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The Targeted Role of SGLT2 Inhibitors in Patients with Diabetic Cardiomyopathy

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Abstract: *Diabetic cardiomyopathy (DCM) is myocardial contractile dysfunction due to the clustered effects of left ventricular hypertrophy, fetal gene reactivation and lipid accumulation in cardiomyocytes. Structural and functional abnormalities of the myocardium, beyond the elicitation of ischemia or hypertension, have been emphasised and called diabetic cardiomyopathy*

Keywords: Diabetic cardiomyopathy

I. INTRODUCTION

Diabetic cardiomyopathy (DCM) is myocardial contractile dysfunction due to the clustered effects of left ventricular hypertrophy, fetal gene reactivation and lipid accumulation in cardiomyocytes. Structural and functional abnormalities of the myocardium, beyond the elicitation of ischemia or hypertension, have been emphasised and called diabetic cardiomyopathy [1,2].

In 1881, Leyden first reported that DCM is a typical complication of diabetes mellitus. Finally, the term "diabetic cardiomyopathy" was proposed by Rubler in 1972 after postmortem studies in diabetic patients with heart failure in whom coronary disease and other structural heart diseases, hypertension, and alcohol had been ruled out as possible causes [3]. A milestone study in 2002 by Finck and colleagues [4] cast light on the transcriptional mechanisms of DCM. These researchers suggested that the transcription factor, peroxisome proliferator-activated receptor (PPAR)-α, along with its transcriptional targets, is upregulated in the hearts of mouse models of diabetes mellitus [4, 5, 6].

In 1972, Rubler et al. reported that there was no evidence of coronary artery disease in autopsy results for four patients with diabetic glomerulosclerosis and heart failure [7]. Myocardial hypertrophy and fibrosis were noted in the hearts of those patients, suggesting that the metabolism is responsible for this result. His description meets the contemporary definition of cardiomyopathy of the European Society of Cardiology [8]. Rubler's observations were supported by results reported by Regan in 1977 [9]. Autopsies of 11 uncomplicated diabetic patients revealed that 9 had no coronary artery disease and most of them died of heart failure. Collagen accumulation was present as perivascular, intermuscular, or replacement fibrosis. Multiple samples of the left ventricle and septum revealed increased levels of triglycerides and cholesterol compared to controls. Therefore, it was suggested that a diffuse extravascular abnormality is a basis for cardiomyopathic features in diabetes [6].

II. PATHOPHYSIOLOGY OF DCM

Cardiomyocytes experience a variety of molecular and metabolic alterations as a result of chronic hyperglycemia. Increased glucose metabolism attributable to hyperglycemia increases oxidative stress through development of ROS from the mitochondria [10]. Reduced cardiac contractility and eventual induction of myocardial fibrosis are the results of oxidative stress brought on by the excessive generation of superoxide in the mitochondrial respiratory chain [11]. ROS and oxidative stress can hasten DNA damage and apoptosis in cardiomyocytes. Oxidative stress-induced DNA damage also activates DNA reparative enzymes such as poly ADP ribose polymerase (PARP) [12].

The enhanced vascular stiffness can be related to hyperinsulinemia's promotion of osteoblast-like phenotypic differentiation of vascular smooth muscle cells. By boosting osteocalcin expression, alkaline phosphatase activity, and the development of mineralized nodules in vascular smooth muscle cells via higher levels of receptor activator of nuclear factor-B, elevated insulin levels may also increase vascular stiffness. Thus, a higher risk of developing CAD in conjunction with DCM is linked to reduced vascular smooth muscle cell and endothelial cell function [6].

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Obesity and diabetes mellitus cause an increase in free fatty acids, which accumulate mostly as triglycerides in adipose tissue. To sustain acceptable levels of ATP synthesis, fatty acid intake and beta-oxidation are increased; but, over time, beta-oxidation becomes unable to fully metabolise all incoming fatty acids, leading to the buildup of free fatty acids (FFA). Through the loss of mitochondrial function, ectopic fat that builds up in organs other than the adipocytes of visceral fat and subcutaneous fat causes the dysfunction of cells and organs such the liver, pancreatic cells, the skeletal muscle, and the myocardium [13].

Hyperglycemia leads to O-Glc-NAcylation of proteins such as CaMKII which plays a key role in the regulation of excitation-contraction coupling [14]. O-GlcNAcylation is a nutrient and stress responsive post-translational modification. Hormones such as insulin, glucagon and ghrelin are secreted in response to systemic metabolic changes and modulate O-Glc-NAcylation signalling in specific cell types and tissues to regulate key response pathways that help maintain metabolic homeostasis. A recent study showed that a sudden increase of glucose or O-linked N-acetylglucosamine is directly responsible for CaMKII-dependent diastolic sarcoplasmic reticulum (SR) Ca^{2+} leak from the ryanodine receptors leading to consequent SR Ca^{2+} load depletion which is consistent with the increase of SR Ca^{2+} leak observed in different early stage of diabetes [14].

