

## SYSTEMIC REVIEW

# Diabetic cardiomyopathy: An update on its pathophysiology with specific emphasis on epigenetics modifications besides treatment - A systematic review

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Diabetes mellitus (DM) represents a significant lifestyle disease. Of the types of DM, type 2 DM aids maximum in the development of cardiovascular disease (CVD) along with diabetic cardiomyopathy (DbCM), which is correlated with significant mortality along with comorbidity in diabetic patients. DbCM is a non-canonical cardiac illness that exhibits cardiac remodelling occurs when there is DM but not when there is any concomitant conditions like hypertension, valve disease, or coronary artery disease (CAD). DbCM is linked to altered mitochondrial structure and function, as well as aberrant cardiac metabolism. Additional physiological and pathological signaling mechanisms include inflammation, oxidative stress (OS), and others; besides, in the diabetic environment, there are various cardiomyopathy-inducing factors such as reactive oxygen species (ROS)-modulated OS, hyperglycemic situations, cytokines-modulated. These mediators induce inflammatory responses, cell death, including apoptosis, pyroptosis, and autophagy, as well as the epigenetic control of abnormal molecular pathways. The last 10-years have demonstrated the importance of miRNAs and long non-coding RNAs (lncRNAs) in controlling key biological processes such cell death, mitochondrial dysfunction, and electrical remodelling. Cardiomyopathy is a significant event regarding cardiac remodeling event in DbCM. Considerable proof exists regarding the part of epigenetics in diabetic correlated cell demise. Epigenetic controlling modes like histone alterations, DNA methylation, and miRNA along with lncRNAs control cardiac cell demise in the diabetic environment. Akin to that, other modes such as mitochondrial impairment and OS are controlled by miRNA along with lncRNAs. Finding these modes has given provision of generation of innovative therapy approaches for DbCM. miRNAs along with lncRNAs have illustrated translational capacity in the form of Besides treatment options, There are other DbCM-specific diagnostic and prognostic biomarkers available. HDACs were further shown to have a crucial role in controlling the pathogenesis of DbCM.

**Keywords:** diabetic cardiomyopathy, cardiac fibrosis, epigenetics modifications, HDACs, SGLT2 inhibitors

## Introduction

### Definition

Diabetic cardiomyopathy (DbCM) represents a cardiovascular disease (CVD) possessing the properties of generation of structural along with functional aberrations

people with diabetes mellitus (DM) who do not also have concomitant conditions including hypertension, valve disease, or coronary artery disease in cardiac tissue (CAD) (1). As per the Framingham Heart Study, women along with men with DM possessed a score of 5 and 2, respectively. Heart failure (HF) has a 4 times higher incidence (2). With a range from 19 to 26%, patients with DM had a higher

prevalence of HF (3). A case-controlled research discovered that HF was 1.3 times more common than expected greater in patients with DM compared with non-diabetic patients (4). A robust association between type 1 diabetes (T1D) patients and type 2 diabetes (T2D) patients was observed with glycated hemoglobin A1c (HbA1c) and (HbA1c). Every 1% increase in HbA1c, a 30 along with 80%. The incidence of HF was higher in T1D than in T2D, respectively. These stood apart from additional risk factors (5). To start with the phase of DbCM possess the properties of exhaustive cardiac hypertrophy in addition to mild to moderate fibrosis resulting in abnormalities of systolic along with diastolic function of the heart (6).

## Environment in blood results

### DbCM

In case of experimental along with clinical studies identification of persistent hyperglycemia, insulin resistance (IR), dysfunctional glucose metabolism, and aberrations in insulin signaling, aberrant observations included the intake of heart inflammation, elevated renin-angiotensin system (RAAS) activity, free fatty acids (FFA), and oxidative stress (OS). Furthermore, abnormal mitochondrial functioning acted as one of the main indicators of metabolic changes that triggered a chain reaction of disease-related events. The three most significant mechanisms of the disease's pathophysiology, namely, the causes of increased cardiomyocyte cell death, left ventricular (LV) hypertrophy, and cardiac fibrosis, are revealed (7).

