently helped us obtain a better understanding of AF. As a result, AF management has advanced in recent years, allowing us to better avoid and control AF.

Calcium channel blockers, such as diltiazem and verapamil, are commonly used and advised for AF in combination with chronic obstructive pulmonary disease or asthma. Since digitalis can lower ventricular rate by raising vagus nerve tension, it is a viable option for individuals in whom other therapies are ineffective or contraindicated, particularly in heart failure and hypotension. Amiodarone can lower ventricular rate in the short term by inhibiting calcium channels and the sympathetic nervous system, however it is not used to regulate ventricular rate in the long run. Amiodarone can be used to regulate heart rate when other medications are ineffective or contraindicated, as well as to treat acute symptoms[30].

IV. CONCLUSIONS

We summarised the pharmacological actions of beta blockers that leads to the masking of hypoglycemic conditions, as well as their related complications, treatment options, and epidemiological evidences. We also highlighted a very important factor that aids in determining the symptoms of hypoglycemia when the beta blockers have masked the major symptoms, which is of tremors and palpitation., where as sweating is still present. Given that beta -blockers are frequently used to treat various cardiovascular conditions and their pharmacological mechanism of action is poorly known, it is of clinical relevance also to elucidate the plausible pharmacodynamic relationship between hypoglycaemia and β-blockers. The pharmacological action of beta blockers that lead to inhibition of hepatic glucose production causing the impairment of hepatic glycogenolysis and gluconeogenesis Non selective beta blockers may also prolong the pre existing hypoglycemic condition hence worsening it. The treatment alternatives for beta blockers

were discussed, for example use of non selective beta blockers rather than selective beta blockers as they lower the chances of developing hypoglycemia in hospitalized patients or the use of diuretics as an alternative treatment of congestive heart failure. Healthcare practitioners need to prevent these adverse events (AEs) through appropriate counselling because the severity of the increased hypoglycaemic risk is greater in extreme ages and because the prevalence of patients with diabetes as a comorbid condition is rising, which has led to global increasing trends in hypoglycaemia and hypoglycaemia-related mortality.

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