III. DIAGNOSIS

Diabetic cardiomyopathy can broadly be sub-fractionated into two stages: the early stage is marked by left ventricular concentric hypertrophy, increased myocardial stiffness, increased atrial filling pressure, and impaired diastolic function; the late stage is marked by an increase in cardiac fibrosis, further impairment in diastolic function, and the development of systolic dysfunction. The definitive diagnosis of diabetic cardiomyopathy cannot be made using any specific criteria, biochemical markers, or physical characteristics. The only method to identify any changes related to the disease is through further investigation because the pathological alterations that occur as the disease progresses are frequently asymptomatic. During stress testing, LV dysfunction may be evaluated using tissue doppler imaging and strain rate imaging [14]. However, it is always recommended to get detailed cardiac investigations done under the care of an interventional cardiologist.

Despite the fact that it is commonly believed that patients with diabetic cardiomyopathy typically have diastolic dysfunction, examinations using strain imaging and cardiac magnetic resonance (CMR) have revealed a subtly present systolic dysfunction and reduced longitudinal contractility without discrete diastolic dysfunction. Myocardial metabolic alterations can be detected using novel diagnostic methods such as magnetic resonance (MR) spectroscopy, which can also measure the amount of triglycerides in the myocardium. Although it is still being researched, it is possible to assess interstitial fibrosis and steatosis using delayed gadolinium enhancement cardiac MRI [14].

3.1 The Role of SGLT2 Inhibitors in the Management of DCM

Recently, the 2022 AHA/ACC/HFSA guideline for the management of heart failure was released which provides recommendations based on contemporary evidence for the treatment of such cases. With the aim of enhancing the standard of treatment and aligning with patients' interests, the recommendations give an evidence-based approach to managing patients with heart failure. Although the guideline is not cited, the publication of a few significant clinical trials may cause it to be revised. According to the 2022 guideline, sodium glucose co-transporter 2 (SGLT2) inhibitors, namely Empagliflozin, Canagliflozin, Dapagliflozin, should be used in patients with heart failure and type 2 diabetes to manage hyperglycemia and lower heart failure-related morbidity and mortality (Class 1, Level A) [15] based on the results of the EMPEROR-Reduced [16], DAPA-HF [17], and DECLARE-TIMI 58 [18] studies [19].

SGLT2 inhibitors are highly effective glucose-lowering agents for use in diabetic patients. Multiple large guidelines groups, including the American Diabetes Association (ADA), recommend SGLT2 inhibitors as an option for patients not meeting individualised glycaemic goals to reduce hyperglycemia and. SGLT2 inhibitors are also a preferred option for diabetic patients when there is a desire to minimise hypoglycaemia and/or to minimise weight gain or promote weight loss. Additionally, the ADA 2022 Standards of Medical Care in Diabetes recommends using SGLT2 inhibitors for their organ protective effects in patients with CKD, ASCVD and/or HF, independent of HbA1c or individualised HbA1c goals [20].

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SGLT2 inhibitors block reabsorption of glucose in the proximal tubule with resulting increases in urinary glucose disposal and mild osmotic diuresis and natriuresis. SGLT2 inhibitors decrease blood glucose levels and are associated with decreases in insulin secretion, improved β-cell function, and improvements in insulin resistance. Blood pressure is improved via mild diuresis/ natriuresis and a reduction in sympathetic tone. Net calorie loss with SGLT2 inhibition is ~200–300 kcal/day mimicking a fasting-like metabolism. Net calorie loss provokes whole-body adaptive responses in energy metabolism by activation of sirtuin-1 and adenosine monophosphate-activated protein kinase with shifts of energy substrates from carbohydrates to fatty acids and ketone bodies. The achieved fasting-like metabolism improves mitochondrial dynamics and oxidative stress. Mimicking systemic hypoxia, SGLT2 inhibition upregulates hypoxia-inducible factors (HIFs; especially HIF-2α) resulting in erythropoietin production with an associated elevation of haematocrit, which may ameliorate organ oxygen delivery. SGLT2 inhibition additionally has anti-inflammatory effects, reduces oxidative stress and apoptosis, and increases autophagy. These changes result in reduced heart and kidney inflammation, fibrosis and structural damage. When considering a glucose-lowering agent in a patient with T2D, the first recommended consideration per the 2022 ADA Standards of Care, and the European Association for the Study of Diabetes (EASD)/European Society of Cardiology (ESC) Consensus Statement is whether the patient has ASCVD, HF or CKD. If a patient has one of these comorbidities, it is recommended to consider incorporating an agent with evidence of benefit into their medication regimen. Within the ADA Standards of Care, agents with 'proven benefit' are operationally defined as those with an expanded indication for improving ASCVD, HF or CKD outcomes. Based on observed HF benefits in patients with and without T2D, the 2022 heart failure guidelines from the American Heart Association/ American College of Cardiology/Heart Failure Society of America recommend SGLT2 inhibitors within their treatment algorithm to improve HF outcomes [20].