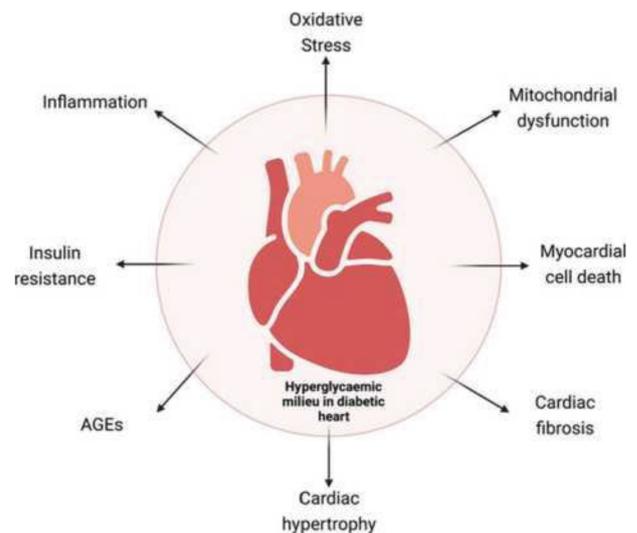
### Biochemical

Mechanistically, numerous molecular modes have been isolated that aid in the pathophysiological alterations in DbCM (Figure 1) [rev in Ref. (8)].

Additionally, GPR40, 5'-AMP-activated protein kinase (AMPK) signaling, activation of the mitogen-activated protein kinase (MAPK) signaling, O-GlcNAcylation of cardiac proteins, a reduction in insulin, abnormal protein kinase C, and peroxisome proliferator-activated receptor (PPAR) are all involved.

### Epigenetic alterations

The etiology of DbCM may be significantly influenced by the dysregulation of miRNAs, circular RNAs (circRNAs), lncRNAs, DNA methylation, and histone posttranslational modifications (such as acetylation, and methylation), according to a recent research (9). After understanding how epigenetic changes contribute to diabetic kidney disease (DKD), diabetic nephropathy, and the association of epigenetic alterations in NAFLD with CVD (10–12), our goal was to evaluate the epigenetic changes in several biological pathways associated with DbCM.



**FIGURE 1** | The many processes involved in diabetic cardiomyopathy are illustrated schematically, courtesy of reference no. (8). AGEs, advanced glycation end products.

## Methods

In this study, we conducted a narrative review utilizing search engines including PubMed, Google Scholar, Web of Science, Embase, and the Cochrane Review Library. We utilized MeSH terms like DbCM, epigenetics, DNA methylation, histone posttranslational modifications, and histone acetylation. CircRNA, miRNAs, lncRNAs, HDAC1-6, cardiac remodeling, cardiomyocyte apoptosis, cardiac hypertrophy, left ventricular hypertrophy, PI3K signaling pathways, autophagy, pyroptosis, valproic acid, sodium butyrate, and SGLT2 inhibitors from 1950 to the present.

## Results

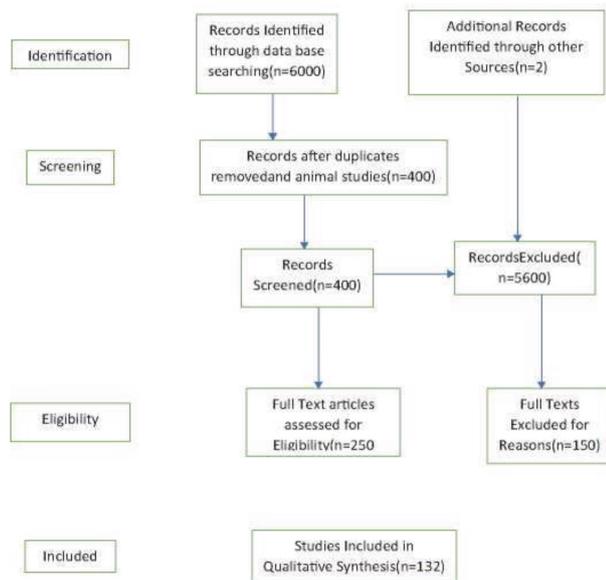
A total of 6,000 articles were discovered, and 132 articles were chosen for this evaluation. They were not meta-analyzed. Figure 2 shows the selection criteria.

