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IMPACT OF SGLT2 INHIBITORS ON MYOCARDIAL MITOCHONDRIAL FUNCTION IN DIABETIC CARDIOMYOPATHY

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ABSTRACT: Cardiovascular events and cardiac insufficiency are regarded as two of the most significant causes of death among the consequences of diabetes.Heart failure eventually results from diabetic cardiomyopathy (DCM), which is characterized by diastolic and systolic dysfunction independent of hypertension and coronary heart disease. This condition is closely associated with a high mortality rate in individuals with diabetes mellitus (DM). A new class of hypoglycemic medication called sodium–glucose cotransporter type 2 inhibitors (SGLT2Is) in the excretion of sodium and glucose in the urine. The effects of SGLT2Is on cardiac iron homeostasis, mitochondrial function, anti-inflammation, anti-fibrosis, antioxidative stress, renin-angiotensin-aldosterone system activity, in the heart have been demonstrated. Diabetic cardiomyopathy is associated with endoplasmic reticulum stress, autophagy, programmed cell death, and intestinal flora. When combined, these modifications maximize the synthesis of myocardial ATP and reduce cardiomyocyte death and cardiac fibrosis.

A new class of hypoglycemic medication called sodium-glucose cotransporter type 2 inhibitors (SGLT2Is) increases the excretion of sodium and glucose in the urine. Empagliflozin dramatically decreased the relative risk of cardiovascular (CV) death and hospitalization for heart failure (HHF) in patients with type 2 diabetes (T2DM) and CV illness (CVD), according to the exciting results of the EMPA-REG clinical study. It is not possible to fully ascribe these positive effects of SGLT2Is to their natriuretic or glucose-lowering properties. SGLT2Is may have direct effects on cardio protection.

Index Terms: SGLT2 inhibitors, diabetic cardiomyopathy,dipeptidyl peptidase 4,reactive oxygen species,sodium hydrogen exchanger,cardiac failure.

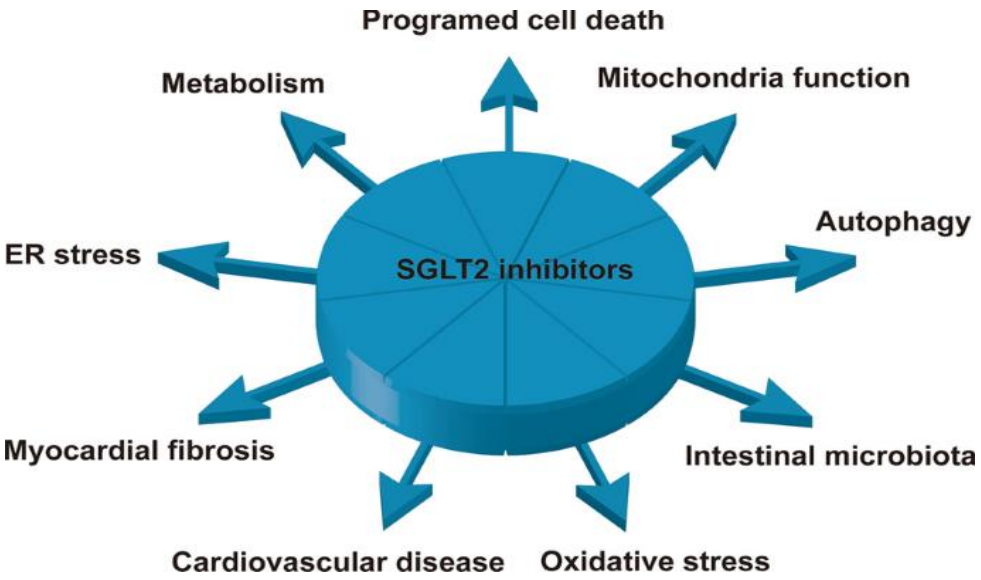

figure:1 SGLT2 inhibitors

INTRODUCTION:

Diabetes may have been identified about 3000 years ago,and as living and health conditions have improved, the disease's incidence and prevalence have risen. Diabetes affects 1 in 11 people now, which is four times more common than it was thirty years ago. Chronic hyperglycemia can harm the heart, resulting in diabetic cardiomyopathy, as well as eye, kidney, and foot disorders.

Myocardial structural and functional abnormalities in the absence of coronary artery disease, hypertension, or other cardiac valvular disease in diabetes mellitus are known as diabetic cardiomyopathy (DCM). Long used as medications to treat diabetes, sodium-glucose cotransporter 2 inhibitors (SGLT2is) have lately been demonstrated to enhance heart function in diabetics.

