Review Article

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An Update on Molecular Modes Implicated in Diastolic Impairment in Early Diabetic Cardiomyopathy; Probable Modes of Therapy &Avoidance-A Narrative Review.

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Abstract

In case of diabetic patients cardiomyopathy is a significant etiology of heart failure (HF); howeverno clarification exists regarding its pathophysiology. Myocardial hypertrophy as well as diastolic impairment are the logo for Diabetic cardiomyopathy (DbCM), whereas systolic function gets impacted in the latter phase of this disease. Previously we had reviewed Diabetic cardiomyopathy (DbCM with emphasis on epigenetic alterations ,miR changes apart from adipocyte impairment in HF induction, role of SGLT2 hampering agents in beneficial Cardiovascular Outcome Trials (CVOT's)and renal benefits, role of sirtuins in macrophage Polarization for Diabesity therapy .Here our aim was to posit the pathophysiological mode implicated in myocardial hypertrophy and escalated myocardial stiffness resulting in diastolic impairment .This myocardial stiffness takes place from cellular and extracellular matrix(ECM) stiffness &cell- matrix crosstalk. Escalated inherent cardiomyocytes stiffness plausibly is the maximum significant cause responsible for myocardial stiffness. It leads to dysfunctional cardiomyocytes cytoskeleton stiffness. Various other modes are implicatedbyT2DM; particularly having significant influence on myocardial stiffening i.e dysfunctional nitric oxide (NO), coronary microvascular impairment, escalated inflammation, as well as Oxidative stress(OS), myocardial Sodium –glucose specific cotransporter 2(SGLT2) modulated actions. Greater insight aids in planning better therapy.Anti diabeticagents, SGLT2 hampering agents have revealed newer ways of benefit ,like sirtuins action , upregulation of nutrient deprivation signaling in addition to downregulation of nutrient surplus signaling, escalated expression &activity of AMP-activated protein kinase(AMPK), Sirtuins (SIRT1), SIRT3 andSIRT6, &Peroxisome Proliferator Activated Receptor γCoactivator -1α(PGC-1α) ,reduction in activation of mammalian target of rapamycin inhibitors (mTOR). Recently Ghosh et al. (2023),advocated targeting sarcoplasmic / cytosolic endoplasmic reticulum Ca^{2+} -ATPase(SERCA2) ,use of imeglimin which escalates insulin action& along with reverses Pancreatic βcells impairment ,use of anti oxidants, angiotensin receptor neprilysin hampering agents(ARNi),NO stimulating agents. More work is being done regarding combination of empagliflozin with linagliptin &others like semaglutide with .Gradually we will get answers by getting more insight.

Keywords : Diabetic cardiomyopathy (DbCM); diastolic impairment; SGLT2 hampering agents; SERCA

Introduction

The incidence of type2 Diabetes mellitus (DM) is constantly escalating and trying to become the maximum significant health issue in the coming future all over the world. While the micro in addition to macrovascular complications have been exhaustively assessed in the past decades, the significance of heart failure (HF) in case of diabetic subjects has just recently caught the interest of investigators. Epidemiological studies have been illustrating that prevalence of HF in diabetic patients is considerably raised, that is a minimum equivalent to 30% (Boonman-de Winter et al., 2012; Thrainsdottir et al., 2005). Prevalence of HF in diabetic men is twice in contrast to six-fold greater prevalence in diabetic women as compared to a comparative non-diabetic population (Kannel et al., 1974). Further studies have illustrated in accordance that HF is the major reason for hospitalized diabetic patients along with significant anticipator of escalated mortality in diabetic patients (Deedwania et al., 2005).

Diabetic patients are usually influenced by a particular kind of cardiomyopathy, known as Diabetic cardiomyopathy (DbCM), to highlight its particular etiology in addition to manifestation along with differentiating it from other kinds of cardiomyopathy.

As per the European Society of Cardiology (ESC) as well as European Association for the study of Diabetes Guidelines (EASD), DbCM by definitions is ventricular impairment which takes place without any other co-morbidities like hypertension ,valvular disease as well as coronary artery disease (CAD)& coronary atherosclerosis in diabetic patients (Ryden et al., 2013). Prevalence of DbCM is determined to be equivalent to1.1% in general population as well as 16.9% in diabetic subjects (Dandamudi et al., 2014). Noticeably, diabetic patients further suffer from other kinds of cardiomyopathy for example ischemic or hypertensive cardiomyopathy which possess separate pathophysiology as well as clinical direction. The presentation clinically is in the form of HF with conserved (≥50%) ejection fraction (HFpEF). Myocardial hypertrophy in addition to diastolic impairment have been believed to be the trademark of DbCM, while systolic function gets impacted in the later phase of the disease (Schannwell et al., 2002). Structural myocardial alterations can be detected early in the disease path, just prior to its initial clinical manifestations, as well. The initial structural alteration is minimum myocardial hypertrophy correlated with interstitial fibrosis along with collagen getting deposited (Shimizu et al., 1993). Apart from macroscopic remodelling, there might be microscopic along with ultrastructural alterations (Van Heerebeek et al., 2012). Various imaging gadgets might be utilized for diagnosing DbCM dependent on morphological properties in addition to investigation of cardiac function. Echocardiography is the maximum utilized imaging strategy regarding evaluation of cardiac morphology along with diastolic in addition to systolic function in view of its accessibility as well as economy .Estimation of diastolic function is conducted by utilization of pulse wave doppler for evaluating transmittal as well as pulmonary venous flow , tissue doppler imaging(TDI) for evaluating myocardial velocities at the time of cardiac cycle in addition to determining the left atrial volume (Galderisi, 2005). It contributes to apart from estimation of diastolic function; follow up with regards to disease propagation from mild diastolic impairment (dysfunctional relaxation) to advancement of stage (pseudo normalization or restriction). Cardiac magnetic resonance imaging (CMRI)has recently become an imaging gadget which might contribute in the diagnosis of different structural in addition to functional conditions of the myocardium inclusive of diastolic impairment, function along with myocardial steatosis. In view of them possessing the capacity of determining the myocardial metabolic aberrations CMRI along with positron emission tomography (PET) might be of use of diagnosing DbCM (Gottleib et al., 2006).

Previously we had reviewed Diabetic cardiomyopathy (DbCM with emphasis on Epigenetics alt, miR changes apart from adipocyte impairment in Heart Failure Induction, role of SGLT2 hampering agents in beneficial Cardiovascular Outcome Trials (CVOT's)and renal benefits, role of sirtuins in macrophage Polarization for therapy of Diabesity (Kaur et al., 2021; Kaur et al., 2022; Kaur et al., 2021; Kaur et al., 2022; Kaur et al., 2019; Kaur et al., 2023; Kaur et al., 2022; Kaur et al., 2023).

Here we try to sum up by making a separate model for the generating a new model for description of the insight of the basic modes as well as their communications, all implicated in the generation of diastolic impairment .This has been feasible in view of the information acquired from significant recently outcomes obtained from clinical as well as basic studies in addition to translation from previous information along with basics of vascular pathology to the myocardial pathology in diabetic patients. It is believed that akin foundational events behind the myocardial as well as vascular pathology are present in these patients having emphasized on Epigenetic modes in DbCM & roles of miR we have not repeated here.

Methods

In this study we conducted a narrative review utilizing search engine PubMed, Google Scholar; Web of Science; Embase; Cochrane review library utilizing the MeSH terms like DbCM; Diabetic Cardiomyopathy (DbCM),Epigenetics; Histone acetylation; SGLT2 hampering agents; advanced glycation end-products(AGE's); miRNAs circRNAs; lnc RNAs HDAC1-6and Cardiac remodelling; Cardiac fibrosis, Cardiac hypertrophy; LV hypertrophy; cardiomyocytes apoptosis; PI3K signalling pathways; autophagy; Pyroptosis; valproic acid; sodium butyrate; SGLT2 inhibitors from 1950 to 2023 till date.

Results

A total of 6000 articles were discovered, 129 articles were selected for this review. They were not meta-analysed was done.

Pathophysiological Events Behind the Diabetic Cardiomyopathy (DbCM) Development

While various parts of the myocardium are implicated in the pathophysiological events of DbCM. Cardiomyocytes, extracellular matrix (ECM) crosstalk amongst them. Dependent on this information that vascular wall is implicated in the vascular myocardial stiffness in diabetic patients, it was posited that there is a probability that cardiomyocytes possess key part in the induction of events of myocardium getting stiffened . For these reasons it is thought that investigation of the complicated mode needs to be initiated with the isolation of the of starting pathological event. The posited mode for the generation addition to propagation is revealed in Figure1 [rev in figure 1].

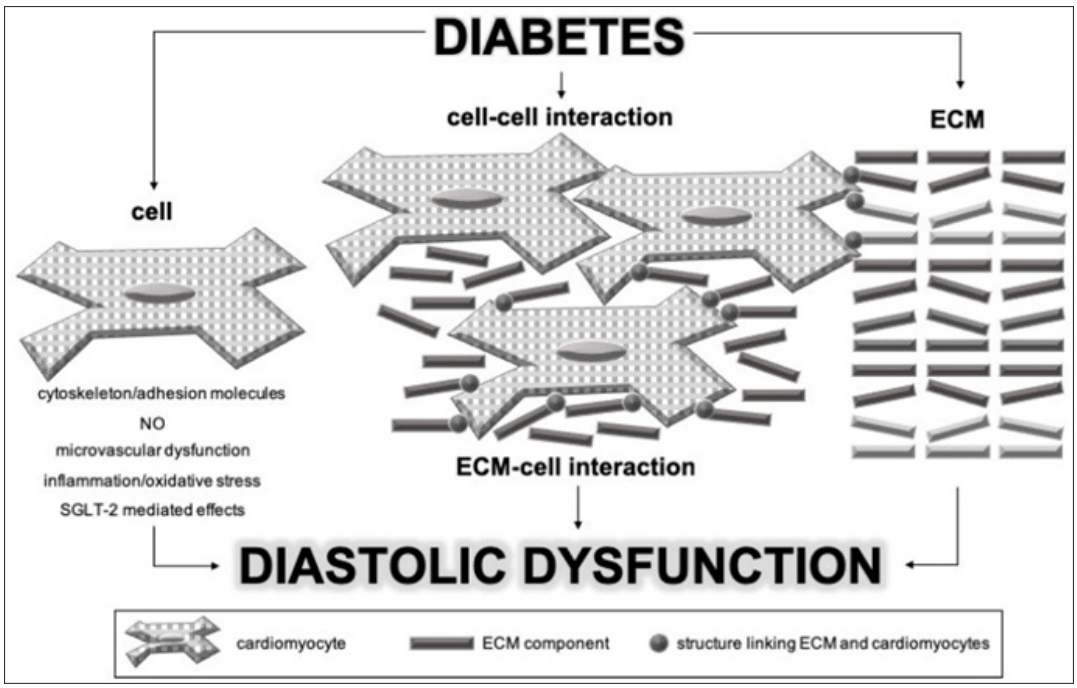

Figure 1

Cortesy ref no- (Nikolajevic Starcevic et al., 2019) - Pathophysiological mechanisms involved in the pathogenesis of diabetic cardiomyopathy.

SGLT-2—sodium glucose cotransporter-2; NO—nitric oxide; ECM—extracellular matrix.

clinical established calcium by G2/M phase cell cycle phase conditions, ion resulting.

The way stated earlier hypertrophy is probably the initial structural myocardial alteration visualized in DbCM. By itself DM facilitates cardiomyocyte hypertrophy as well as contractile impairment along with diminished quantities (Depre et al., 2000). Diminished cardiomyocyte numbers followed by their hypertrophy might be the outcome of activation of apoptosis as well as decreased proliferation capacity; hypertrophy is probably compensatory in the following scenario (Wilson et al., 2018).

- The initial functional alterations is cardiomyocyte stiffening, in view of escalated tone, dysfunction of their cytoskeleton, or both of which get stimulated by DM is implicated. Different other modes, in particular impacted by DM apparently are significantly responsible for escalating cardiomyocyte stiffness
- dysfunction of myocardial nitric oxide (NO), pathways
- coronary microvascular impairment
- escalated inflammation along with myocardial oxidative stress(OS) in addition to
- myocardial- Sodium –glucose specific cotransporter 2(SGLT2)- associated abnormalities.

Cardiomyocytes with escalated inherent cell stiffness alters their phenotype to greater fibrinogenic. Hyperglycaemia might further stimulate this fibrinogenic phenotype that is independent of inherent modes (Russo & Frangogiannis, 2016). Fibrinogenic phenotype of cardiomyocytes possess the properties of escalated generation as well as liberation of cytokines which stimulate fibroblast proliferation in addition to proinflammatory mediators which stimulate fibrosis via activation of transforming growth factorβ 1(TGF-β1), tumour necrosis factor alpha(TNFα) , interleukin-1(IL-1) [24].

ECM possesses a significant part in the conservation of myocardial- architecture as well as geometry of the chamber (Weber et al., 1994). Collagen fibres weave at the time of systole whereas uncoil at the time of diastole thereby sustenance of cardiomyocyte arrangement. On the straightening of the fibres ,they further hindered more expansion as well as confer protection to cardiomyocytes from extra stretching (Fomovsky et al., 2010).As described earlier ECM in the patients with DbCM express microscopic alterations like perivascular as well as interstitial fibrosis in addition to collagen getting deposited in particular type I as well as III (Shimizu et al., 1993; VanHoeven & Factor, 1990)].This takes place mainly secondary to fibrinogenic phenotype of cardiomyocytes that in turn further stimulates the generation of greater collagen from fibroblast. The association amongst myocardial stiffness as well as collagen quantities is not linear pointing to involvement of certain extra factors in the generation of stiffness (Weber et al., 1993). Apart from total collagen quantities as well as expression of type I collagen, myocardial stiffness is further based on the extent of collagen cross linking (Weber et al., 1994; Berg et al., 1999).In diabetic patients greater levels of advanced glycation end-products(AGE's) aid in fibrosis as well as diastolic stiffening by escalating the quantities of cross linking (Aronson, 2003). Cross linking of collagen molecules avoid their enzymatic breakdown resulting in escalated collagen quantities in ECM (Norton et al., 1996).

In view of separate pathophysiological modes, it is plausible to distinguish amongst cell stiffness along with ECM stiffness. Alterations in matrix stiffness alter cell- matrix crosstalk along

with activate cellular mechanoreceptors thereby escalating inherent cell stiffness as well as facilitate its liberating phenotype. This pathological positive feedback loop (cell stiffness- matrix stiffness- cell stiffness) is shut in leading to diastolic impairment along with ultimately HF. These pathophysiological events are further detailed.