## Molecular modes along with epigenetic controlling in DbCM

### DbCM along with cardiac remodeling

#### Normal cardiac alteration in the diabetic heart vis-a-vis DbCM

The DbCM often coexists with a number of vascular disorders. Atherosclerosis may be worse in T2DM for a variety of reasons, such as obesity, dyslipidemia, hyperinsulinemia, oxidative stress, low-grade inflammation, anomalies in the metabolism, such as hyperglycemia



**FIGURE 2 |** Screening criteria.

and a rise in the production of advanced glycation end products (AGEs), and autonomic dysfunction instability, to name a few. stroke, peripheral artery disease, and heart disease are examples of macroangiopathy consequences, whereas retinopathy, neuropathy, and nephropathy are the hallmarks of microangiopathy. Regarding this, it has been discovered that albuminuria and cardiac strain are clearly related in T1DM patients, but SGLT-2 inhibitors have been reported to protect renal function and avoid HF in T2DM patients. Additionally, DCM takes place in association with cardiovascular risk factors including Obesity in general and hypertension make diagnosis and treatment more challenging. The World Health Organization classified obesity as a major risk factor for the development of T2DM in 2014 as one of the stated that more than 600 million individuals were obese globally. Lipid buildup can happen in the obesity and type 2 diabetes (T2DM) are associated with metabolic imbalance and lipotoxicity, which include the main causes of diabetes-related ventricular dysfunction. Additionally, hyperinsulinemia brought on by obesity stimulates the release of VLDL lipoproteins, *de novo* lipogenesis (DNL), and the expression of lipogenic genes in the liver. These insulin resistance and cardiovascular risk factors distinguish type 2 diabetes (T2DM) from type 1 diabetes (T1DM), whose etiology is primarily driven by genetic factors [rev in Ref. (13)].

Diastolic dysfunction has been identified as an early functional change in the diabetic myocardium. Between 40 and 75% of people with type 1 or type 2 diabetes are thought to have diastolic dysfunction using tissue Doppler imaging and conventional echocardiography. Systolic dysfunction may continue to develop, although typically at a later stage of the illness, which creates a significant challenge for diagnosis when using canonical echocardiography. However,

modest changes in systolic function have been identified in 24% of individuals with DM who do not have CAD or LV hypertrophy using strain evaluation and peak systolic velocity calculations. Diastolic failure may not necessarily be the first functional alteration in diabetics since systolic dysfunction can sometimes be present in diabetics with acceptable diastolic function DbCM, according to a recent study that used systolic strain measurement.

Cardiomyocyte hypertrophy along with fibrosis is a significant characteristic of DbCM. Cardiac fibrosis possesses a considerably robust part in the pathophysiology of the disease in case of the human diabetic heart. Robust collagen fibers are deposited in the interstitial area along with perivascular space in the cardiomyocytes with diabetes (14). The majority of the aggravating collagen pathways fibers (type I and type II), the wingless-related integration site (WNT), and transforming growth factor beta (TGF- $\beta$ ) signaling pathways are being deposited (15). In addition, the remodeling of matrix metalloproteinases (MMPs) that results in the deregulated breakdown of extracellular matrix (ECM) in diabetic heart aids further (15, 16). TGF- $\beta$ 1 pathway activation and escalated breakdown of ECM take place secondary to RAAS stimulation, leading to accelerated cardiac remodeling, modulated signaling, and hyperglycemia along with IR (17). Reduction in the accessibility of nitric oxide (NO), oxidative stress (OS), increased cardiac collagen deposition, and levels of fibronectin cause interstitial fibrosis when the TGF- $\beta$ 1 signaling pathway is activated in conjunction with insulin signaling dysregulation (18). The use of several clinical and animal studies for cardiac fibrosis present in case of diabetes-triggered HF (15, 18) has made it possible to provide amazing proof.