SGLT2Is have an unexpectedly substantial cardioprotective impact in patients with type 2 diabetes (T2DM), who are at high risk of cardiovascular diseases (CVDs), according to recent CV-outcomes trials. Empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS Program), and dapagliflozin (DECLARE-TIMI 58) trials all demonstrated a decrease in CV mortality and hospitalization for HF (HHF) in T2DM patients within months of starting SGLT2Is.

DCM has a complicated pathophysiology, and possible mechanisms are still being studied. Key elements in the pathogenesis of DCM include insulin resistance, hyperglycemia, and hyperlipidemia. In patients with diabetes mellitus, lipid-metabolism issues frequently result in cardiac dysfunction and cause significant injury to the heart. The first anti-diabetic drugs that successfully lower the risk of cardiovascular death and heart failure in people with type 2 diabetes are sodium-glucose cotransporter-2 inhibitors (SGLT2i).

DCM is a particular CM that significantly lowers the quality of life for DM patients and is a significant complication that results in high rates of death and disability. However, a number of researchers have demonstrated that SGLT2 inhibitors directly exhibit heart-protective benefits.In both situations, it is thought that SGLT2 inhibitors protect cardiomyocytes by restoring their mito class of recently developed antidiabetes drugs known as sodium-glucose cotransporter 2 inhibitors (SGLT2is) offers strong glucose-lowering effects,mitochondrial activity.

Long used as medications to treat diabetes, sodium-glucose cotransporter 2 inhibitors (SGLT2is) have lately been demonstrated to enhance heart function in diabetics. Dapagliflozin decreased heart failure in T2DM (type 2 diabetes mellitus) patients with cardiovascular disease by 27% in a randomized controlled trial. For empagliflozin and canagliflozin, the efficacy was 35% and 33%, respectively . The advantages of SGLT2i for diabetic cardiomyopathy, including the mechanism, are the main topic of this review .

Prospects for the future are also covered. Given the sharp drop in HHF risk, it is possible that the advantages of SGLT2Is stem from reduced DCM rather than metabolic improvement. This review summarizes the direct and probable molecular mechanisms of SGLT2Is for the treatment and prevention of DCM, as well as improvements in heart structure and function.

CLASSIFICATION OF NOVEL ANTIDIABETIC AGENTS:

SGLT2 Inhibitors:-

Examples:-

- Empagliflozin
- Dapagliflozin
- Canagliflozin

MOA:

- Inhibit the SGLT2 transporter, which typically reabsorbs salt and around 90% of filtered glucose from the renal tubule.
- This lowers the reabsorption of salt and glucose.

Consequently:

- Glycosuria, or the excretion of glucose in the urine, reduces blood glucose.

Osmotic diuresis and sodium excretion (natriuresis) reduce plasma volume and blood pressure

Side Effets:

- ✓ Gential fungal infection
- ✓ Urinary tract infection
- ✓ Frequent urination
- ✓ Diabetic ketoacidosis
- ✓ Severe dehydration and lower blood sugar level(hypoglycemia)

GLP-1 Receptor Agonists:

Examples:

- Liraglutide
- Semaglutide
- Dulaglutide

MOA:

- Pancreatic β-cells secrete insulin in response to glucose. Pancreatic α-cells secrete glucagon in response to excessive glucose.
- Reduce the rate of glucose absorption by delaying stomach emptying.
- Reduce food intake and lose weight by stimulating the hypothalamus to increase satiety.

Side Effects:

- ✓ Nausea
- ✓ vomiting
- ✓ diarrhea
- ✓ constipation
- ✓ stomach emptying(Gastroparesis)

✓ inflammation of the pancreas(pancreatitis)

DPP-4 INHIBITORS:

Example:

- Sitagliptin
- Vildagliptin
- Linagliptin

MOA:

- Inhibitors of DPP-4 (dipeptidyl peptidase-4) prevent the enzyme from breaking down the incretin hormones GLP-1 and GIP.

By blocking DPP-4, they

- Boost GIP and GLP-1 levels in the body
- Boost the amount of glucose-dependent insulin secreted by pancreatic β-cells
- Reduce the amount of glucagon secreted by pancreatic α-cells
- Decrease the synthesis of glucose in the liver
- Reduce blood sugar, particularly after meals (postprandial).