Diabetic Cardiomyopathy (DbCM) Models

Regarding assessment of the modes in various animal models were utilized. Animal models utilized for this purpose studies generated diabetes which is either diet or drug stimulated or transgenic (Riehle et al., 2018). Despite provision by animal models forms a suitable base for DbCM studies there are certain variations dependent on animal kinds, insulin resistance (IR) along with elimination (Russo & Frangogiannis, 2016). Streptozocin- possesses the capacity of inducing type1 Diabetes mellitus, a drug which in greater quantities, has the capacity of damaging βcells of the islets of Langerhans in the Pancreas, thus resulting in insulin-based status. It is utilized in rodents models. generation of aggravated myocardial fibrosis, cardiomyocyte hypertrophy stiffness, augmentation of cell demise , reduction in cardiomyocytes contractile function in addition to left ventricular hypertrophy takes place (Riehle et al., 2018; Hao et al., 2015).Akin actions with myocardial fibrosis along with collagen accrual have further been illustrated in larger animal models, like mongrel dogs, rhesus monkeys where insulin based diabetes induction was stimulated by alloxan delivery (Russo & Frangogiannis, 2016; Haider et al., 1981). Conversely transgemice like akita mice (Ins 2WT/C96Y) generated diastolic impairment as well as lipotoxicity without significant cardiac fibrosis along with hypertrophy (Haider et al., 1981). Other transgenic mice models have further been utilized like non obese Diabetes (NOD) mouse models as well as OVE26 (Riehle et al., 2018).

Type2 Diabetesmellitus (T2DM) mouse models are constituted specifically of rodents, where insulin resistance (IR) along with elimination gets formed by diet or transgenic mice (Russo & Frangogiannis, 2016). Diet induced animal models are composed of mice fed high fat diet (HFD),or the ones labelled as'' western'' diet .The myocardial alterations in these animals are indistinct, which takes greater time for generation (Riehle et al., 2018). However subsequently following certain time ventricular hypertrophy, myocardial fibrosis as well as reduction in contractile function generates (Riehle et al., 2018; Qin et al., 2012). Generally utilized by T2DM transgenic models comprise of obese ob/ob mice, IR, along with T2DM (db/db) models. These are mice generally with truncated leptin receptor or totally leptin deficient. Thereby they are generally resistant to leptin actions. They generate overweight/obesity very rapidly along with display signs of IR along with DM in further path (Russo & Frangogiannis, 2016). Cardiac fibrosis associated with left ventricular hypertrophy in addition to diastolic impairment has been found in these models (Sloan et al., 2011). Noticeably, the number of pathological properties found in these T2DM models is mainly based on time of T2DM implying watching /follow up. Zucker diabetic fatty (ZDF)fa/fa rats as well as Goto-Kakizaki (GK) rats basically generate akin properties as detailed earlier (Russo & Frangogiannis, 2016; Riehle et al., 2018). Direct animal models of DbCM are just transgenic; are inclusive of mice with cardiomyocytes specific overexpression of the transcription factor for Peroxisome Proliferator Activated Receptor α (MHC-PPARα) as well as cardiomyocytes selective insulin receptor knockout transgenic (CIRKO) mice. Their hearts illustrated akin properties like the hearts of T2DM patients, specifically illustrating diastolic impairment in addition to diminished cardiac contractility (Riehle et al., 2018; Boudina et al., 2009). In view of shared pathological properties of DbCM in humans along with animal models the latter contribute to investigations of the mechanism of action pathways apart from therapeutic targets.

Diabetes Mellitus along with Escalated Inherent Cardiomyocytes Stiffness

Alterations of cardiomyocytes morphology is taking place on macroscopic as well as microscopic levels in the timeline of DM. Histological evaluation of cardiomyocytes from diabetic mice revealed irregular nucleus size along with fragmentation of actin fibres in addition to diffuse as well as irregular actin organization, specifically in cortical areas (Boudina et al., 2009). Furthermore, of greater significance is that cardiomyocytes alter their mechanical characteristics. Various paradigms utilized for assessment of alterations of mechanical properties of diabetic cardiomyocytes validated that escalated cellular stiffness is a significant factor in myocardial stiffness as well as that by definition resting tension (RT) is the passive force at the same sarcomere length. Escalated RT in association with escalated myocardial stiffness (Benech et al., 2014) has been displayed RT in contrast to the ones from nondiabetic mice in animal models to be correlated with both ageing along with obesity (Van Heerebeek et al., 2008). Cardiomyocytes identified from diabetic mice expressed escalated RT in contrast to the ones from nondiabetic mice (Benech et al., 2014). As per the accessible outcomes cytoskeleton alterations aid considerably to the complicated network of filaments along with tubules which conduct mechanical as well as chemical stimuli amongst cells. The cytoskeleton is further implicated in sustenance of cell stability by distribution of the cell constituents (Fletcher & Mullins, 2010). Atomic force microscopy (AFM) is escalatingly getting utilized for determining cytoskeleton constituents in addition to viscoelastic characteristics of live cells. This approach aids in quantification of alterations in myocyte sarcolemma, sarcomeric skeleton as well as cytoskeleton proteins inclusive of actin, titin, as well as tubulin. Conversely, it aids in determination of elastic modulus of live cells (Kuznetsova et al., 2007). In a recent study that utilized AFM it was illustrated that the elastic modulus of diabetic cardiomyocytes was significantly escalated in contrast to nondiabetic cardiomyocytes. Furthermore, they found alterations in actin distribution as well as actin filaments were disarrayed along with undergo degradation in diabetic cardiomyocytes. Thereby conclusions drawn where alterations in inherent mechanical characteristics were in all probability not associated with contractile status of cell proteins; but instead of to direct alterations in material characteristics due to diabetes per say. The same study further displayed greater

adherent forces in diabetic cardiomyocytes in contrast to non-diabetic cardiomyocytes, implying escalated numbers as well as/or activation status of cell surface adhesion molecules (Benech et al., 2014). Normal function of cardiomyocytes is based on the appropriate regulation of Ca^{2+} quantities at the time of contraction- relaxation cycle (Boudina & Abel, 2007). Depolarization of the cardiomyocyte membrane results in opening of voltage-based L kind Ca^{2+} channels aiding in entry of Ca^{2+} ions in cell. The escalating intracellular quantities of Ca^{2+} stimulates further liberation of Ca^{2+} cytoplasmic, from the -sarcoplasmic reticulum (SR) through Ca^{2+} release channels (ryanodine receptor). Reduction of cytoplasmic quantities of Ca^{2+} aids in cardiomyocytes relaxation in diastole. At the time of relaxation Ca^{2+} quantities come back to diastolic quantities basically by reuptake of Ca^{2+} to SR by sarcoplasmic / endoplasmic reticulum Ca^{2+} -ATPase (SERCA2)- in addition to sarcolemmal Na^{+}- Ca^{2+} exchanger as well as sarcolemmal Ca^{2+} -ATPase . SERCA2 possesses the maximum significant part in sustenance of Ca^{2+} quantities at the time of relaxation in view of it being responsible in about 70% of the reuptake of Ca^{2+} (Bers, 2008). Expression of SERCA2 is reduced in T2DM in view of glucotoxicity, in addition to escalated OS (Benech et al., 2014; Suarez et al., 2008). Diminished SERCA2 expression results in reduction of Ca^{2+} that has been reuptaken in addition to lessening of SR Ca^{2+} quantities. In form of a sequel lesser Ca^{2+} is accessible with regards to next contraction resulting in dysfunctional cardiomyocyte contractility. Conversely, escalated cytoplasmic Ca^{2+} quantities accessible at the time of diastole results in dysfunctional cardiomyocyte relaxation found in DbCM (Suarez et al., 2008; Shimizu et al., 1993). Nevertheless, certain publishers posited that escalated cell stiffness is independent of membrane Ca^{2+} as well as cytoplasmic quantities of Ca^{2+} in view of escalated cardiomyocyte stiffness was validated at various intracellular quantities of Ca^{2+} (Benech et al., 2014). This indicated that disarrayed cytoskeleton distribution secondary to T2DM by itself portrays a foundational event behind escalated cell stiffness in DbCM.

Structural as well as functional alterations in titin, a sarcomeric protein which works in form of a molecular spring, sustains sarcomere stability in addition to estimate the passive myofilaments possessed the capacity of distension –are further directly influenced by DM. Mechanical characteristics of titin are based on its isoform's constitution as well as post-translational modifications like phosphorylation along with disulfide bonding secondary to OS (Hopf et al., 2018). In the cardiac muscle 2 titin isoforms are present

- smaller N2B isoform which is just constituted ofN2B,
- larger N2BA isoform that possesses bothN2B as well as N2A elements.

In case of human N2BA: N2B isoform ratio is about 30:70. Cardiomyocytes obtained from diabetic patients illustrate greater expression of N2BA: N2B titin isoform ratio, which is believed to be greater cooperative in contrast to nondiabetic cardiomyocytes. However, titin dependent passive tension of diabetic cardiomyocytes is enhanced in contrast to nondiabetic cardiomyocytes. Probably this is in view of changed titin phosphorylation by insulin lacking/dysfunctional insulin signalling as well as disulfide bonding secondary to escalated OS in DM (Hopf et al., 2018).

Nitric Oxide (NO) along with Enhanced Contractile Status in Diabetic Cardiomyocytes

NO Signalling is believed to be dysfunctional as well as directly implicated in the pathophysiology of DbCM. Production of NO takes place by nitric oxide synthase; having 3 isoforms

- endothelial nitric oxide synthase(eNOS)
- inducible nitric oxide synthase(iNOS)
- neuronal nitric oxide synthase(nNOS).These get in various regions of cardiomyocytes (Khanna et al., 2014).

Placement of eNOSis in the caveolae as well as implicated in the constitutive generation of NO which diminished heart rate, contraction along with oxygen utilization, whereas escalating diastolic relaxation. Furthermore, it possesses antiapoptotic effects along with hampers accrual as well as adhesion of platelets. Its vasodilatory effects get modulated by guanylate cyclase activation. Placement of neuronal nitric oxide synthase (nNOS) is in the sarcoplasmic reticulum, where it controls various receptor actions like SERCA2, ryanodine receptor as well as L kind of Ca2+ channels. At the time of basal situations, eNOS along with nNOS are implicated in NO generation, which abrogates inotropic responsiveness along with facilitates cardiomyocytes relaxation. Protection gets conferred by NO. eNOS action is canonically diminished in diabetic patients, resulting in elimination of NO (Farah et al., 2018). Occasionally NO might be possessing an inimical part, when it exists in escalated quantities in the cardiomyocytes. In conditions of hyperglycaemia, OS, as well as hyperinsulinemia, iNOS can further form toxic quantities of NO. Escalated quantities of NO result in contractile impairment, whereas in case of substrate scarcity, iNOS can undergo uncoupling along with initiate Reactive oxygen(ROS)/nitrosative species(RNS). With this an environment full of inflammation as well as Oxidative fatty stress (OS), resulting in direct tissue injury at one end ,with as well as nitration of actin in addition to other possesses inimical action on the cytoskeleton proteins as well as channels, changing their structure along with inimical action on contractile function. Akin eNOS uncoupling has further been detailed in diabetic myocardium further possessing inimical actions (Khanna et al., 2014; Farah et al., 2018).In total NO possesses very significant part in diabetic myocardium. Whereas in regulated restricted quantities, it confers protection -aiding in efficacious cardiomyocytes relaxation. Conversely, on its exhaustion or escalated quantities alters the microenvironmental transfer leads to diminished relaxation- escalated contraction '' states of cardiomyocytes; thereby aiding in in escalated myocardial stiffness.

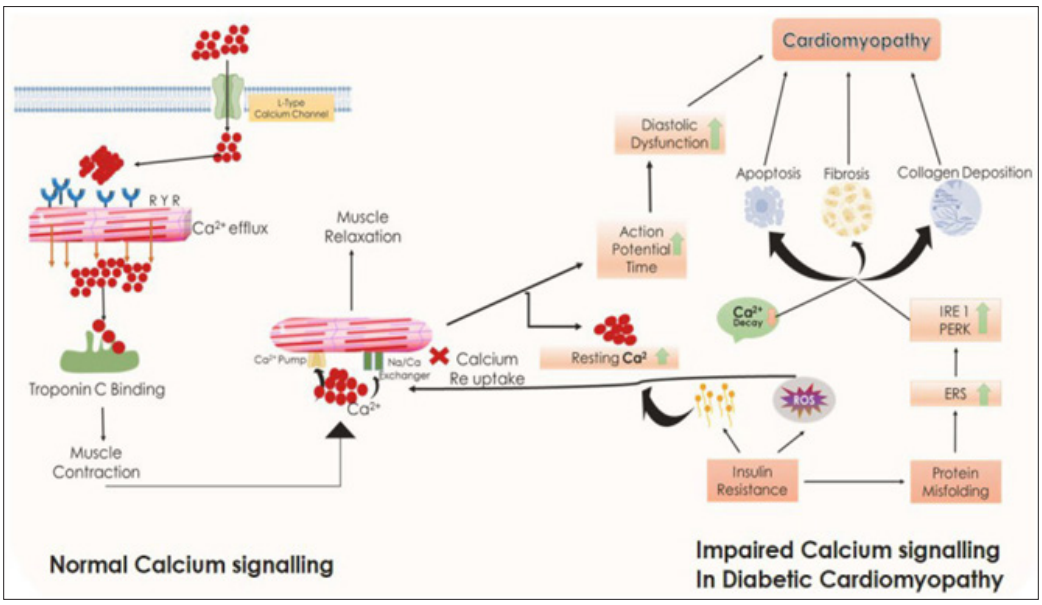

Figure 2

Courtesy ref no- (Ghosh et al., 2023)-Comparison of normal calcium signaling with diabetic cardiomyopathy calcium signaling. Black arrows represent downstream events. ERS, endoplasmic reticulum stress; IRE1, inositol-requiring kinase-1; PERK, protein kinase R-like endoplasmic reticulum kinase; ROS, reactive oxygen species.

Inflammation along with Oxidative stress (OS) in diabetic Cardiomyocytes

Diabetes mellitus is believed to be a complicated metabolic condition, having the properties of escalated OS along with inflammation. Broad acknowledgement is present regarding complicated association amongst oxidative as well as nitrosative stress along with proinflammatory modes possess very significant part in the generation of microvascular along with macrovascular diabetic complications. Greater insight of DbCM pathophysiology resulted in the appreciation regarding these modes take part in the pathogenesis of DbCM.