Enhancement of LV hypertrophy as protracted by the existence of greater LV mass along with its correlation with DM has been extensively corroborated (19). The most important foundation for human cardiac hypertrophy is LV thickening (20). Regarding the overall increased LV mass, Myocardial cell death, cardiac fibrosis, and hypertrophy must be considered (21). Besides cardiac hypertrophy, other parameters aiding in DbCM generation are IR, hyperglycemia in the environment, OS that results in the activation of cardiac hypertrophy genes like  $\beta$ -myosin heavy chain ( $\beta$ -MHC), atrial natriuretic factor (ANP), and brain natriuretic peptide (BNP) (22). Escalated insulin amounts further stimulate cardiac hypertrophy formation. Insulin-like growth factor (IGF-1) stimulates cardiac hypertrophy formation via extracellular signal-regulated kinase (ERK1/2) along with the phosphatidyl inositol 3-kinase (PI3K) signaling pathways (23). The contribution of DM to the development of cardiomyocyte hypertrophy has been further shown in a number of investigations using animal models of DbCM (24).

## Epigenetics controlling of cardiac remodeling in DbCM

### ***Effects of hyperglycemia as well as hyperinsulinemia on miRNAs***

MicroRNAs represent non-coding RNAs that control cellular gene expression. Abnormal expression of around 30% (alias 300/1000 total RNAs) has been seen in the heart tissue of DM individuals (25). In DbCM, several miRNAs have been identified to control cardiac hypertrophy and fibrosis. Diabetes-induced mice's cardiac tissue has been reported to dramatically upregulate miRNA-21-like genes (26). By directly influencing the fork head box protein O3 (Fox3), miRNA-212 has been found to regulate the occurrence of cardiac hypertrophy (27). In DbCM, Rac 1 activated kinase (Pak1) and cell division control protein 42 homolog (Cdc42) expression levels. According to Raut et al., miRNA-30c caused an increase. It has been demonstrated that other miRNAs, namely, miRNA-181a and miRNA-200c, play a substantial role in cardiac remodeling (27–29). miRNA-199a levels were higher in cardiac hypertrophy (26). Recent studies have demonstrated that blocking miRNA-199a, which is a coactivator of the peroxisome proliferator activated receptor (PPAR), can prevent heart hypertrophy by restoring mitochondrial fatty acid oxidation. The diabetic heart exhibited downregulation of miRNA-30a, miRNA-1, and miRNA-29b (25). The miRNA 144 and miRNA 133 were the two miRNAs with the most relevance in the pathophysiology of diabetes-modified heart failure, out of all the essential orchestrating miRNAs (29). Singh et al. depicted miRNA-200c (28) to promote cardiac hypertrophy by modifying the expression of dual specific phosphatase 1 (DUSP1) in DbCM (30).

In a diabetic murine model, miRNA-133a was reduced (31). Additionally, it was demonstrated that miRNA-133 levels improved systolic function in addition to reducing fibrosis by reducing collagen levels (32). A biomarker for myocardial fibrosis called miRNA 21 has been identified (33). Numerous studies have shown that in a hyperglycemic environment and in diabetic hearts. In rat cardiac fibroblasts, miRNA 21 levels are increased, which encourages collagen production and fibroblast growth (34). MiRNA 21 also disrupted the JNK and p38 MAPK signalling pathways, which had a direct impact on the activity of the dual specific phosphatase 8 (DUSP8).