Side Effects:

- Upper respiratory tract infections
- Urinary tract infections
- Severe Joint pains(Arthralgia)
- Headache
- Allergic Reactions

Dual GLP-1 Receptor Agonist:

- Tirzepatide

MOA:

Both are activated by dual GLP-1/GIP receptor agonists:

- Glucagon like peptide(GLP-1) Receptors
- Glucose-dependent insulinotropic polypeptide (GIP) receptors

This leads to:

- Insulin secretion from pancreatic β-cells that is reliant on glucose. Secretion of glucagon, particularly through GLP-1 action when glucose levels are high
- Reduced food intake due to delayed stomach emptying, slower glucose absorption, satiety, and appetite caused by central nervous system impacts
- Increased metabolic effects and improved insulin sensitivity (partially due to GIP receptor activation).

Side Effects:

- Nausea
- Vomiting
- Diarrhea

- Pancreatitis
- Abdominal pain

SGLT2 INHIBITORS IMPROVED HEART FUNCTION:

It is unclear exactly how SGLT2 works in the heart. Cardiomyocytes expressSGLT1, which SGLT2i may target to alleviate heart failure [13]. It has been demonstrated that blocking SGLT1 with canagliflozin lowers the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in cardiomyocytes, which prevents the generation of superoxide and reduces inflammation [13]. In addition to being regulated by their target receptors, SGLT2i may be helpful as a first-line therapy for heart failure.Dapagliflozin's direct activation of AMP-activated protein kinase (AMPK) may lessen cardiac fibrosis brought on by lipopolysaccharide .

SGLT2 INHIBITORS AND MYOCARDIAL MITOCHONDRIA:

Heart contraction is powered by aerobic respiration, which takes place in the mitochondria of cardiomyocytes. In diabetic cardiomyopathy, excessive blood sugar, insulin resistance, and obesity lead to mitochondrial malfunction.It is common for mitochondria to split and merge.Mitochondria create a vast, linked network when cells are under mild stress.Mitochondria fission and fragmentation occur when cells are under extreme stress.Cardiomyocyte mitochondria undergo dynamin-related protein 1 (Drp1)-mediated fission in response to hyperglycemia; if this process is overdone, it can lead to fragmentation, the generation of ROS, increased oxidative stress, and even cell death.

DIABETIC CARDIOMYOPATHY:

Diabetic cardiomyopathy mechanisms. Cardiomyocytes experience endoplasmic reticulum (ER) stress, oxidative stress, inflammation, and mitochondrial dysfunction as a result of metabolic alterations brought on by hyperglycemia and hyperlipidemia. The renin-angiotensin-aldosterone system (RAAS), cardiac sympathetic nerve activity, and calcium-handling dysfunction can all be triggered by oxidative damage, ER stress, and inflammation. Diastolic and systolic dysfunction are caused by these alterations, which also mediate cardiac hypertrophy and microvascular dysfunction