Hyper glycemia is believed to be the maximum significant factor resulting in OS in DM. Hyper glycemia associated with IR as well as hypertriglyceridemia, restricts cardiomyocytes capacity of utilization of glucose in the form of energy source, escalating free fatty acids(FFA) along with resulting in escalated generation of ROS (Jia et al., 2018).The main source of ROS generation in myocardium are mitochondrial, endothelial cell as well as neutrophils (Liu et al., 2014). Nonmitochondrial source, inclusive of nicotinamide adenine dinucleotide phosphate reduced form (NADPH) oxidases in addition to xanthine oxidases as well as microsomal P-450 activity might further aid in considerably escalated ROS formation (Giacco & Brownlee, 2010). Escalated quantities of ROS result in cellular injury via numerous modes inclusive of i) Oxidative manipulation of proteins, modulating the generation as well as function of NO in addition to manipulating the intracellular signalling pathway resulting in cellular hypertrophy, apoptosis along with necrosis (Takano et al., 2003). Escalated OS in myocardium is correlated with, Oxidative manipulation of proteins, responsible for contractility, excitation- contraction-coupling, protein folding antioxidant defense, glucose as well as fatty acids metabolism along with Ca2+ handling (Varga et al., 2015). Lastly oxidative injury might further change the ECM architecture by activation of Matrix Metalloproteinases as well as facilitating production of AGEs (Giacco & Brownlee, 2010; King et al., 2003). Apoptosis along with necrosis of cardiomyocytes as well as endothelial cells are further significant characteristics of DbCM, resulting in reduction in cardiomyocytes numbers along with expansion of extracellular space (Cai & Kang, 2003). Apoptosis is not implicated in scar production as well as accrual of interstitial collagen, whereas necrosis is correlated with extracellular space broadening along with escalated collagen accrual of collagen resulting in escalated fibrosis along with ECM stiffness (Eckhouse & Spinale, 2012). Furthermore, hyperglycaemia is implicated in chronic low-grade inflammation that is usually accompanied by DM (Diamant et al., 2005). Inflammatory signalling in cardiomyocytes in general takes place in the form of an early reaction to myocardial damage in addition to is correlated with an enhanced generation of mitochondrial as well as cytosolic ROS. Enhanced inflammation along with Oxidative stress result in activation of nuclear factor κB (NFκB) is acknowledged to lead to collagen along with fibronectin generation along with formation of proinflammatory cytokines (Taqueti et al., 2018). NFκB might result in induction of expression of varied kinds of proinflammatory cytokines inclusive of interleukins (Tumor necrosis factor alpha(TNFα) , interleukin -1β(IL-1β), interleukin-6,IL-8,) along with chemokines(monocyte chemoattractant protein 1(MCP1) , adhesion molecules(like selectin as well as intercellular cell adhesion molecule[ICAM]-1], vascular cell adhesion molecule[VCAM]-1]) , along with migration of leukocytes in the myocardium (Lorenzo et al., 2018; Jia et al., 2016). These action have been found apart from cardiomyocytes ,in coronary endothelial as well as smooth muscle cells in addition to fibroblasts (Jia et al., 2018). Escalated generation of proinflammatory mediators resulting in fibroblasts proliferation along with activation is implicated in myocardial fibrosis that

significantly aids in interstitial myocardial stiffness in DbCM.

Coronary Microvascular Impairment in Diabetes

DM directly leads to coronary microvascular impairment to working of myocardium having the properties of reduction in its vasodilatory reaction to variable stimuli. Different modes are implicated namely

- endothelial impairment (disarrayed ratio amongst local vasodilators; specifically, is lesser NO quantities along with vasoconstrictors)
- impairment of coronary smooth muscle cells
- sympathetic impairment (enhanced α adrenergic reaction with pro constricting) along with subsequent microvascular remodelling (working tissue getting replaced by lesser working tissue) (Kibel et al., 2017; Paulus et al., 2013). These events are dependent on local inflammation stimulated by hyperglycaemia) mitochondrial fragmentation as well as impairment,
- ROS generation, in addition to
- nitro tyrosine generation; all these events result in endothelial cell impairment having the properties of expression of vascular cell adhesion molecule (VCAM), selectins resulting in leukocyte migration into the subendothelial space.

Subendothelial leukocytes in turn are implicated in greater ROS formation as well as inflammation getting potentiated (Paulus et al., 2013). These modes are akin to those detailed previously. In total they injure the endothelial cells further which result in reduction of NO bioavailability. As a sequel vasodilatory reaction of the coronary vessels is diminished (Kibel et al., 2017; Taqueti et al., 2018). This latter accompanied by enhanced profibrotic cytokines signalling might aid in reduction of coronary arteries as well as escalated myocardial fibrosis observed in DbCM. Thereby this vicious cycle gets finished. Coronary microvascular impairment via detailed modes results in microvascular ischemia. This in turn causes dysfunctional coronary flow reserves which result in cardiomyocytes damage as well as fibrosis implicated in diastolic impairment (Taqueti et al., 2018). In the description of environment, the events become self-perpetuating resulting in overt HF.

Different transporters along with substrate metabolism in cardiomyocytes in DM

Ideal working of myocardium is based on the generation basically of enough adenosine triphosphate (ATP) via mitochondrial oxidative phosphorylation (OXPHOS), as well as to a lesser degree glycolysis (Kaplan et al., 2018). The maximum significant energy in healthy myocardium is FFA oxidation that gives provision of 70% regenerated ATP, however other substrates (like glucose, lactate amino acids as well as Ketone bodies(KB)] might further be utilized for ATP generation (Taegetmyer, 1994; Is fort et al., 2014). DM is correlated with a myriad of myocardial metabolic abnormalities influencing fuel supply in addition to utilization.

Glucose is hydrophilic, hence does not possess the capacity of traveling via the cardiomyocytes plasma membrane by passive diffusion. As a sequel its transport requires 2 inimitable kinds of glucose transporter (GLUT) [alias facilitative transporters] along with Sodium –glucose specific cotransporter 2(SGLT2) (Szablewski, 2017). GLUTs are from a super family of facilitative glucose transporters which is composed of 14 members. They get encoded by soluble carrier family 2 member 4 (SLC2A4), with their expression is tissue– particular. The maximum enrichment i.e., 70% of all GLUT transporters in the heart is GLUT4. Its placement is in intracellular membrane chambers. GLUT4 translocation takes place to the cell surface on stimulation by insulin, hypoxia, catecholamines etc when it can escalate greater quantities of glucose influx into cardiomyocytes by 10-20 times (Barger et al., 2000). Furthermore, GLUT1exists in great quantities, with reduction of its quantities from neonatal period till adulthood. It is implicated in basal glucose transport. in addition to its expression is further stimulated by chronic hypoxia/long-term fasting (Kraegen et al., 1993). SGLT's encoded by SLC5A genes (altogether12), all portray Na+-/ substrate cotransporters (which transports sugars, inositol, lactate, urea, proline as well as ions). Expression of six genes takes place in the human heart. SGLT1 is the maximum expressed which has colocalization with GLUT1 in the sarcolemma. It is a controller of glucose uptake secondary to hormonal stimuli (Banerjee et al., 2009). Conversely, SGLT2 have not been observed in human cardiomyocytes (Kaplan et al., 2018).

Insulin has been illustrated to impact transmembrane glucose transport by escalating transcription of GLUT4 along with GLUT1 transporters facilitating translocation of glucose transporter proteins to the plasma membrane as well as escalating their action (Garvey et al., 1993). Thereby in the absence of insulin sensitivity secondary to either insulin deficiency or IR, there is diminished myocardial glucose utilization. In view of no glucose utilization switching of substrates takes place, specifically escalating ATP generation by FFA. This latter further results in IR as well as reduction in GLUT4 accessibility, generating a vicious cycle (Stratmann & Tshoepe, 2011). Conversely, an escalation of SGLT1 expression takes place in diabetic hearts. This is believed to be a compensatory mode in view of decline in cardiac expression of factor of GLUT4 along with GLUT1.This kind of compensatory mode is specifically observed in T2DM (Banerjee et al., 2009). Transportation of FFA into cardiomyocytes takes place by passive diffusion(just minimal %age or via 3 unique long chain FFA transporters like CD36 plasma membrane associated fatty acid binding protein(FABP) as well as fatty acid transport protein(FATP) (Schwenk et al., 2008). CD36 along with FABP, CD36 working lone or promoter for FABP are implicated in maximum of FFA uptake by cardiomyocytes. These transporters generate the functional pool in view of their placement in the sarcolemma as well as implicated in energy uptake. Moreover, there exists a storage pool with placement in the intracellular chamber whose enrolment take place by different stimuli like contractile action in addition to insulin.On enrollment,for the transporters to get functional; a vesicle modulated event take place (Schwenk et al., 2008). At the time of DM an escalated CD36 quantities occurs in sarcolemma, that is constant transfer of the said transporter proteins; not secondary to escalated expression.

As per certain investigators this is the maximum crucial process in the formation of DbCM (Schwenk et al., 2008). Dysfunctional myocardial metabolism of FFA takes place in DM in view of escalated circulating quantities as well as escalated FFA uptake in view of upregulation of in addition to escalated translocation of CD36/ FABP along with FATP to the sarcolemma (Lopaschuck et al., 2010). β oxidation of FFA is further documented to be enhanced in DM leading to escalated quantities of acetylCoA that hampers pyruvate dehydrogenase with further reduction of glucose as well as lactate in diabetic myocardium (Taegetmyer, 1994; Isfort et al., 2014). Enhanced β oxidation further promotes the FFA transport to mitochondrial that is a maximum significant controlling step regarding FFA metabolism (Isfort et al., 2014). Once mitochondrial oxidative capacity gets surpassed, enhanced FFA enter the nonoxidative pathways resulting in generation of toxic intermediates like ceramide. Enhanced FFA oxidation in mitochondria is correlated with escalated generation of ROS, resulting in lipid peroxidation along with dysfunctional mitochondrial energy metabolism (Lee & Kim, 2017).

DM influences the utilization of other substrate of energy metabolism. It reduces lactate uptake, dysfunctional pyruvate oxidation along with enhanced Ketone bodies (KB) uptake (Isfort et al., 2014; Chatham & Forder, 1993). KB comprising of acetoacetate, 3 β-hydroxy butyrate portray energy enriched substance generated from the FFAs in the liver. Aberrations of insulin as well as escalated quantities of counter controlling hormones in DM are correlated with escalated Ketogenesis in view of enhanced transportation of FFA in the mitochondria along with their escalated β oxidation (Laffel, 1999). Escalated acetylCoA that cannot get inclusive in tricarboxylic acidcycle (TCA) get oxidized to generate KB in hepatocytes. In view of acetylCoA is formed by both KB as well as FFA oxidation, a natural competition amongst KB as well as FFA for aiding in tricarboxylic acid cycle (TCA) occurs that is not impacted by DM (Wentz et al., 2010). The pathological situations like badly regulated DM; the escalated quantities of circulating KB hampers glucose utilization as well as lactate but further the FFAs utilization-the major substrate for energy metabolism. In contrast to glycolysis the FFAs utilization is equivalent to 10%lesser effectiveness for formation of ATP after adjusting for oxygen utilization (Wang et al., 2006). As a sequel dysfunctional energy metabolism might result in both contractile impairment in addition to diastolic impairment in view of it being an energy-utilizing event. DM is further correlated with escalated catabolism of amino acids; thereby restricting the accessibility of amino acids for protein generation. Moreover, DM is further correlated with diminished RNA quantities as well as hamper protein generation (Sharma & Neill, 2006).

Sodium –glucose cotransporter 2(SGLT2)- modulated action in cardiomyocytes

Ion decontrolling results in disarrayed cardiomyocytes contraction in addition to relaxation is the property of diabetic myocardium. Specifically, Ca^{2+} in addition to Na^{+} homeostasis is changed. This is secondary to diminished Na^{+} /K^{+} action along with Na^{+}- Ca^{2+} exchanger (NCX) action with simultaneously escalated Na^{+}/H^{+} exchanger (HNE) action resulting in cytosol Na^{+}- burden (Lambert et al., 2015). An escalated SGLT1 expression has been observed to be perturbed in diabetic failing heart whereas no SGLT2 expression has been observed in healthy or diseased cardiomyocytes. Promising results were obtained in Cardiovascular Outcome Trials (CVOT's) for SGLT2 hampering agents which were basically substantially selective for the hampering of (empagliflozin as well as dapagliflozin), thereby cannot be responsible for their actions on any of the SGLT (Kaplan et al., 2018). Present information pointed that the improvement action observed with SGLT2 hampering agents in myocardium of HF may be secondary to direct hampering of the HNE. This results in reduction of intracellular Na^{+}-burden as well as escalated Ca^{2+} uptake by mitochondria in addition to its efflux in the extracellular space (in all probability via NCX action. As a sequel diminished Ca^{2+} quantities as well as more appropriate Ca^{2+} tackling at the time of the heart cycletake place (Kaplan et al., 2018; Sano, 2017). Certain outcomes further indicated that SGLT2 hampering agents directly escalated phosphorylation of myofilaments controlling proteins, independent of modulation of glucose or Ca^{2+} metabolism, thereby diminished myocardial stiffening (Pabel et al., 2018). Furthermore improvement of diastolic impairment was further correlated with its antifibrotic effects which get modulated via the reduction of serum as well as glucocorticoid regulated kinase (SGK1/Enac) profibrotic pathway, that is other considerably expressed along with activated in diabetic hearts (Habibi et al., 2017).

Conversely, decontrolling of metabolic pathways further possesses a significant part in diabetic myocardium undergoing failure. In view of IR, metabolism gets shifted to lipolysis followed by subsequent FA as well as triglycerides (TG) accrual in the cardiomyocytes that accompanied by hampering of glucose oxidation resulting in myocardial steatosis along with cytotoxicity (Kaplan et al., 2018). Furthermore, diminished glucose oxidation results in glucose accrual as well as generation of advanced glycation end-products (AGE) which are implicated in OS in addition to crosslinking of collagen Fibers aiding in myocardial stiffness as well as diastolic impairment (Mudaliar & Smit, 2016). Moreover, mitochondrial impairment exists with the properties of diminished oxidative phosphorylation (OXPHOS) in addition to decreased generation of ATP. In association with FA accrual, they escalate ROS generation resulting in direct cytotoxicity as well as inflammation (Montaigne et al., 2014). SGLT2 hampering agents have been illustrated to directly shift myocardial energy use to KB as well as FFA utilization whereas resulting in FA accrual. KB possesses greater energy efficacy resulting in lesser oxygen utilization, produce lesser ROS, have antioxidant action in addition to sustain mitochondrial intactness; thereby impacting practically full pathophysiological modes leading to escalated myocardial stiffness (Kaplan et al., 2018; Ferranini et al., 2016; Suzuki et al., 2014).

Further than the diabetic state, recently, Youssef et al. (2023) illustrated how SGLT2 hampering agents have possessed the capacity not only in DM but much farther than simple

glycaemic control like abrogate cardiac remodelling, escalate myocardial working, as well as diminish mortality due to heart failure. Additionally, SGLT2- hampering agents possess the capacity of modifications of adipocytes in addition to their generation of cytokines, like adipokines as well as adiponectin, which escalates insulin sensitivity along with postpones diabetes onset. Conversely, SGLT2 hampering agents have been association with reduction of total hip bone mineral deposition as well as escalated hip bone resorption inT2DM patients. Greater outcomes are required to assess the part of SGLT2 hampering agents on cancer. Lastly, the actions of SGLT2- hampering agents on neuroprotection apparently is both direct and indirect, as per to scientific work using different experimental models. SGLT2- hampering agents result in improvement of vascular tone, elasticity, as well as contractility by diminishing oxidative stress, inflammation, insulin signalling pathways, along with endothelial cell proliferation. They further result in improvement of brain working, synaptic plasticity, acetylcholinesterase activity, and decrease amyloid plaque, production as well as control of the mTOR pathway in the brain, which diminishes brain injury in addition to cognitive reduction (Youssef et al., 2023).

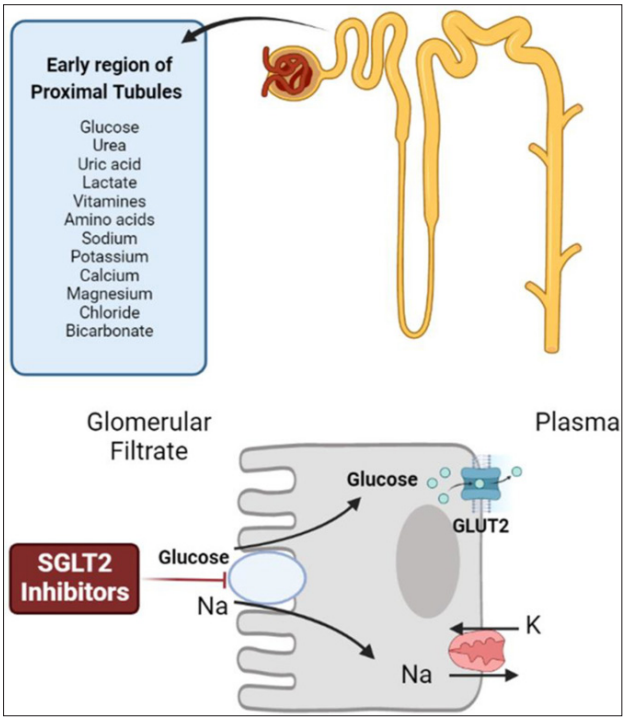

Figure 3.