### ***Effects of hyperglycemia and hyperinsulinemia on LncRNAs***

Long non-coding RNAs are longer than miRNAs. LncRNAs are a different class of non-coding RNAs that have been linked to several disease pathways (35). The LncRNAs with localization in the nucleus work while cytoplasmic lncRNAs often collaborate with miRNAs to control

post-transcriptional gene expression. Several lncRNAs, notably DbCM, which supports cardiac fibrosis and hypertrophy, have been linked to the pathogenesis of CVD. Due to miRNA-150 and miRNA-93's ability to act as sponges for anti-hypertrophic miRNAs, myocardial infarction-associated transcript (MIAT) functions as prohypertrophic lncRNAs. Furthermore, MIAT amounts were greater in the myocardium besides the possessed competitive action with miRNA-24 amounts for controlling TGF- $\beta$  expression, hence cardiac fibrosis (36). Ablating silencing lncRNA Kcnq1ot1 mitigated TGF- $\beta$  signaling, hence decreasing fibrotic injuries in diabetic mice (37). Dysregulation of both miRNAs along with lncRNAs results in hyperglycemia-associated myocardial injury.

### ***Effects of hyperglycemia and hyperinsulinemia on histone modifications***

Furthermore, it has been discovered that cardiac remodeling in DbCM is significantly influenced by histone changes. Non-specific hindering-dependent. In animal models of diabetic heart disease, inhibition of histone deacetylases (HDACs) has been shown to reduce myocardial hypertrophy and fibrosis through increasing the acetylation of glucose transporter 1 and MAPK-modulated phosphorylation (38). Utilization of specific HDAC3 hampering agents like RGF966 further illustrated the enhancement of cardiac function and reverted the DM stimulated cardiac remodeling in diabetic mice. Thus, it was revealed that RGF966 resulted in the reduction of cardiac hypertrophy by modulating the epigenetics of the ERK1/2 pathways modulated via DUSP5 (39). Conversely, Sirt2 is believed to possess advantageous action on DCM. It causes enhancement from cardiac contractile impairment in case of leptin-deficient db/db mice via a histone Sirt2, a deacetylase, directed a route that indicated its potential to function as a therapeutic molecule in DbCM (40).

## Part of epigenetics in controlling cell demise modes in DbCM

### ***Modes of cell demise***

In the year 2018, the NCCD cell death nomenclature committee demise described various kinds of totally physiological controlled cell death, which is in general labeled as programmed cell death (PCD). Different kinds of PCD have been detailed, including apoptosis (extrinsic along with intrinsic), autophagy-based cell demise, mitochondrial permeability, transit-guided necrosis, ferroptosis, pyroptosis, parthanotos, entotic cell demise, NETotic cell demise, lysosomal-based cell demise, and immunogenic cell demise (41). As per this review, we detailed type I cell demise (apoptosis), type II cell demise (autophagy-based), and pyroptosis.

Definitions of cell demise modes are discussed as follows:

### **(i) Apoptosis**

Apoptosis represents an event where there is a stoppage of cell growth along with division, instead of spillage of its constituents into the surrounding microenvironment; however, finally, it results in cell demise. Apoptosis is further known as programmed cell death (or “cellular suicide”).

Apoptosis is a foundational physiological event. Its decontrolling has been correlated with different pathologies along with diseases including immune reactions, toxicity of drugs, infections, tumors, and metabolic conditions. Apoptosis possesses the properties of cell shrinking, chromatin condensations, DNA fragmentation, nuclear fragmentation, and blebbing of the cell membrane.

### **(ii) Autophagy**

The word “autophagy” comes from the Greek words “auto” (self) and “phagy” (to eat). Type II cell demise represents the necessary, controlled, conserved catabolic events that modulate recycling along with the breakdown of various cytoplasmic constituents of the eukaryotic cell. Autophagy plays a considerably significant part in cancer and autophagy correlated proteins (ATG). Till now, the double part of autophagy in cancer propagation along with hampering remains debatable. Autophagy possesses a dynamic tumor repressor or tumor-facilitating part in different stages of cancer generation. At the time of early tumor generation, autophagy results in avoidance of the tumor getting started and hampers cancer propagation through survival pathways along with quality regulatory modes. Nevertheless, once the tumor propagates along with forms an end stage, besides exposure to environmental stress, autophagy works in the form of a dynamic recycling system that aids in the survival along with the growth of generated tumors along with facilitates cancer acceleration via metastasis. Therefore, this pointed out that autophagy modulation might prove to be an efficacious interventional approach regarding cancer therapy.