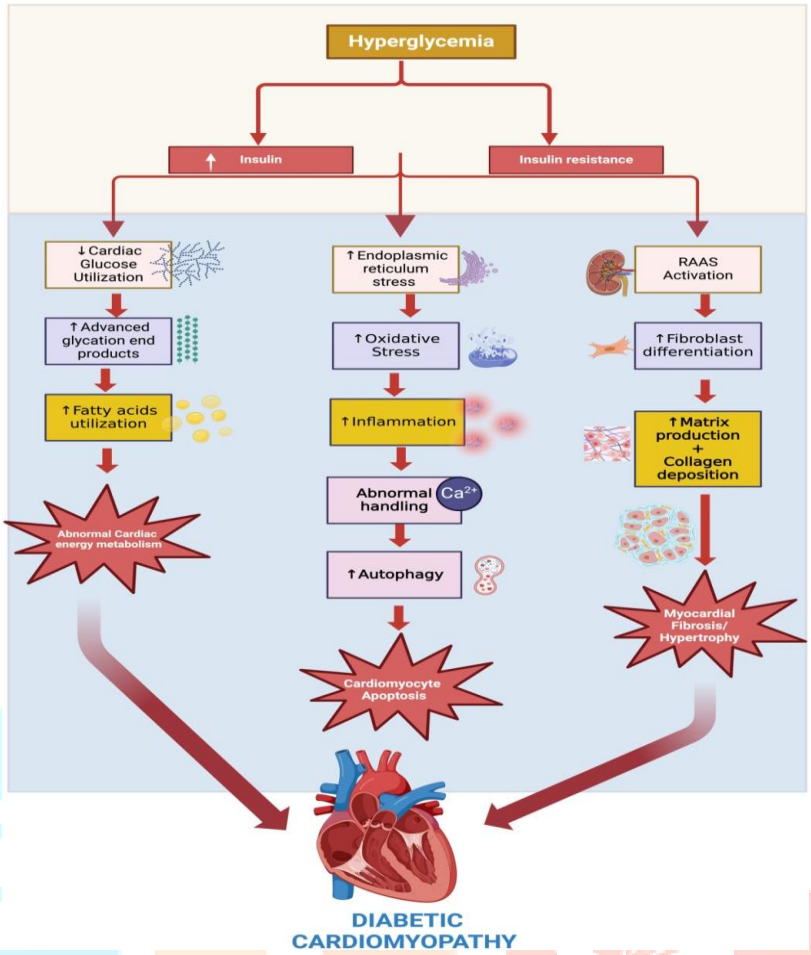

figure 2: diabetic cardiomyopathy

MECHANISM OF ACTION OF SGLT2 INHIBITORS ON DCM:

By combining systemic and direct effects on the heart, SGLT2 inhibitors prevent diabetic cardiomyopathy.They directly prevent detrimental intracellular processes including fibrosis, oxidative stress, and mitochondrial dysfunction while also lowering cardiac strain through diuresis and encouraging a very effective energy shift towards ketone metabolism in the heart.

Hemodynamic and metabolic shifts:

Hemodynamic and metabolic shifts are part of the mechanism of action. Sglt2 inhibitors diminish preload and afterload by acting as moderate diuretics.Systemically, they change the heart's preference for more efficient glucose and ketone bodies over oxygen-demanding free fatty acids.

cellular ion regulation:

These medications improve diastolic function and prevent arrhythmias by reducing intracellular Na+ and Ca+2 excess in the heart by blocking the sodium-hydrogen exchanger (NHE).

Reduction of fibrosis and hypertrophy:

They reduce myocardial stiffness and collagen deposition by blocking signaling pathways including TGF beta-Smad, which inhibits pathological cardiac remodeling.

BENEFITS OF DIABETIC CARDIOMMYOPTHY:

SGLT2 (sodium-glucose cotransporter-2) inhibitors have emerged as a significant therapy option for diabetic cardiomyopathy, especially in those with heart failure and type 2 diabetes. Beyond just decreasing blood sugar, they also benefit the kidneys and cardiovascular system.

Inhibitors of SGLT2 can:

- Alleviate symptoms including exhaustion and dyspnea.
- Heart failure that progresses slowly and has a maintained or decreased ejection fraction.
- Decrease cardiovascular mortality in certain patients.
- Reduce the rate at which diabetic kidney disease advances.
- Reduce blood pressure, body weight, and blood glucose levels somewhat.

ADEVERSE EFECTS:

- ✓ fungal infections of the genitalia.
- ✓ more frequent urination.
- ✓ little dizziness or loss of volume.
- ✓ Uncommon yet significant:
- ✓ Euglycemic diabetic ketoacidosis (particularly during surgery, acute sickness, or extended fasting).
- ✓ Genital infections are more prevalent than urinary tract infections.
- ✓ hypotension among those who are vulnerable.
- ✓ Fournier gangrene is rare.

CONCLUSION:

We primarily concentrated on fundamental research to clarify the pharmacological mechanism of SGLT2i and associated signaling pathways or targets for the management of diabetic cardiomyopathy in this review. Research has demonstrated that SGLT2i can alleviate diabetic cardiomyopathy through enhancing myocardial metabolism, repairing mitochondrial function, improving microcirculatory conditions, decreasing myocardial fibrosis, lowering oxidative stress, preventing programmed death, controlling autophagy, preventing ER stress, and controlling intestinal flora.There is currently no practical way to stop DCM from developing. The development of DCM and consequent HF cannot be stopped by merely reducing blood sugar. SGLT2Is provide surprisingly potent cardioprotective effects in T2DM patients, independent of glucose reduction, according to CV-outcome trials. The direct potential mechanism of SGLT2Is on the heart itself in a hyperglycemic condition is the subject of an increasing number of investigations. This review evaluated relevant research on SGLT2Is in the prevention and treatment of DCM. The cardioprotective effects of SGLT2Is include reduced sympathetic nerve activity, O-GlcNAcylation, RAAS inhibition, enhanced ketone-body metabolism and advantageous metabolic effects, improved mitochondrial function, microcirculation, anti-inflammation, antifibrosis, and antioxidative stress

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