Courtesy ref no-(Youssef et al., 2023)-. Mechanism of action of SGLT2 inhibitors.

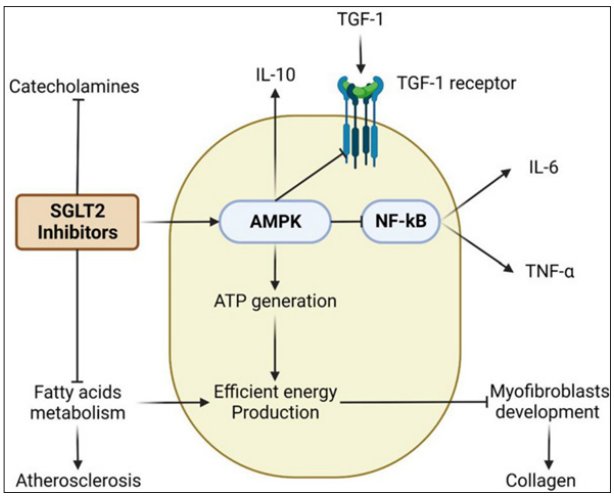

Figure 4

Courtesy ref no-(Youssef et al., 2023) - Cardiac effects of SGLT2 inhibitors.

Extracellular matrix (ECM) in normal Physiology along with Pathophysiological situations in Diabetic Myocardium

Cardiac ECMis a complicated network of collagen as well as elastin fibres, various cell kinds (cardiomyocytes, fibroblast, macrophages leukocytes etc) in addition to macromolecules like glycoproteins along with glycosaminoglycans in addition to growth factors, cytokines as well as extracellular proteases (Wight et al., 2011). ECM is necessary for sustenance of myocardial structure by communicating myocytes, causing alignment of contractile elements, transmitting force along with avoidance of extra extension as well as interference with myocytes (Norton et al., 1996). These days realization has dawned that ECM further possesses significant part in mechanosensing along with mechanotransduction in addition to control of cytoskeleton stress as well as its morphology.

DM possesses considerable action over expression, distribution as well as manipulation of ECM constituents in organs (Law et al., 2012). Escalated collagen laying specifically collagen type 1 along with III is part of the initial morphological changes in diabetic myocardium (Shimizu et al., 1993; Russo & Frangogiannis, 2016; VanHoeven & Factor, 1990). Fibroblasts portray about 2/3rd of the cells in the myocardium, that possess a crucial part in the ECM turnover in view of them being implicated in generation as well as breakdown of ECM constituents. Other populations of cells embedded in matrix might further aid in the profibrotic events by modulating fibroblasts phenotype as well as function (Russo & Frangogiannis, 2016). As conveyed earlier, DM is correlated with cardiomyocytes shifting to fibrinogenic phenotype, having the properties of escalated generation as well as cytokines which stimulate fibroblasts proliferation along with activation in addition to proinflammatory modulators which stimulate fibrosis via activation of immune cells; angiotensin II, TGF-β1, TNF-α,IL-1[24]. Escalated collagen generation in all probability is the maximum significant pathophysiological mode of cardiac fibrosis in DbCM; however, escalated proliferation potential of myocardial fibroblasts has further been revealed in DM patients (Law et al., 2012). Lastly

breakdown of collagen fibres is changed in DM in view of reduced generation along with dysfunctional activity of Matrix Metalloproteinases (Westermann et al., 2007). Reduction in breakdown of collagen fibres aids in collagen accrual as well as ECM fibrosis.

Experimental proof indicates that variable separate modulators might further facilitate in DM correlated fibrosis inclusive of neurohumoral factors, inflammatory cytokines, growth factors as well as endothelin -1, adipokines along with ROS (Kaur et al., 2020). Angiotensin converting enzyme (ACE2) hampering has been displayed to be correlated with decreased collagen laying down along with perivascular fibrosis in various rat models of DbCM (Singh et al., 2008).This pointed that enhanced renin-angiotensin-–aldosterone – system (RAAS) activity found in diabetic myocardium might be implicated in the pathogenesis of DbCM (Senador et al., 2009).

Escalated myocardial fibrosis is the trademark of DbCM; however, all ECM constituents get impacted by DM. Escalated quantities of AGEs might avoid further avoids enzymatic breakdown of collagen (Aronson, 2003; Norton et al., 1996). Escalated proof pointed that AGEs might modulate inflammation, formation of ROS in addition to fibrosis (Russo & Frangogiannis, 2016). Alterations in ECM proteoglycans quantities of, diminished quantities of heparan sulfate as well as escalated quantities of Chondroitin sulfate (CS) along with dermatansulfate (DS) been further documented in DM (Heickendorff et al., 1994).

Crosstalk Amongst cells along with ECM in diabetic myocardium

Continuous exposure of cells takes place to numerous external mechanical along with chemical stimuli, which manipulate their structure as well as working. In contrast to external chemical stimuli that have been acknowledged for long time in the form of robust modulators of cellular structure as well as working, whereas external mechanical stimuli have been only recently considered. Mechanical stimuli might be translated into biochemical signal by an event known as mechanotransduction. The event of mechanosensitivity & mechanotransduction in cardiomyocytes are complicated in view of cardiomyocytes react to external mechanical forces in addition to produce internal mechanical forces also. Cardiomyocytes have been illustrated to react to variable mechanical stimuli inclusive of static as well as dynamic in addition to compressive as well as tensile stress along with shear stress in addition to substrate stiffness (Saucermann et al., 2019). No clarification exists regarding the mode by which sensing of ECM stiffness takes place by cells. Certain investigators posited that in a cell that was static, robustly anchored to ECM constituents, internal as well as external forces get equilibrated. Altering the force balance in either way leads to cell contraction, extension, or translocation (Ingber, 2006). It has been posited that fibroblasts possessed the capacity of utilization of adhesion forces regarding the mechanical characteristics of their milieu (Bershadsky et al., 2006). Dependent on the accessibility of outcomes the maximum significant for mechanosensitivity & mechanotransduction are integrins, focal adhesion, actomyosin contractility as well as mechanosensitive ion channels (Saucermann et al., 2019; Ingber, 2006).

Cytoskeleton portrays a complicated structure implicated in sustenance of cellular shape, internal distribution along with stability in view of its communication with ECM constituents; it possessed the capacity of shifting mechanical stimuli outside in; in addition to inside out. Spread of the cytoskeleton forces to the ECM gets promoted by complexes transmembrane proteins alias integrins along with correlated intracellular constituents. These complexes are further elemental regarding sensing of external mechanical forces (Saucermann et al., 2019). Within the cells integrins are correlated with proteins that associate them to the actin cytoskeleton in addition to signalling proteins required for cardiomyocytes contractility getting modulated (Carter et al., 1990). While outside the cells integrins are correlated with ECM proteins like collagen, laminin as well as fibronectin (Teoh et al., 2012). After binding of cardiac fibroblasts to ECM; integrins collect for generation of complexes known as focal adhesions that are believed tobe an initial mechanosensing organelle (Balaban et al., 2001). It has been illustrated those focal adhesions size is based on mechanical stress: substrate stiffness, on one side as well as conversely cytoskeletal forces on the other side (Lapidos et al., 2004). Apart from integrins multiple proteins take part in communication amongst the cytoskeleton along with ECM constituents like dystrophin, sarcoglycans, dystroglycans, syntrophin, sarcospan as well as caveolin 3 (Crisp et al., 2006). Mechanical stimuli are further transferred to the nucleus of the cell. It has been illustrated that mechanotransduction possesses the capacity of modulating gene expression in fibroblasts (Cadre et al., 1998).

ECM is broadly acknowledged in the form of controller of cytoskeleton stress in addition to its morphology, as well as it has been illustrated that modifications of cells takes place along with sustenance of cytoskeleton of their Mechanical stimuli from ECM (Ingber, 2006). Moreover, as described earlier cardiomyocytes identified from diabetic rats expressed escalated quantities of along with /or activation of adhesion molecule on the cell surface (Qin et al., 2012). This might change the event of mechanosensing, result in precise or escalated cellular reaction to specific ECM stiffness. Thereby escalated myocardial stiffness takes place from a positive feedback loop in which escalated ECM stiffness alterations in cardiomyocytes cytoskeleton, hence aiding in escalated inherent cell stiffness in addition to alteration in their phenotype to greater fibrinogenic. Sequentially ECM fibrosis in addition to ECM stiffness that keep on escalating which further impacts the cardiomyocytes cytoskeleton.

Ion channels which are mechanosensitive, specifically calcium associated are further believed to be in the form of probable pathways by which cardiomyocytes might sense in addition to react to external mechanical burden. Escalated stretching of cells have been displayed to result in downregulation of SERCA2 expression thereby restricting the Ca^{2+}) uptake from the cytosol into the endoplasmic reticulum (Limbu et al., 2015). Sequentially with specifically enhanced stretching

leads to escalated intracellular Ca^{2+} quantities, hence leads to escalated cellular stiffness in view of dysfunctional relaxation (Suarez et al., 2008; Belke et al., 2004). Stretch has been further documented to stimulate an escalation of ROS in an event based on the membrane -bound NADPH Oxidase 2 (Hollekim-Strand et al., 2014).

Probable targets for avoidance along with treatment of diastolic impairment in Diabetes

The cytoskeletal characteristics which generate cell stiffness as well as enhanced ECM stiffness pathological crosstalk amongst them are elements that generate a pathologic vicious cycle resulting in diastolic impairment as well as heart failure. For avoidance along with treatment of DbCM, in an efficacious manner, this vicious cycle needs to be stopped. There are various stages at which probable successful management application might be attempted. Accumulating evidence indicates that nonpharmacological strategies in addition to lifestyle alteration, (weight reduction, stoppage of smoking as well as aerobic exercise) are correlated with promising structural as well as functional cardiac alterations along with HF risk in patients with Diabetes (Hollekim-Strand et al., 2014; Schmidt et al., 2013) Of these aerobic exercises apparently possess the maximum significant part in avoidance of HF. In randomized controlled trial (RCT), it was that aerobic exercises escalate systolic function as well as avoidance of systolic HF, while its actions on diastolic impairment are controversial (Schmidt et al., 2013). Meta-analysis illustrated that aerobic exercises possess the capacity of diastolic impairment in case initiated early in the disease path. It has further been demonstrated that high intensity aerobic exercise was correlated with improvement of diastolic dysfunction in patients with type2 Diabetes mellitus (T2DM) (Hollekim-Strand et al., 2014).

Apart from healthy lifestyle facilitation greater concentration of researchers is on finding pharmacological answers for avoidance along with treatment of diastolic impairment in DM. Quantities of medicine possessing efficacy regarding systolic HF along with improvement of quality of life in such patients are on the rise. Conversely, till now no treatment is accessible for treatment of diastolic HF. Researchers evaluated more common utilized medicines like aldosterone receptor antagonists, angiotensin IIreceptor antagonists, angiotensin convertase hampering agents, β blockers, calcium channels antagonists, statins or their combination which were demonstrated to be efficacious in the treatment of diastolic impairment in animal models did not possess any significant advantages (Chen et al., 2018).

For the avoidance of cardiovascular complications, it is well acknowledged that great glycemic regulation portrays one of the maximum significant effects (Lunder et al., 2019).Rat models studies illustrated that great glycemic regulation is further correlated with lesser Prevalence of DbCM in view of diminished cardiomyocytes hypertrophy in addition to decreased collagen getting deposited (Lunder et al., 2019). With the acknowledged information with regards to the initial targets for avoidance along with treatment of DbCM have been looked amongst anti diabetic medicines. Thus far, certain substances that belong to 2 greater groups SGLT2 hampering agents, along with glucagon like peptide 1(GLP-1) receptor antagonists (GLP-1-RA), have illustrated certain advantages regarding this. Certain SGLT2 hampering agents apparently possess a direct action on the reduction of myocardial stiffness, works antifibrotic, shifting myocardial energy ingestion to KB;thus work with promise in improvement of diastolic impairment (Kaplan et al., 2018; Pabel et al., 2018; Habibi et al., 2017; Ferranini et al., 2016; Suzuki et al., 2014). Regarding 2 of substances; like empagliflozin as well as canagliflozin have been illustrated in large trials regarding decrease of major adverse cardiovascular events (MACE) by 14% in contrast to placebo (Zinman et al., 2015; Neal et al., 2017). Moreover, empagliflozin diminished the number cardiovascular events by 38% (Zinman et al., 2015) whereas number was 13% for canagliflozin (Neal et al., 2017).

Recent updates on advantageous actions of SGLT2-hampering agents

Recently Packer (2022) reviewed the update on the advantageous actions of Sodium –glucose specific cotransporter 2(SGLT2) - hampering agents. SGLT2- hampering agents generate an inimitable fashion of advantageous evolution as well as propagation of cardiomyopathy along with nephropathy, that possesses the properties of diminished oxidative as well as endoplasmic reticulum (ER) stress, mitochondrial health replacement, escalated mitochondrial bio generation, a reduction in proinflammatory as well as profibrotic pathways along with conservation of cellular in addition to organ inherentness along with viability. Considerable validation points that this canonical fashion of reactions might be reasoned out by the actions of SGLT2- hampering agents to facilitate cellular housekeeping by escalating autophagic flux, an action which might be associated with the actions of such agents for generating concomitant upregulation of nutrient deprivation signalling in addition to downregulation of nutrient surplus signalling, the way presenting by an escalation in the expression along with activity of AMP-activated protein kinase(AMPK), Sirtuins (SIRT1), SIRT3 as well as SIRT6, along with Peroxisome Proliferator Activated Receptor γCoactivator -1α(PGC-1α) as well as reduction in activation of mammalian target of rapamycin inhibitors (mTOR) .The unique fashion of cardioprotective as well as renoprotective actions of SGLT2- hampering agents got ameliorated by particular hampering/knockdown of autophagy, AMPK as well as Sirtuins. In the clinical scenario, this design of differentially escalated proteins by Proteomic evaluation of the blood acquired at the time of randomized controlled triasl (RCT), agrees with these observations. Clinical studies have further illustrated that SGLT2- hampering agents facilitate gluconeogenesis, ketogenesis in addition to erythrocytosis as well as diminished uricemia, the emblem of nutrient deprivation signalling as well as the key statistical modulator the capacity of SGLT2- hampering agents for reduction of risk of HF as well as robust renal processes. The effects of SGLT2-hampering agents to exaggerate autophagic flux is found in secluded cells as well as tissue which do not express SGLT2; thereby not exposed to alterations in glucose or ketones in their milieu along with might be associated with the capacity

of these agents to directly bind to sirtuins or mTOR. Alterations in renal or cardiovascular physiology or metabolism can't be reasoned out by the advantageous actions of SGLT2- hampering agents in Clinical scenario / experimental ones. The direct molecular actions of SGLT2- hampering agents in secluded cells agree with the belief that SGLT2 works in the form of nutrient excess sensor, thereby its hampering results in nutrient deprivation signalling with its associated cytoprotective actions which can be attenuated by hampering/ knockdown of autophagy, AMPK as well as ssirtuinssee Fig 4-7.