### **Kinds of autophagy**

Dependent on the administration approach, three kinds of autophagy have been detected toward the lysosome, namely, (i) macroautophagy, (ii) microautophagy, and (iii) chaperone-modulated autophagy (CMA) (42). Macroautophagy is the maximum function along with the properties of kinds of autophagy implicated creating a double membrane autophagosome that results in the elimination of injured organelles or undesired cellular constituents by administration to lysosomes for breakdown along with recycling. Different studies have documented that macroautophagy and macroautophagic cell demise represent antitumor reactions. In case of microautophagy, the cargo comprised of (organelles or cytoplasmic constituents) crosstalk directly undergoes fusion with lysosomes for

breakdown along with recycling. Microautophagy is more particular in contrast to macroautophagy besides results in the transmission of signals of molecules existent on the surface of injured small organelles like mitochondria and peroxisomes, resulting in particular fusion among lysosomes and these organelles. Based on the organelles whose targeting takes place, the produced autophagic vesicles are labeled by particular names. Mitochondria, peroxisomes, lipids, and RNA are labeled as smitophagy, peroxophagy, lipophagy, and ribophagy, respectively. Intriguingly, CMA reflects the chaperone based selection of cytoplasmic proteins meant for targeting by lysosomes, and their translocation takes place across the membranes of lysosomes for breakdown. A distinctive characteristic of this kind of autophagy is the direct transfer of these proteins without the requirement of selectivity of the proteins broken down besides the generation of extra vesicles. The upregulation of CMA is correlated with cancer cells survival besides proliferation.

### **(iii) Pyroptosis**

Pyroptosis is the inflammation-stimulated cell demise.

DbCM possesses a robust correlation with greater cardiomyocyte cell demise.

Apoptosis along with autophagy represents the considerably significant decontrolled modes implicated in this event (43). Cardiomyocytes, fibroblasts, and endothelial cells have all shown significantly higher rates of apoptosis in the cardiac tissue of individuals with DbCM. Cardiomyocyte death rates were at their highest, and they were followed by fibroblasts and endothelial cells in that order (44). Enhanced cardiomyocyte cell demise causes cell depletion cardiomyopathy and cardiac failure are caused by heart remodelling such cardiac hypertrophy and fibrosis (45).

Heart remodelling, Cardiomyopathy and heart failure are brought on by conditions, such as cardiac fibrosis and hypertrophy (45) are posited to be the main factors responsible for triggering cardiomyocytes cell demise in diabetic hearts (46). Hyperglycemia modulates these effects via local escalated angiotensin II (AngII) (47). More recently, Kobayashi et al. (48) have demonstrated that hyperglycemia might further stimulate cardiomyocytes cell demise via induction of lysosomal membrane permeability along with escalated Heart remodelling, Cardiomyopathy and heart failure are brought on by conditions, such as cardiac fibrosis and hypertrophy (45).

### **Epigenetics controlling of apoptosis**

The expression of numerous miRNAs got dysregulated in hyperglycemia-stimulated cardiomyocytes apoptosis and diabetic heart (26). This includes the expression of miRNA-30c, miRNA-483-3p, and miRNA-181. Among these are miRNA-378, miRNA-34a, miRNA-1, miRNA-195, and miRNA-144 are some examples of miRNAs. It was shown that H9c2 cardiomyocytes treated with hyperglycemia had elevated miRNA-1, which accelerated apoptosis. They