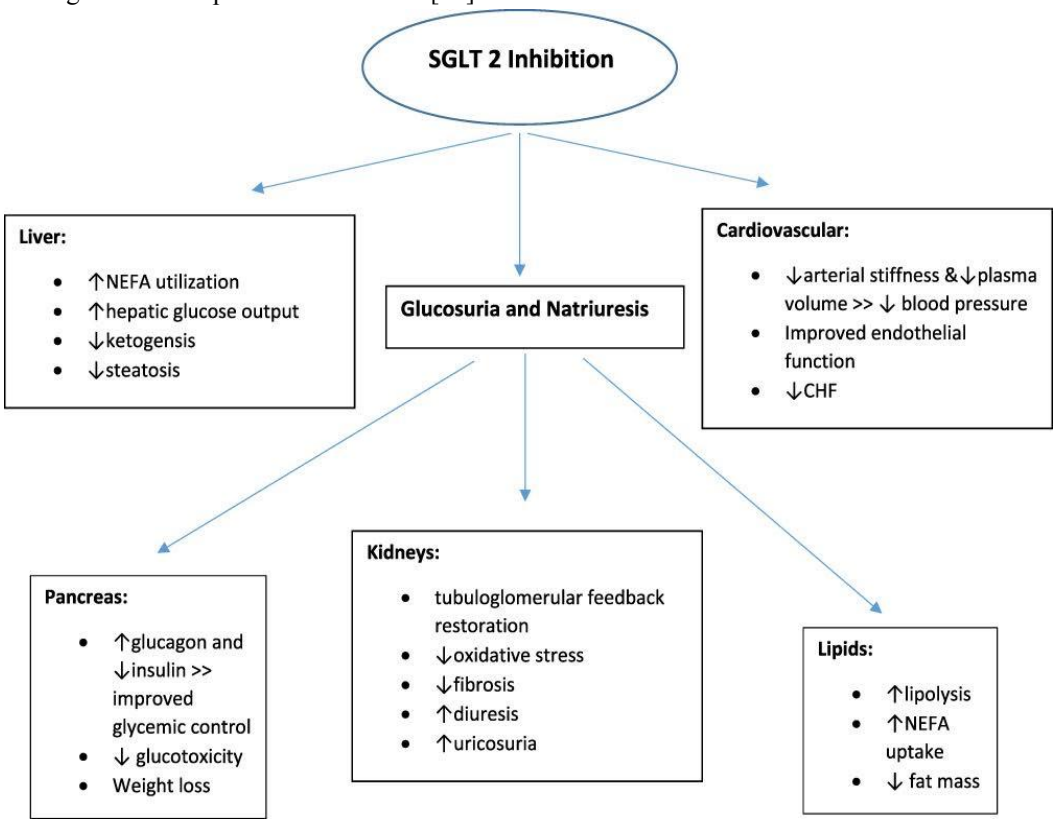

Image Courtesy : *Clinical Evaluation of Dapagliflozin in the Management of CKD: Focus on Patient Selection and Clinical Perspectives. (n.d.). Clinical Evaluation of Dapagliflozin in the Management of CKD: Focus on Patient Selection and Clinical Perspectives. International Journal of Nephrology and Renovascular Disease.*

In order to lower mortality and HF hospitalisations, clinical practise guidelines advise (class IA) patients with HFrEF to begin dapagliflozin and empagliflozin early in addition to the traditional foundational therapy (betablockers,

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RASi/ARNI, and MRA). Recent AHA guidelines recommend SGLT2 inhibitors in class IIA (the highest among the other outcome-modifying treatments) for patients with HFmrEF and HFpEF, basing this recommendation solely on data from the EMPEROR-Preserved trial (although published results from the DELIVER trial are anticipated to strengthen current treatment recommendations in this population). Dapagliflozin and empagliflozin can both be taken once day at a dose of 10 mg, without regard to food. Together, these findings highlight the need of timely treatment beginning and support early sustained therapeutic improvements with SGLT2 inhibitors in patients with HF. Additionally, SGLT2 inhibitors are simple to incorporate into complex HF therapy (single dosage, minimal effect on blood pressure, no effect on heart rate), fitting nearly all treatment modalities. In light of the widespread eligibility for these drugs, and the ensuing anticipated significant therapeutic benefit in the treated population, clinical inertia should be avoided [21, 22, 23, 24]

IV. CONCLUSION

Regardless of ejection fraction, diabetes condition, or care-setting aspect, SGLT2 inhibitors lower the risk of clinical events in a wide range of patients with DCM. Their early and consistent clinical benefit has been established, and there are no significant safety concerns. Therefore, SGLT2 inhibitors should be swiftly started as part of the initial therapy in all patients with DCM, barring any contraindications. Physicians should feel comfortable using these medications in order to put them to use and reduce any potential side effects.

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