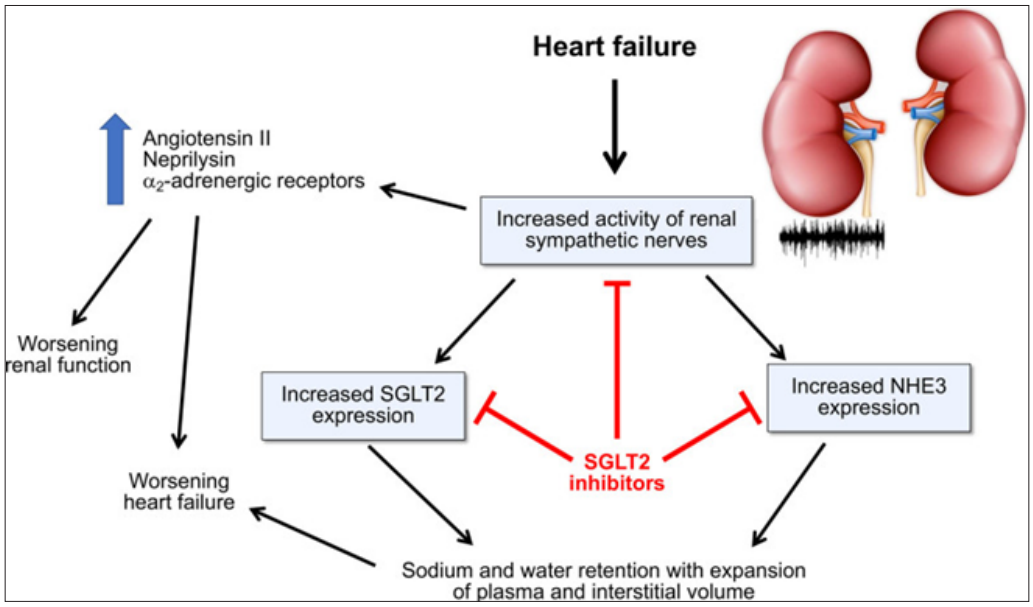

Figure 5

Courtesy ref no- (Packer, 2022)-Proposed framework by which SGLT2 (sodium-glucose cotransporter 2) inhibitors might exert cardio protective and nephroprotective effects by acting to mute renal sympathetic nerve activity and promote natriuresis and osmotic diuresis.

NHE3 indicates sodium-hydrogen exchanger isoform 3.

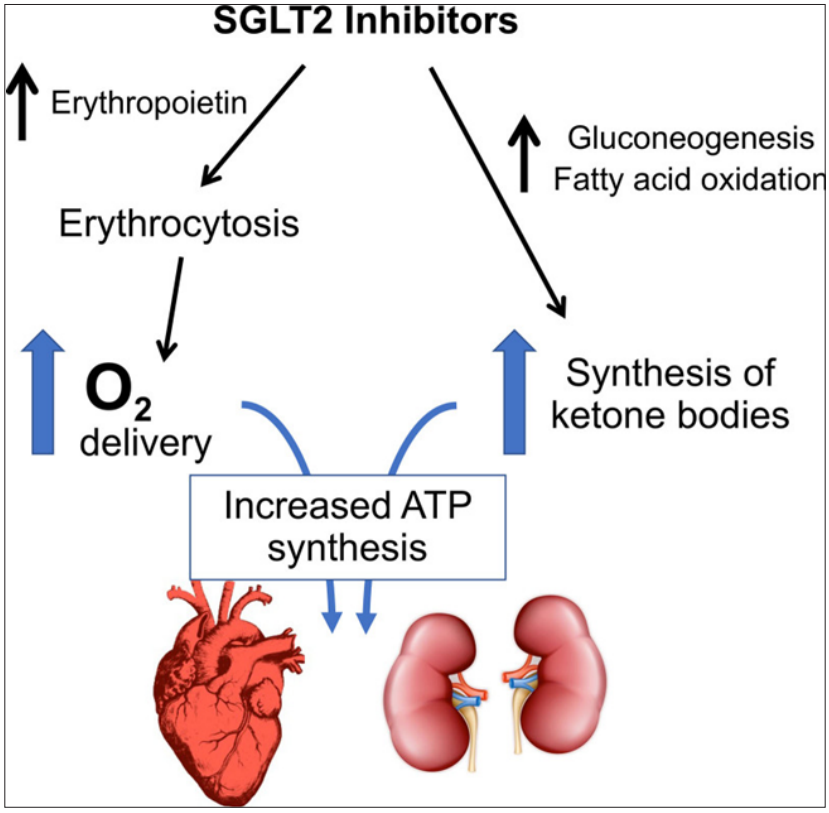

Figure 6

Courtesy ref no- (Packer, 2022)-Proposed framework by which SGLT2 (sodiumglucosecotransporter 2) inhibitors might act to increasedelivery of substrates that could lead to enhanced synthesis of ATP (adenosine triphosphate).

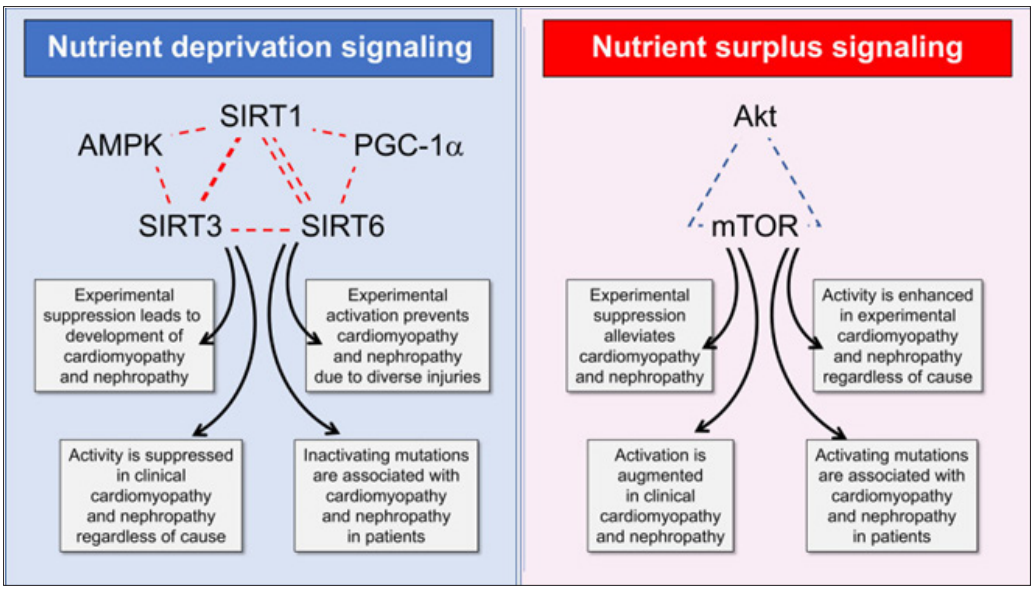

Figure 7

Courtesy ref no- (Packer, 2022) - Effect of nutrient deprivation and nutrient surplus signaling on the evolution and progression of cardiomyopathy and nephropathy in experimental and clinical settings.

Akt indicates protein kinase B; AMPK, adenosine monophosphate–activated protein kinase; mTOR, mammalian target of rapamycin; PGC-1α, peroxisome proliferator–activated receptor γ coactivator 1-α; SIRT1, sirtuin 1; SIRT3, sirtuin 3; and SIRT6, sirtuin 6.

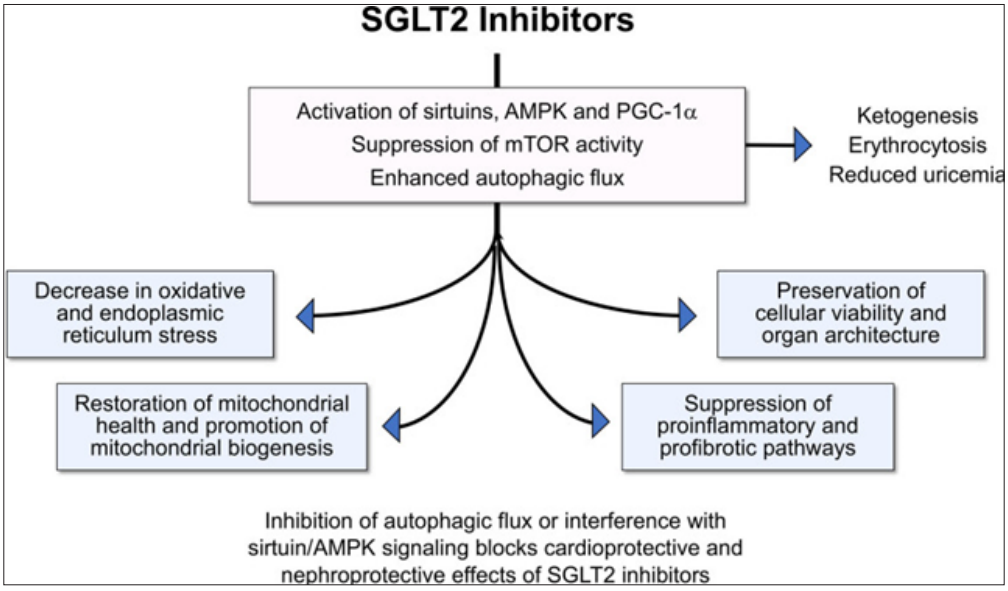

Figure 8

Courtesy ref no-(Packer, 2022)-- Proposed framework by which SGLT2 (sodium-glucose cotransporter 2) inhibitors can modulate nutrient deprivation signaling and thereby enhance autophagic flux and reduce cellular stress.

AMPK indicates adenosine monophosphate–activated protein kinase; mTOR, mammalian target of rapamycin; and PGC-1α, peroxisome proliferator–activated receptor γ coactivator 1-α.

Akin effectiveness in diminished MACE was illustrated in GLP-1-RA; with liraglutide vs semaglutide i.e., 13% as well as 26% respectively in contrast to placebo (Marso et al., 2017; Marso et al., 2016). Liraglutide further diminished cardiovascular mortality in 22% whereas this action was not with semaglutide (Marso et al., 2017). Clarification for these actions is not found till now; however apparently they might be in view of improvement of the endothelial impairment, diminished BP, escalated cardiomyocytes viability hampering of atherosclerosis (Sposito et al., 2018).

With greater insight with regards to pathophysiological modes beneath HF with conserved (≥50%) ejection fraction (HFpEF) escalates, greater attention gets concentrated on medicines which disrupts events resulting in DbCM. Thereby the lack of NO in cardiomyocytes in addition to coronary endothelium has caught great attention. Riociguat along with Vericiguat are direct stimulators of soluble guanylate cyclase resulting in escalated, generation of cyclic guanosine monophosphate (cGMP) that escalates NO bioavailability leading systemic as well as pulmonary vasodilation. Moreover, riociguat confers cardiovascular protection other than NO bioavailability since it decreases cardiac fibrosis, diminishes left ventricular mass in addition to atrial natriuretic peptide (ANP) quantities in animal models of hypertension (Sharkovska et al., 2010). There is restriction of number of studies on them on HF; however it has been illustrated that riociguat results in improvement of HF with decreased (<40%) ejection fraction (HFrEF) (Bonderman et al., 2013). Conversely, the first study on vericiguat in patients with HFpEF , illustrated improvement of QOL; however was not correlated with improved plasma quantities of N-terminal pro hormone of brain natriuretic peptide(NT- pro BNP) or with Ultrasonographic paradigm of diastolic impairment (Pieske et al., 2017).

Inflammation possesses a significant part in the pathogenesis of DbCM, which makes medicines utilized for diminishing systemic inflammation a remarkably intriguing probable target for confer protection along with treatment of DbCM. Cardiac function studies in patients with Rheumatoid Arthritis who received treatment with interleukin-1 receptor blocker by anakinra displayed improvement of myocardial contractility in addition to relaxation just after single dose of this medicine. Moreover, anakinra delivery was correlated with improvement of the coronary flow reserve as well as brachial artery flow modulated dilation (FMD) just after 3 hrs of delivery (Ikonomidis et al., 2008). One more study reported that interleukin-1β blockade avoided further worsening of myocardial systolic / diastolic function after myocardial infarction (MI) in animal model (Toldo et al., 2014). The first RCT with regards to assessment of correlation amongst anakinra along with HFpEF: in patients with escalated paradigms of systemic inflammation has not been completed. Van Tassel et al. (2017) are contrasting anakinra actions (until 12wks) with placebo regarding Clinical paradigms. Cardiovascular processes and ultrasonographic paradigm of diastolic impairment as well as FMD. Although this study was inclusive of 30 patients, its awaited outcomes would be intriguing. In view of DM possesses escalated systemic inflammation, it might be anticipated that anti-inflammatory substances might be possessing greater profound action in contrast to non-diabetic people (Van Tassel et al., 2017).

More recently, of the newer agents in HFrEF; like angiotensin receptor neurolysin hampering agents (ARNi), have further been posited for HFpEF treatment. natriuretic peptides (NP) possess cardioprotective action by hampering RAAS decreasing sympathetic drive with extra antiproliferative in addition to antihypertrophic actions. Breakdown of NP processing takes place by 2 modes- neprilysin-an enzyme for Breakdown ii) NP receptor modulated clearance. Sequentially neurolysin hampering leads to escalated NP quantities. Conversely, once RAAS hampering takes place by angiotensin receptor blockers; this effect gets escalated with NP's thus giving the rationale for total blockade (Van Tassel et al., 2017). In case of HFpEF ARNi apparently possess a part since they escalate quantities of cGMP in the cardiomyocytes via direct in activation of NP receptors. This leads to escalated phosphorylation of titin; specifically, N2B isoform with a sequential diminished cardiomyocytes stiffness (Gori et al., 2019). The of ARNi in DbCM has been illustrated in STZ rats that received combination treatment telmisartan along with thiorphan, this thiorphan being a neprilysin hampering agent. Positive protective actions were displayed in this study via diminished inflammation, antifibrotic effect in addition to anti apoptotic effect with extra reverting of histone acetylation in rat hearts (Malek & Gaekwad, 2019).

Conclusions

HF comprises the main reason for hospitalization as well as significant anticipator of escalated mortality in patients with DM. DbCM constitutes a significant etiology of HF in diabetic patients; however its pathophysiological insight has not been attained thus far. That in all probability remains the absence of efficacious avoidance along with treatment approaches.

Here we posited the probable pathophysiological modes implicated in myocardial hypertrophy as well as myocardial stiffness resulting in diastolic impairment in patients with Diabetes. This model is dependent on the acknowledgement regarding vascular stiffness pathophysiology in view of the thought that akin elemental event leads to myocardial stiffness. Dependent on the accessible results, one can presume that changed mechanical characteristics of myocardium in DbCM are not alone responsible for alterations in ECM however further to alterations in inherent mechanical characteristics of cardiomyocytes. Since these 2 issues crosstalk in sustenance myocardial structure as well as function; it is posited that their crosstalk further alters in patients with type2 Diabetes; thereby further facilitating generation of cellular in addition to ECM stiffness. There is a probability that by itself DM is the maximum significant factor impacting cellular in addition to ECM stiffness; nevertheless, different other modes need to be taken into account .Of these most significant factors are dysfunctional myocardial NO pathway, coronary microvascular impairment , escalated ,OS, as well as SGLT2 modulated actions .