proved that miRNA-1 encourages cardiomyocyte death by suppressing the expression of IGF1. Increased IGF1 miRNA-1 Expression was demonstrated to inhibit the release of cytochrome c induced by glucose and to increase apoptosis by modulating IGF1 (47). Abundant miRNA-34a expression was seen in cardiomyocytes besides controlling a number of proteins, including as the prosurvival protein Sirtuin 1, are expressed (SIRT 1). When cardiomyocytes were given glucose, diabetic hearts and miRNA-34a were found to be upregulated treatment. Fomison Nurse et al. (49) showed that in hyperglycemia- treated cultured cardiomyocytes, the elevation of SIRT 1 was downregulated by miRNA-34a, and miRNA-34a caspase activity that encourages apoptosis was enhanced. The observed decrease in hyperglycemia-stimulated cardiomyocyte apoptosis caused by miRNA-34a interference points to the possibility of a therapeutic (49) component Through the inhibition of its target gene IGF1, miRNA-483-3p was shown by Qiao et al. (50) to be involved in hyperglycemia- stimulated cardiomyocytes' death. MiRNA-483-cleaved 3p's expression has been seen in hyperglycemic cardiomyocytes and diabetic mice (28). The facilitation of cardiomyocytes apoptosis by these miRNAs was by uncontrolled p53-p21 axis (28). That upregulation of miRNA-195 stimulates apoptosis in streptozocin (STZ), as well as leptin- deficient mice type 2 diabetic murine hearts by downregulation of SIRT 1 as well as B cell leukemia 2 (Bcl2) (51). Both hearts and cardiomyocytes exhibited altered miRNA- 144 expression in hyperglycemic conditions. In T2D, the upregulation of miRNA-144-3p was discovered (52). Karolina et al. explained how miRNA-144 regulates IRS1 expression in diabetes. In case of hyperglycemia-treated cardiomyocytes, Song et al. (53) revealed that miRNA- 144 targeted C1q/TNF-related protein [CTRP3/c-Jun-N- terminal kinase (JNK)] pathway along with hampering of miRNA-144 ameliorated cardiomyocytes apoptosis. In a different study, Tan et al. (54) revealed that miRNA-144 was decreased in hyperglycemia-treated cardiomyocytes along with diabetic hearts (54). Significant mitochondria functional enhancement occurred subsequent to the cellular expression of Rac 1 of the Rac family of small GTPases, which in turn regulated apoptosis, and miRNA-144 together reduced myocyte apoptosis through AMPK phosphorylation besides PPAR7/coactivator-1a (PGC-1a) deacetylation (52). Therefore, additional investigation is needed to determine the precise miRNA component. Changes in the phosphatidyl inositol 3-kinase (PI3K)/AKT protein kinase signaling, which lead to the spread of DbCM, stimulated apoptosis, fibrosis, and hypertrophy of cardiomyocytes (55). Myocardial hypertrophy, fibrosis, and apoptosis were inhibited by the overexpression of miRNA-203 because it inhibited PIK3CA and PI3K/AKT signaling (55). Recent research has suggested that the miRNA- 532 gene is positively correlated with cardiomyocytic apoptosis in diabetic heart disease. It has been shown that miRNA-532 is elevated in T2D, which decreases its main target,

the antiapoptotic protein (ARC). In cardiomyocytes treated with hyperglycemia, miRNA-532 overexpression resulted in proapoptotic caspases being activated as well as the opposite being true (56). Another study found that the heart of diabetes patients expressed less antiapoptotic protein. In the diabetic myocardium, downregulation of myocardial Hsp60 as a result of posttranscriptional manipulation by miRNA-1 and miRNA-206 was a strong proapoptotic signal (57).