Greater insight with regards to all the implicated in the pathophysiology of as well as propagation of DbCM would aid in better therapeutic strategies. These newer revelations regarding SGLT2- hampering agents might aid in better treatment in combination with modulation of the Epigenetic modifications as well as miRdetailedin our previous article on DbCM.

References

1. Ghosh, N., Chacko, L., Bhattacharya, H., Vallamkondu, J., Nag, S., Dey, A., Karmakar, T., Reddy, P. H., Kandimalla, R., & Dewanjee, S. (2023). Exploring the complex Relationship Diabetes and cardiovascular complications: understanding Diabetic cardiomyopathy and promising therapies. *Biomedicines, 11*(4), 1126. DOI: https://doi.org/10.3390/biomedicines11041126
2. Boonman-de Winter, L. J., Rutten, F. H., Cramer, M. J., Landman, M. J., Liem, A. H., Rutten, G. E. H. M., & Hoes, A. W. (2012). High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type2Diabetes. *Diabetologia, 55*(8), 2154-62. DOI: https://doi.org/10.1007/s00125-012-2579-0
3. Thrainsdottir, I. S., Aspelund, T., Thorgeirsson, G., Gudnason, V., Hardarson, T., Malmberg, K., Sigurdsson, G., & Rydén, L. (2005). The association between glucose abnormalities and Heart failure in the population based Reykjavic study. *Diabetes Care, 28*(3), 612-6. DOI: https://doi.org/10.2337/diacare.28.3.612
4. Kannel, W. B., Hjortland, M., & Castelli, W. P. (1974). Role of Diabetes in congestive Heart failure: the Framingham Heart Study. *Am J Cardiol, 34*(1), 29-34. DOI: https://doi.org/10.1016/0002-9149(74)90089-7
5. Deedwania, P. C., Giles, T. D., Klibaner, M., Ghali, J. K., Herlitz, J., Hildebrandt, P., Kjekshus, J., Spinar, J., Vitovec, J., Stanbrook, H., & Wikstrand, J. (2005). Efficacy, safety and tolerability of metoprolol CR/XLin patients with Diabetes and chronic heart failure: experiences from MERIT-HF. *Am Heart J, 149*(1), 159-67. DOI: https://doi.org/10.1016/j.ahj.2004.05.056
6. Authors/Task Force Members, McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J. G. F., Coats, A. J. S, Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma, T. N….. et al., Kathrine Skibelund, A. (2013). ESC Guidelines on Diabetes, prediabetes, and cardiovascular disease of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the study of Diabetes (EASD). *Eur Heart J, 34*(39), 3035-87. DOI: https://doi.org/10.1093/eurheartj/eht108
7. Dandamudi, S., Slusser, J., Mahoney, D. W., Redfield, M. M., Rodeheffer, R. J., & Chen, H. H. (2014). The prevalence of Diabetic cardiomyopathy: a population based study in Olmsted County, Minnesota. *J Card Fail, 20*(5), 304-9. DOI: https://doi.org/10.1016/j.cardfail.2014.02.007
8. Schannwell, C. M., Schneppenheim, M., Perings, S., Plehn, G., & Strauer, B. E. (2002). Left ventricular diastolic dysfunction as an early manifestation of Diabetic cardiomyopathy. *Cardiology, 98*(1-2), 33-9. DOI: https://doi.org/10.1159/000064682
9. Shimizu, M., Umeda, K., Sugihara, N., Yoshio, H., Ino, H., Takeda, R., Okada, Y., & Nakanishi, I. (1993). Collagen remodelling inmyocardia of patients with Diabetes. *J Clin Pathol, 46*(1), 32-6. DOI: https://doi.org/10.1136/jcp.46.1.32
10. Van Heerebeek, L., Franssen, C. P., Hamdani, N., Verheugt, F. W., Somsen, G. A., & Paulus, W. J. (2012). Molecular and cellular basis for diastolic dysfunction. *Curr Heart Fail Rep, 9*(4), 293 -302. DOI: https://doi.org/10.1007/s11897-012-0109-5
11. Galderisi, M. (2005). Diastolic dysfunction and diastolic heart failure: diagnostic, prognostic and therapeutic aspects. Cardiovasc Ultrasound, 3, 9. DOI: https://doi.org/10.1186/1476-7120-3-9
12. Gottlieb, I., Macedo, R., Bluemke, D. A., & Lima, J. A. (2006). Magnetic resonance imaging in the evaluation of non- ischemic cardiomyopathies: current application and future perspectives. *Heart Fail Rev, 11*(4), 313 -23. DOI: https://doi.org/10.1007/s10741-006-0232-z
13. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2021). Role of Adipocyte impairment in Heart Failure Induction in subjects that are obese along with prediabetes and overt Diabetes mellitus -A Systematic Review. J *Cardiol & Card Disord, 2*(2), 1-21. Retrieved from https://unisciencepub.com/storage/2021/07/Role-of-Adipocyte-Impairment-in-Heart-Failure-Induction-in-Subjects.pdf
14. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2022). An Update on the Risk Factors Correlating NAFLD with Cardiovascular Disease: Specifically Mitochondrial- Fatty Acids β Oxidation in Liver with Therapeutic Approaches of Avoidance of CVD Associated Mortality-ASystematic Review. *J Endocrinol, 6*(1), 000164. DOI: 10.23880/oaje-16000164
15. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2021). Potential role of Epigenetic Modulation in prevention or therapy for Diabetic Kidney Disease-still a dream or a reality –A Systematic Review. *J Diab Nephro Diab Mgmt, 1*(1), (1-26). Retrieved from https://snipub.com/wp-content/uploads/2021/05/SNI-JDNDM-21-01.pdf
16. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2022). Diabetic Cardiomyopathy: An Update on its Pathophysiology with Specific Emphasis on Epigenetics Modifications Besides Treatment-A systematic review. BOHR International *Journal of Current Research in Diabetes and Preventive Medicine, 1*(1), 1–16. DOI: https://doi.org/10.54646/bijrdpm.001
17. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2019). Advantage of Cardiovascular Outcome Trials (CVOT's) for SGLT2 (Sodium Glucose Transporter 2) Inhibitors in Type 2 Diabetes Mellitus (T2 DM). *EC Endocrinology and Metabolic Research, 4*(9), 38-44.
18. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2020). Optimizing cardiovascular outcome in Type 2 diabetes mellitus with better control of diabetes mellitus with empigliflozin and hypertension with renin angiotensin system inhibitors and manidipine preferably of the dihydropyridones. *Obes Res Open J. 7*(1), 13-25. DOI: http://dx.doi.org/10.17140/OROJ-7-141
19. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2023). Are we any Close to Utilizing Targeting SIRT Signaling Pathway for Enhancing the Oocyte Quality in Women with Advanced Maternal age: Bringing from Bench to Bedside: A Narrative Review. *J Gynaecol,8*(1), 1-17- DOI: 10.23880/oajg-16000257.

20. Kaur, K. K., Allahbadia, G. N., & Singh, M. (2021). Targeting macrophage Polarization for therapy of Diabesity –The feasibility of early improvement of insulin sensitivity and insulin resistance -a comprehensive systematic review. *World Journal of Advance Healthcare Research, 8*(1), 6- 25. DOI: https://doi.org/10.15406/jdmdc.2021.08.00216
21. Kaur, K. K., Allahbadia, G. N., & Singh M. (2022). An update on Mechanistic Modes in AGEs Stimulated & ER and Inflammatory Stress- Modulated Control of the GLUT4 expression(SLC2A4 promoted)and Atherogenesis in Diabetes mellitus -A Narrative review. *Mathews J Cytol Histol, 6*(1), 21. Retrieved from https://www.mathewsopenaccess.com/scholarly-articles/an-update-on-mechanistic-modes-in-ages-stimulated-er-and-inflammatory-stress-modulated-control-of-the-glut4-expression-slc2a4-promoted-and-atherogenesis-in-diabetes-mellitus-a-narrative-review.pdf
22. Nikolajevic Starcevic, J., Janic, M., & Sabovic, M. (2019). Molecular mechanisms responsible for diastolic dysfunction in Diabetes mellitus patients. *Int J Mol Sci, 20*(5), 1197. DOI: https://doi.org/10.3390%2Fijms20051197
23. Depre, C., Young, M. E., Ying, J., Ahuja, H. S., Han, Q., Garza, N., Davies, P. J., & Taegtmeyer, H. (2000). Streptozocin-induced changes in cardiac gene expression in the absence of severe contractile dysfunction. *J Mol Cell Cardiol, 32*(6), 985-96. DOI: https://doi.org/10.1006/jmcc.2000.1139
24. Wilson, A. J., Gill, A. K., Abudalo, R. A., Edgar, K. S., Watson, C. J., & Grieves, D. J. (2018). Reactive oxygen species signaling in the Diabetic heart: emerging prospect of therapeutic targeting. *Heart, 104*(4), 293-9. DOI: https://doi.org/10.1136/heartjnl-2017-311448
25. Russo, I., & Frangogiannis, N. G. (2016). Diabetes associated cardiac fibrosis. Cellular effectors, molecular mechanisms and therapeutic opportunities. *J Mol Cell Cardiol*, 90, 84-93. Retrieved from https://pubmed.ncbi.nlm.nih.gov/26705059/
26. Weber, K. T., Sun, Y., Tyagi, S. C., & Cleutjens, J. P. (1994). Collagen network of the myocardium: function, structural remodelling and regulatory mechanisms. *J Mol Cell Cardiol, 26*(3), 279-92. DOI: https://doi.org/10.1006/jmcc.1994.1036
27. Fomovsky, G. M., Thomopoulos, S., & Holmes, J. W. (2010). Contribution of extracellular matrix to the mechanical properties of the heart. *J Mol Cell Cardiol, 48*(3), 490-6. DOI: https://doi.org/10.1016/j.yjmcc.2009.08.003
28. Van Hoeven, K. H., & Factor, S. M. (1990). A comparison of the pathological spectrum of hypertensive, diabetic and hypertensive diabetic heart disease. *Circulation, 82*(3), 848-55. DOI: https://doi.org/10.1161/01.cir.82.3.848
29. Weber, K. T., Brilla, J., & Janicki, J. S. (1993). Myocardial fibrosis: functional significance and regulatory factors. *Cardiovasc Res, 27*(3), 341-8. DOI: https://doi.org/10.1093/cvr/27.3.341
30. Berg, T. J., Snorgaard, O., Faber, J., Torjesen, P. A., Hildebrandt, P., Mehlsen, J., & Hanssen, K. F. (1999). Serum levels of advanced glycation end-products are associated with left ventricular diastolic dysfunction in patients with type1Diabetes. *Diabetes Care, 22*(7), 1186-90. DOI: https://doi.org/10.2337/diacare.22.7.1186
31. Aronson, D. (2003). Cross linking of glycated collagen in the pathogenesis of arterial and myocardial stiffening of ageing and Diabetes. *J Hypertens, 21*(1), 3-12. DOI:https://doi.org/10.1097/00004872-200301000-00002
32. Norton, G. R., Candy, G., & Woodiwiss, A. J. (1996). Aminoguanidine prevents decreased myocardial compliance produced by Streptozocin-induced Diabetes. *Circulation, 93*(10), 1905-12. DOI: https://doi.org/10.1161/01.cir.93.10.1905
33. Riehle, C., & Bauersachs, J. C. (2018). Of mice and men: models and mechanisms of Diabetic cardiomyopathy. *Basic Res Cardiol, 114*(1), 2. DOI: https://doi.org/10.1007%2Fs00395-018-0711-0
34. Hao, P. P., Yang, J. M., Zhang, M. X., Zhang, K., Chen, Y. G., Zhang, C., & Zhang, Y. (2015). Angiotensin-(1-7) treatment mitigates right ventricular fibrosis as distinctive feature of Diabetic cardiomyopathy. *Am J Physiol Heart Circ Physiol, 308*(9), H1007- H1019. DOI: https://doi.org/10.1152/ajpheart.00563.2014
35. Haider, B., Yeh, C. K., Thomas, G., Ooldwurtel, H. A., Lyons, M. M., & Regan, T. J. (1981). Influence of Diabetes on the myocardium and coronary arteries of rhesus monkeys fed an Atherogenic diet. *Circ Res, 49*(6), 1278-88. DOI: https://doi.org/10.1161/01.res.49.6.1278
36. Basu, R., Oudit, G. Y., Wang, X., Zhang, L., Ussher, J. R., Lopaschuk, G. D., & Kassiri, Z. (2009). Type1 Diabetic cardiomyopathy in the Akita (Ins 2WT/C96Y) mouse model is characteristized by lipotoxicity and diastolic dysfunction with preserved systolic function. *Am J Physiol Heart Circ Physiol, 297*(6), H2096- H2108. DOI: https://doi.org/10.1152/ajpheart.00452.2009
37. Sloan, C., Tuinei, J., Nemetz, K., Frandsen, J., Soto, J., Wride, N., Sempokuya, T., Alegria, L., Bugger, H., & Abel, E. D. (2011). Central leptin signaling is required to normalize fatty acids oxidation rates in caloric restricted ob/ob mice. *Diabetes, 60*(5), 1424-34. DOI: https://doi.org/10.2337/db10-1106
38. Boudina, S., Bugger, H., Sena, S., O'Neill, B. T., Zaha, V. G., Ilkun, O., Wright, J. J., Mazumder, P. K., Palfreyman, E., Tidwell, T. J., Theobald, H., Khalimonchuk, O., Wayment, B., Sheng, X., Rodnick, K. J., Centini, R., Chen, D., Litwin, S. E., Weimer, B. E., & Abel, E. D. (2009). Contribution of impaired myocardial signaling to mitochondrial dysfunction and Oxidative stress in the heart. *Circulation, 119*(9), 1272-83. DOI: https://doi.org/10.1161/circulationaha.108.792101
39. Benech, J. C., Benech, N., Zambrana, A. I., Rauschert, I., Bervejillo, V., Oddone, N., Damián, J. P. (2014). Diabetes increases stiffness of live cardiomyocytes measured by Atomic force microscopy nano indentation. *Am J PhysiolCell Physiol, 307*(10), C910- C919. DOI: https://doi.org/10.1152/ajpcell.00192.2013
40. van Heerebeek, L., Hamdani, N., Handoko, M. L., Falcao-Pires, I., Musters, R. J., Kupreishvili, K., Ijsselmuiden,

A. J., Schalkwijk, C. G., Bronzwaer, J. G., Diamant, M., Borbély, A., van der Velden, J., Stienen, G. J., Laarman, G. J., Niessen, H. W., & Paulus, W. J. (2008). Diastolic stiffening of the failing heart: importance of fibrosis, advanced glycation end products and resting tension. *Circulation, 117*(1), 43-51. DOI: https://doi.org/10.1161/circulationaha.107.728550

41. Fletcher, D. A., & Mullins, R. D. (2007). Cell membrane and cytoskeleton. *Nature, 463*(7280), 485-92. DOI: https://doi.org/10.1038%2Fnature08908
42. Kuznetsova, T. G., Starodubtseva, M. N., Yegorenkov, N. I., Chizhik, S. A., & Zhddanov, R. I. (2007). Atomic force microscopy and cell elasticity. *Micron, 38*(8), 824-33. DOI: https://doi.org/10.1016/j.micron.2007.06.011
43. Boudina, S., & Abel, E. D. (2007). Diabetic cardiomyopathy revisited. *Circulation, 115*(25), 3213-23. DOI: https://doi.org/10.1161/circulationaha.106.679597
44. Bers, D. M. (2008). Calcium cycling and signaling in cardiac myocytes. *AnnuRev Physiol*, 70, 23-49. DOI: https://doi.org/10.1146/annurev.physiol.70.113006.100455
45. Suarez, J., Scott, B., & Dillmann, W. H. (2008). Conditional increase in SERCA2 protein is able to reverse contractile dysfunction and abnormal calcium function is established Diabetic cardiomyopathy. *Am J Physiol Reg Integr Comp Physiol, 295*(5), R1439-R1445. DOI: https://doi.org/10.1152%2Fajpregu.00736.2007
46. Hopf, A. E., Andresen, C., Kötter, S., Isić, M., Ulrich, K., Sahin, S., Bongardt, S., Röll, W., Drove, F., Scheerer, N., Vandekerckhove, L., De Keulenaer, G. W., Hamdani, N., Linke, W. A., & Krüger, M. (2018). Diabetes – induced cardiomyocyte passive stiffening is caused by impaired insulin dependent titin modification can be modulated by neuregulin 1. Circ Res, 123(3), 1661-74. DOI: https://doi.org/10.1161/circresaha.117.312166
47. Farah, C., Michael, L. Y. M., & Balligrand, J. L. (2018). Nitric oxide signaling in cardiovascular health and disease. *Nat Rev Cardiol, 15*(5), 292-316. DOI: https://doi.org/10.1038/nrcardio.2017.224
48. Khanna, S., Singh, G. B., & Khullar, M. (2014). Nitric oxide synthases and Diabetic cardiomyopathy. *Nitric oxide*, 43, 29-34. DOI: https://doi.org/10.1016/j.niox.2014.08.004
49. Jia, G., Hill, M. A., & Sowers, J. R. (2018). Diabetic cardiomyopathy: an update of mechanisms contributing to the Clinicalentity. *Circ Res, 122*(14), 624-38. DOI: https://doi.org/10.1161/circresaha.117.311586
50. Liu, Q., Wang, S., & Cai, L. (2014). Diabetic cardiomyopathy and its mechanisms: role of Oxidative stress and damage. *J Diabetes Investig, 5*(6), 623-34. DOI: https://doi.org/10.1111%2Fjdi.12250
51. Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circ Res, 107*(9), 1058-70. DOI: https://doi.org/10.1161/circresaha.110.223545
52. Takano, H., Zou, Y., Hasegawa, H., Akazawa, H., Nagai, T., & Komuro, I. (2003). Oxidative stress induced signal transduction pathways in cardiac myocytes: involvement of ROS in heart diseases. *AntiOxidRedox Signal, 5*(6), 789-94. DOI: https://doi.org/10.1089/152308603770380098
53. Varga, Z. V., Giricz, Z., Liaudet, L., Hiaudet, G., Ferdinandy, P., & Pacher, P. (2015). Interplay of Oxidative, nitrosative / nitrosative stress, inflammation, cell death and autophagy in Diabetic cardiomyopathy. *Biochim Biophys Acta, 1852*(2), 232-42. DOI: https://doi.org/10.1016/j.bbadis.2014.06.030
54. King, M. K., Coker, M. L., Goldberg, A., Mc Elmurray, J. H. 3rd., Gunasinghe, H. R., Mukherjee, R., Zile, M. R., O'Neill, T. P., & Spinale, F. G. (2003). Selective Matrix Metalloproteinase inhibition with developing heart failure: effects on left ventricular function and structure. *Circ Res, 92*(2), 177-85. DOI: https://doi.org/10.1161/01.res.0000052312.41419.55
55. Cai, L., & Kang, Y. J. (2003). Cell death and Diabetic cardiomyopathy. *Cardiovasc Toxicol, 3*(3), 219-28. DOI: https://doi.org/10.1385/ct:3:3:219
56. Eckhouse, S. R., & Spinale, F. G. (2012). Changes in the myocardial interstitium and contribution to the progression of heart failure. *Heart Fail Clin, 8*(1), 7-20. DOI: https://doi.org/10.1016%2Fj.hfc.2011.08.012
57. Diamant, M., Lamb, H. J., Smit, J. W. A., de Roos, A., & Heine, R. J. (2005). Diabetic cardiomyopathy in uncomplicated type2 Diabetes is associated with the Metabolic Syndrome(MetS) and systemic inflammation. *Diabetologia, 48*(8), 1669-70. DOI: https://doi.org/10.1007/s00125-005-1821-4
58. Taqueti, V. R., Solomon, S. D., Shah, A. M., Desai, A. S., Groarke, J. D., Osborne, M. T., Hainer, J., Bibbo, C. F., Dorbala, S., Blankstein, R., & Di Carli, M. F. (2018). Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J, 39*(10), 840-9. DOI: https://doi.org/10.1093/eurheartj/ehx721
59. Lorenzo, O., Picastoste, B., Ares Carrasco, S., Ramirez, E., Egido, J., & Tunos, J. (2011). Potential role of nuclear factor κB in Diabetic cardiomyopathy. *Mediat Inflamm*, 2011, 652097. DOI: https://doi.org/10.1155/2011/652097
60. Jia, G., De Marco, V. G., & Sowers, J. R. (2016). Insulin resistance and hyperinsulinemia in Diabetic cardiomyopathy. *Nat Rev Endocrinol, 12*(3), 144-53. DOI: https://doi.org/10.1038/nrendo.2015.216
61. Kibel, A., Selthofer-Relatic, K., Drenjancevic, I., Bacun, T., Bosnjak, I., Kibel, D., & Gros, M. (2017). Coronary microvascular function in Diabetes mellitus. *J Int Med Res, 45*(6), 1901-29. DOI: https://doi.org/10.1177/0300060516675504
62. Paulus, W. J., & Tshoppe, C. (2013). A novel paradigm of heart failure with preserved ejection fraction: co-morbidities drive myocardial dysfunction and remodeling through Coronary microvascular and endothelial inflammation. *J Am Coll Cardiol, 62*(4), 263-71. DOI: https://doi.org/10.1016/j.jacc.2013.02.092
63. Kaplan, A., Abidi, E., El-Yazbi, A., Eid, A., Booz, G. W., & Zouein, F. A. (2018). Direct cardiovascular impact of SGLT2 inhibitors: mechanisms and effects. *Heart Fail Rev, 23*(3), 419-37. DOI: https://doi.org/10.1007/s10741-017-9665-9

64. Taegetmyer, H. (1994). Eenergy diabetic metabolism of the heart: from basic concepts to Clinical applications. *Curr Prob Cardiol, 19*(2), 59-113. DOI: https://doi.org/10.1016/0146-2806(94)90008-6
65. Isfort, M., Stevens, S. C., Schafer, S., & Jong, C. J. (2014). Metabolic dysfunction in Diabetic cardiomyopathy. *Heart Fail Rev, 19*(1), 35-48. DOI: https://doi.org/10.1007/s10741-013-9377-8
66. Szablewski, L. (2017). Glucose transporters in healthy heart and in cardiac disease. *Int J Cardiol*, 230, 70-5. DOI: https://doi.org/10.1016/j.ijcard.2016.12.083
67. Barger, P. M., Brandt, J. M., Leone, T. C., Weinheimer, C. J., & Kelly, D. P. (2000). Deactivation Peroxisome Proliferator Activated Receptor alpha during cardiac hypertrophic growth. *J Clin Investig, 105*(12), 1723-30. DOI: https://doi.org/10.1172/jci9056
68. Kraegen, E. W., Sowden, J. A., Halstead, M. B., Clark, P. W., Rodnick, K. J., Chisholm, D. J., & James, D. E.(1993). Glucose transporters glucose transporter and in vivo glucose uptake in skeletal and cardiac muscle: fasting insulin stimulation and immuno isolation studies of GLUT1 and GLUT4. *Biochem J*, 295 (Pt 1), 287-93. DOI: https://doi.org/10.1042/bj2950287
69. Banerjee, S. K., Mc Gaffin, K. R., Pastor-Soler, N. M., & Ahmad, F. (2009). SGLT1 is a novel glucose transporter that is perturbed in disease states. *Cardiovasc Res, 84*(1), 111 -8. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2741348/
70. Garvey, W. T., Hardin, D., Juhanszova, M., & Dominguez, J. H. (1993). Effects of Diabetes on myocardial glucose transport systems in rats: implications for Diabetic cardiomyopathy. *Am J Physiol*, 264(3 Pt 2), H 837- H 844. DOI: https://doi.org/10.1152/ajpheart.1993.264.3.h837
71. Stratmann, B., & Tshoepe, D. (2011). The diabetic heart: sweet, fatty and stressed. *Expert Rev Cardiovasc Ther, 9*(9), 1093-6. DOI: http://dx.doi.org/10.1586/erc.11.109
72. Schwenk, R. W., Lilken, J. J., Bonen, A., & Glatz, J. F. (2008). Regulation of sarcolemma glucose and fatty transporters in cardiac disease. *Cardiovasc Res, 79*(2), 249-58. DOI: https://doi.org/10.1093/cvr/cvn116
73. Lopaschuck, G. D., Ussher, J. R., Folmes, C. D., Jswal, J. S., & Stanley, W. C. (2010). Myocardial fatty acids metabolism in health and disease. *Physiol Rev, 90*(1), 207-58. DOI: https://doi.org/10.1152/physrev.00015.2009
74. Lee, W. S., & Kim, J. (2017). Diabetic cardiomyopathy: where we are and where we are going. Korean *J Intern Med, 32*(3), 404-21. DOI: https://doi.org/10.3904%2Fkjim.2016.208
75. Chatham, J. C., & Forder, J. (1993).A 13CNMRstudy 0f glucose oxidation in the intact functioning rat heart following Diabetes induced cardiomyopathy. *J Mol Cell Cardiol, 25*(10), 1203-13. DOI: https://doi.org/10.1006/jmcc.1993.1133
76. Laffel, L. (1999). Ketone bodies (KB): A review of physiology, pathophysiology and application of monitoring to Diabetes. *Diabetes Metab Res Rev, 15*(6), 412-26. DOI:https://doi.org/10.1002/(sici)1520-7560(199911/12)15:6%3C412::aid-dmrr72%3E3.0.co;2-8
77. Wentz, A. E., d'Avignon, D. A., Weber, M. L., Cotter, D. G., Doherty, J. M., Kerns, R., Nagarajan, R., Reddy, N., Sambandam, N., & Crawford, P. A. (2010). Adaptation of myocardial substrate metabolism to a ketogenic nutrient environment. *JBiol Chem, 285*(32), 24447-56. DOI: https://doi.org/10.1074/jbc.m110.100651
78. Wang, J., Song, Y., Wang, Q., Kralik, P. M., & Epstein, P. N. (2006). Causes and characteristics of Diabetic cardiomyopathy. *Rev Diabet Stud, 3*(3), 108-17. DOI: https://doi.org/10.1900/rds.2006.3.108
79. Sharma, V., & Mc Neill, J. H. (2006). Diabetic cardiomyopathy: Where are we 40yearslater. *Can J Cardiol, 22*(4), 305-8. DOI: https://doi.org/10.1016/s0828-282x(06)70914-x
80. Lambert, R., Srodulski, S., Peng, X., Margulies, L. B., Despa, F., & Despa, S. (2015). Intracellular Na^+ concentration ([Na^{+-}])is elevated in diabetic hearts due to enhanced - Na^+ - glucose cotransport. *J Am Heart Assoc, 4*(9), e002183. DOI: https://doi.org/10.1161/jaha.115.002183
81. Sano, M. (2017). Haemodynamic Sodium –glucose specific cotransporter inhibitors. *J Clin Med Res, 9*(6), 457-60. DOI: https://doi.org/10.14740%2Fjocmr3011w
82. Pabel, S., Wagner, S., Bollenberg, H., Bengel, P., Kovács, Á., Schach, C., Tirilomis, P., Mustroph, J., Renner, A., Gummert, J., Fischer, T., Van Linthout, S., Tschöpe, C., Streckfuss-Bömeke, K., Hasenfuss, G., Maier, L. S., Hamdani, N., & Sossalla, S.(2018). Empagliflozin directly improves cardiac diastolic dysfunction in human heart failure. *Eur J Heart Fail, 20*(12), 1690-1700. DOI: https://doi.org/10.1002/ejhf.1328
83. Habibi, J., Aroor, A. R., Sowers, J. R., Jia, G., Hayden, M. R., Garro, M., Baroon, B., Mayoux, E., Rector, R. S., Whaley- Connell, A., & DeMarco, V. G. (2017). Sodium –glucose specific cotransporter 2(SGLT2) inhibition and Empagliflozin improves diastolic dysfunction in a female rodent model of Diabetes. *Cardiovasc Diabetol*, 16, 9. DOI: https://doi.org/10.1186%2Fs12933-016-0489-z
84. Mudaliar, S., Alloju, S., Henry, R. R. (2016). Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. *Diabetes Care, 39*(7), 1115-22. DOI: https://doi.org/10.2337/dc16-0542
85. Montaigne, D., Marechal, X., Coisne, A., Debry, N., Modine, T., Fayad, G., Potelle, C., El Arid, J. M., Mouton, S., Sebti, Y., Duez, H., Preau, S., Remy-Jouet, I., Zerimech, F., Koussa, M., Richard, V., Neviere, R., Edme, J. L., Lefebvre, P., & Staels, B. (2014). Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type2 but not in obese patients. *Circulation, 130*(7), 554-64. DOI: https://doi.org/10.1161/circulationaha.113.008476
86. Ferranini, E., Mark, M., & Mayoux, E. (2016). CV Protection in EMPA-REG OUTCOME trial: a Thrifty Substrate Hypothesis. *Diabetes Care, 39*(7), 1108-1114. DOI: https://doi.org/10.2337/dc16-0330
87. Suzuki, M., Takeda, M., Kito, A., Fukazawa, M., Yata, T., Yamamoto, M., Nagata, T., Fukuzawa, T., Yamane, M., Honda, K., Suzuki, Y., & Kawabe, Y. (2014). Tofogliflozin,

a Sodium –glucose cotransporter 2 inhibitor, attenuates body weight gain and fat accumulation in Diabetic and obese animal models. *Nutr Diabetes, 4*(7), e125. DOI: https://doi.org/10.1038/nutd.2014.20
88. Youssef, M. E., Yahya, S., Popoviciu, M. S., Cawalu, S., Abd-Eldayem, M. A., & Saaber, S. (2023). Unlocking the full potential of SGLT2 inhibitors: expanding applications beyond. *Int J Mol Sci, 24*(7), 6039. DOI: https://doi.org/10.3390/ijms24076039
89. Wight, T. N., & Potter Perigo, S. (2011). The extracellular matrix: an active or passive player in fibrosis. *Am J Physiol Gastroenterol Liver Physiol, 301*(6), G950-G955. DOI: https://doi.org/10.1152/ajpgi.00132.2011
90. Law, B., Fowlkes, V., Goldsmith, J. G., Carver, W., & Goldsmith, E. W. (2012). Diabetes- induced alterations in the extracellular matrix and their impact on myocardial function. *Microscop Microanal, 18*(1), 22-34. DOI: https://doi.org/10.1017%2FS1431927611012256
91. Westermann, D., Rutschow, S., Jäger, S., Linderer, A., Anker, S., Riad, A., Unger, T., Schultheiss, H. P., Pauschinger, M., & Tschöpe, C. (2007). Contribution of inflammation and cardiac Matrix Metalloproteinasesactivity to cardiac failure in Diabetic cardiomyopathy: the role of angiotensin type 1receptorantagonism. *Diabetes, 56*(3), 641-6. DOI: https://doi.org/10.2337/db06-1163
92. Singh, V. P., Le, B., Khode, R., Baker, K. M., & Kumar, R. (2008). Intracellular angiotensin II production in diabetic rats is correlated with cardiomyocytes apoptosis, Oxidative stress and cardiac fibrosis. *Diabetes, 57*(12), 3297-3306. DOI: https://doi.org/10.2337%2Fdb08-0805
93. Senador, D., Kanakamedala, K., Irigoyen, M. C., Morris, M., & Elased, K. M. Cardiovascular and autonomic phenotype of DB/DB diabetic mice. *Exp Physiol, 94*(6), 648-58. DOI: https://doi.org/10.1113/expphysiol.2008.046474
94. Heickendorff, L., Ledet, T., & Rasmussen, L. M. (1994). Glycosoaminoglycans in the human aorta in Diabetes mellitus: a study of tunica media from areas with and without Atherosclerotic plaques. *Diabetologia, 37*(3), 286-92. DOI: https://doi.org/10.1007/bf00398056
95. Saucermann, J. J., Tan, P. M., Buchholz, K. S., McCullough, O. D., & Omens, J. H. (2019). M mechanical regulation of gene expression in cardiac myocytes and fibroblasts. *Nat Rev Cardiol, 16*(6), 361-378. DOI: https://doi.org/10.1038/s41569-019-0155-8
96. Ingber, D. E. (2006). Cellular mechanotransduction: putting all the pieces together. *FASEB J, 20*(7), 811-27. DOI: https://doi.org/10.1096/fj.05-5424rev
97. Bershadsky, A., Kozlov, M., & Geiger, B. (2006). Adhesion mediated mechanosensitivity: a time to experiment and a time to theorize. *Curr Opin Cell Biol, 18*(5), 472-81. DOI: https://doi.org/10.1016/j.ceb.2006.08.012
98. Traister, A., Li, M., Aafaqi, S., Lu, M., Arab, S., Radisic, M., Gross, G., Guido, F., Sherret, J., Verma, S., Slorach, C., Mertens, L., Hui, W., Roy, A., Delgado-Olguín, P., Hannigan, G., Maynes, J. T., & Coles, J. G. (2014). Integrin linkedkinase mediates force transduction in cardiomyocytes by modulating SERCa2a/PLN function. NatCommun, 5, 4533. DOI: https://doi.org/10.1038/ncomms5533
99. Carter, W. G., Kaur, P., Gil, S. G., Gahr, P. G., & Wayner, E. A. (1990). Distinct function for integrins α3β1 infocal adhesions and α6β4/bullous pemphigoid antigen in a new stable anchoring contact (SAC) of keratinocytes: relation to hemidesmosomes. *J Cell Biol, 111*(6 Pt 2), 3141-54. DOI: https://doi.org/10.1083/jcb.111.6.3141
100. Teoh, C. M., Tam, J. K., & Tran, T. (2012). Integrin and gpcr crosstalk in the regulation of asm contraction signaling in asthma. J Allergy, 2012, 341282. DOI: https://doi.org/10.1155/2012/341282
101. Balaban, N. Q., Schwarz, U. S., Riveline, D., Goichberg, P., Tzur, G., Sabanay, I., Mahalu, D., Safran, S., Bershadsky, A., Addadi, L., & Geiger, B. (2001). Force and integrins focal adhesion assembly: a close relationship studied using elastic micropatterned substrate. *Nat Cell Biol, 3*(5), 466-72. DOI: https://doi.org/10.1038/35074532
102. Lapidos, K. A., Kakkar, R., & McNally, E. M. (2004). The dystrophin glycoprotein complex: signaling strength and integrity of the sarcolemma. *Circ Res, 94*(8), 1023-31. DOI:https://doi.org/10.1161/01.res.0000126574.61061.25
103. Crisp, M., Liu, Q., Roux, K., Rattner, J. B., Shannon, C., Burke, B., Stahl, P. D., & Hodzic, D. (2006). Coupling of the nucleus and cytoplasmic: role of the linc complex. *J Cell Biol, 172*(1), 41-53. DOI: https://doi.org/10.1083/jcb.200509124
104. Cadre, B. M., Qi, M., Eble, D. M., Shannon, T. R., Burke, D. M., & Samarel, A. M. (1998). Cyclic stretch downregulates Calcium transporter gene expression inneonatal rat ventricular myocytes. *J Mol Cell Cardiol, 30*(11), 247-59. DOI: https://doi.org/10.1006/jmcc.1998.0788
105. Limbu, S., Hoang Troang, T. M., Prosser, B. L., Lederer, W. F., Jafri, M. S. (2015). Modeling local x RoS and calcium signaling in the heart. *Biophys J, 109*(10), 2037-50. DOI: https://doi.org/10.1016/j.bpj.2015.09.031
106. Belke, D. D., & Dillmann, W. H. (2004). Altered cardiac calcium handling in Diabetes. *Curr Hypertens Rep, 6*(6), 424-9. DOI: https://doi.org/10.1007/s11906-004-0035-3
107. Hollekim-Strand, S. M., Bjorgass, M. R., Albrektsen, G., Tjonna, A. E., Wisloff, U., & Ingul, C. B. (2014). High intensity interval exercise improves cardiac function in patients with type2 Diabetes mellitus and diastolic dysfunction; randomized controlled trial. *Am Coll Cardiol, 64*(16), 1758-60. DOI: https://doi.org/10.1016/j.jacc.2014.07.971
108. Schmidt, J. F., Andersen, T. R., Horton, J., Brix, J., Tarnow, L., Krustrup, P., Andersen, L. J., Bangsbo, J., Hansen, P. R. (2013). Soccer training improves cardiac function in men with type2 Diabetes. *Med SciSports Exerc, 45*(12), 223-33. DOI: https://doi.org/10.1249/mss.0b013e31829ab43c
109. Chen, B., Geng, J., Gao, S. X., Yue, W. W., & Liu, Q. (2018). Eplerenone modulates interleukin-33/Sst2 and IL-1β in left ventricular systolic dysfunction after myocardial infarction (MI). *J Interferon Cytokines Res, 38*(3), 137-44. DOI: https://doi.org/10.1089/jir.2017.0067
110. Lunder, M., Janic, M., & Sabovic, M. (2018). Prevention of vascular complications in Diabetes mellitus patients: focus on the arterial wall. *Curr Vasc Pharmacol, 17*(1), 6-15.

DOI: http://dx.doi.org/10.2174/15701611166661802061137 55
111. Tate, M., Deo, M., Cao, A. H., Hood, S. G., Huynh, K., Kiriazis, H., Du, X. J., Julius, T. L., Figtree, G. A., Dusting, G. J., Kaye, D. M., & Ritchie, R. H. (2017). Insulin replacement limits progression of Diabetic cardiomyopathy in the low dose streptozocin induced diabetic rats. *DiabetesVasc Dis Res, 14*(5), 423-33. DOI: https://doi.org/10.1177/1479164117710390
112. Zinman, B., Lachin, J. M., & Inzucchi, S. E. (2016). Empagliflozin, Cardiovascular outcomes and mortality in Type2 Diabetes. *N Engl J Med, 374*(11), 1094. DOI: https://doi.org/10.1056/nejmc1600827
113. Neal, B., Perkovic, V., Mahaffey, K. W., De Zeeuw, D., Fulcher, G., Erundu, N., Shaw, W., Law, G., Desai, M., & Mathews, D. R. (2017). Canagliflozin and Cardiovascular and renal events in type2 Diabetes. *N Engl J Med, 377*(7), 644-57.DOI: https://doi.org/10.1056/nejmoa1611925
114. Packer, M. (2022). Critical re analysis of the mechanisms underlying Cardiorenal benefits of SGLT2 inhibitors and reaffirmation of nutrient deprivation signaling / autophagy hypothesis. *Circulation, 146*(18), 1383-1405. DOI: https://doi.org/10.1161/circulationaha.122.061732
115. Marso, S. P., Daniels, G. H., Brown-Frandsen, K., Kristensen, P., Mann, J. F., Nauck, M. A., Nissen, S. E., Pocock, S., Poulter, N. R., Ravn, L. S., Steinberg, W. M., Stockner, M., Zinman, B., Bergenstal, R. M., Buse, J. B. (2017). Liraglutide and Cardiovascular Outcomes in type2 Diabetes. *N Engl J Med, 375*(4), 311-22. DOI: https://doi.org/10.1056/nejmoa1603827
116. Marso, S. P., Bain, S. C., Consoli, A., Eliaschewitz, F. G., Jódar, E., Leiter, L. A., Lingvay, I., Rosenstock, J., Seufert, J., Warren, M. L., Woo, V., Hansen, O., Holst, A. G., Pettersson, J., & Vilsbøll, T. (2016). Semaglutide and Cardiovascular Outcomes in patients with type2 Diabetes. *N Engl J Med, 375*(19), 1834-44. DOI: https://doi.org/10.1056/nejmoa1607141
117. Sposito, A. C., Berwanger, O., de Carvalho, L. S. F., & Saraiva, J. F. K. (2018). Glp-1ras in type2 Diabetes: mechanisms that underlie cardiovascular effects and overview of Cardiovascular Outcomes data. *Cardiovasc Diabetol, 17*(1), 157. DOI:https://doi.org/10.1186/s12933-018-0800-2
118. Sharkovska, Y., Kalk, P., Lawrenz, B., Godes, M., Hoffmann, L. S., Wellkisch, K., Geschka, S., Relle, K., Hocher, B., Stasch, J. P. (2010). Nitric oxide independent stimulation of soluble guanylate cyclase reduced organs damagein experimental low renin and high renin models. *J Hypertens, 28*(8), 1666-75. DOI: https://doi.org/10.1097/hjh.0b013e32833b558c
119. Bonderman, D., Ghio, S., Felix, S. B., Ghofrani, H. A., Michelakis, E., Mitrovic, V., Oudiz, R. J., Boateng, F., Scalise, A. V., Roessig, L., & Semigran, M. J. (2013). Riociguat for patients with pulmonary hypertension caused by systolic left ventricular dysfunction: phase ii double blind, randomized placebo controlled dose ranging haemodynamic study. *Circulation, 128*(5), 502-11. DOI: https://doi.org/10.1161/circulationaha.113.001458
120. Pieske, B., Maggioni, A. P., Lam, C. S. P., Pieske-Kraigher, E., Filippatos, G., Butler, J., Ponikowski, P., Shah, S. J., Solomon, S. D., Scalise, A. V., Mueller, K., Roessig, L., & Gheorghiade, M. (2017). Vericiguat in patients with worsening heart failure and preserved ejection fraction: results of soluble guanylate cyclase stimulator in heart failure patients with preserved ef (Socrates- preserved) study. *Eur Heart J, 38*(15), 1119-27. DOI: https://doi.org/10.1093/eurheartj/ehw593
121. Ikonomidis, I., Lekakis, J. P., Nikolaou, M., Paraskevaidis, I., Andreadou, I., Kaplanoglou, T., Katsimbri, P., Skarantavos, G., Soucacos, P. N., & Kremastinos, D. T. (2008). Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with Rheumatoid Arthritis interleukin-1 by anakinra. *Circulation, 117*(20), 2662-9. DOI: https://doi.org/10.1161/circulationaha.107.731877
122. Toldo, S., Mezzaroma, E., Bressi, E., Marchetti, C., Carbone, S., Sonnino, C., Van Tassell, B. W., & Abbate, A. (2014). Interleukin-1β blockade improves left ventricular systolic / diastolic function and restores contractility reserve in severe ischemic cardiomyopathy in the mouse. *J Cardiovasc Pharmacol 64*(1), 1-6. DOI: https://doi.org/10.1097/fjc.0000000000000106
123. Van Tassell, B. W., Buckley, L. F., Carbone, S., Trankle, C. R., Canada, J. M., Dixon, D. L., Abouzaki, N., Oddi-Erdle, C., Biondi-Zoccai, G., Arena, R., Abbate, A. (2017). Interleukin-1 blockade in heart failure with preserved ejection fraction: rationale and design of the diastolic heart failure anakinra response trial (D-HART2). *Clin Cardiol, 40*(9), 626-32. DOI: https://doi.org/10.1002/clc.22719
124. Gori, M., D'Ella, E., & Senni, M. (2019). Secubitril/ valsartantherapeutic strategy in hfpef: Clinical insight and perspectives. *Int J Cardiol*, 281, 158-65. DOI: https://doi.org/10.1016/j.ijcard.2018.06.060
125. Malek, V., & Gaikwad, A. B. (2019). Telmisartan and thiorphan combination treatment attenuates fibrosis and apoptosis in Diabetic cardiomyopathy. *Cardiovasc Res, 115*(2), 373-84. DOI: https://doi.org/10.1093/cvr/cvy226
126. Qin, F., Siwik, D. A., Luptak, I., Hou, X., Wang, L., Higuchi, A., Weisbrod, R. M., Ouchi, N., Tu, V. H., Calamaras, T. D., Miller, E. J., Verbeuren, T. J., Walsh, K., Cohen, R. A., & Colucci, W. S. The polyphenols resveratrol and S17834prevent the structural and functional sequelae of Diet induced metabolic heart disease in mice. *Circulation, 125*(14), 1757-64. DOI: https://doi.org/10.1161/circulationaha.111.067801
127. Chen, J. Y., Tsai, P. J., Tai, H. C., Tsai, R. L., Chang, Y. T., Wang, M. C., Chiou, Y. W., Yeh, M. L., Tang, M. J., Lam, C. F., Shiesh, S. C., Li, Y. H., Tsai, W. C., Chou, C. H., Lin, L. J., Wu, H. L., & Tsai, Y. S. (2013). Increased aortic stiffness and attenuated lysyl oxidase activity in obesity. *Arterioscler Thromb Vasc Biol, 33*(4), 839-46. DOI: https://doi.org/10.1161/atvbaha.112.300036
128. Grutzner, A., Garcia, M. S., Kotter, S., Badilla, C. L., Fernandez, J. M., & Linke, W. A. (2009). Modulation of titin based stiffnessby disulfide bonding in the cardiac titin N2B unique sequence. *Biophys J, 97*(3), 825-34.

DOI: https://doi.org/10.1016%2Fj.bpj.2009.05.037
129. Chen, C. S. (2008). Mechanotransduction: A field pulling together. *J Cell Sci J, 121* (Pt 20), 3285-92. DOI: https://doi.org/10.1242/jcs.023507.