Apart from miRNAs, different lncRNAs got isolated that were implicated in the modulation of cardiac cell demise in hyperglycemic or diabetic situations (58). Reduction in the expression of lncRNAs H19 in hyperglycemia-treated cardiomyocytes was seen along with enhanced ventricular function in diabetic mice by impeding reduced apoptosis (59). H19 functioned by inhibiting miRNA-675, which modifies the production of the proapoptotic protein VDAC and speeds up cell death (59). Yang et al. (37) illustrated the enhanced expression of one more lncRNA Kcnq1ot1 in the mice's diabetic hearts. Furthermore, they illustrated that hampering of lncRNA Kcnq1ot1 enhanced cardiac function besides ameliorating pyroptosis (37). Metastasis lung adenocarcinoma transcript1 (MALAT1) represents one more lncRNA that controls hyperglycemia-stimulated cardiomyocytes apoptosis (60). MALAT1 was further demonstrated to result in the downregulation of. By sponging and activating the inflammasome with the NLR family pyrin domain NLRP3 and TGF- $\beta$ /Smad, one can increase the levels of miRNA-141 or miRNA-181a-5p signaling (61). Additionally, EZH2 (enhancer of gene) study has demonstrated that MALAT1 influences the overexpression of ATP-binding cassette transporter A1 (ABCA1) and the death of cardiomyocytes homolog2 (EZH2), a histone methyltransferase (62). Along with DbCM, another lncRNA known as HOTAIR has been demonstrated to offer protection against heart cell death under hyperglycemic circumstances. Along with its cardiac overexpression, HOTAIR was shown to be reduced in the hearts of diabetic mice, which slowed the death of the cardiomyocytes in STZ diabetic mice (63). It has been shown that it may control the levels of miRNA-34a by increasing the antiapoptotic target protein SIRT1 and functioning as competitive endogenous RNAs (ceRNAs). In cardiomyocytes treated with hyperglycemia, another lncRNA, MEG3, is increased. MEG3 causes apoptosis by sponging miRNA-145 and raising proapoptotic levels of PDCD4 (64). Later, NKILA (nuclear factor B interacting lncRNA) was found to be significantly greater in individuals with DbCM, in addition to lower hyperglycemia-driven cardiac cell death caused by *in vitro* silencing (63). In AC 16 cardiomyocytes treated with hyperglycemia, similar quantities of lncRNAs known as LUCAT1 (lung-associated cancer transcript1) were discovered, and aldosterone synthase (CYP11B2) was downregulated to block decreased hyperglycemia-stimulated cardiomyocyte apoptosis (65).

Three crucial epigenetic mechanisms that control gene expression and related physiological processes are DNA, histone methylation, and acetylation processes. A portion of these mechanisms has not yet been thoroughly examined, but future research suggests that they may play a substantial role. In cardiomyocytes treated with hyperglycemia, HDAC1 controlled the inhibition of IGF1R, according to Yu et al. (66). They showed that, in addition to the link between histone4 and IGF1R being diminished, the correlation between histone4 and p53 HDAC1 is enhanced (66). The apoptosis that hyperglycemia induced in cardiomyocytes was also demonstrated to be inhibited by HDAC1 suppression by raising Diabetic GLUT1 acetylation and decreased caspase 3 activity rats. (67). Further evidence that ER stress is that a substantial DbCM regulator comes from the stimulation of apoptosis in cardiac cells (68). Guo et al.'s findings that SIRT1 activation reduced cardiomyocytes from diabetic rats with ER stress and apoptosis were in agreement with the epigenetic modulation of ER stress in DM-stimulated cardiac apoptosis (67). Puthanveetil et al. (69) showed that Foxo1 controlled the effects of hyperglycemia on the production of Indonesian nitric oxide synthase (iNOS) in cardiomyocytes, which increased protein nitrosylation. In hyperglycemic conditions, Foxo1 regulated caspase 3's nitrosylation, which led to increased cell death (69).

### **Epigenetics controlling of autophagy**

Autophagy represents a physiological event meant to eliminate or recycle injured cell constituents like organelles, proteins along with metabolites from the cell. It is a significant event meant for the sustenance of cell homeostasis. Suppression and escalation Cardiomyocytes exposed to hyperglycemia and diabetic hearts both exhibit signs of autophagy (70, 71). Increased autophagy was seen in the hearts of diabetic mice given fructose (IC3BII; LC2B-1 ratio, pointed that myocardial autophagy was activated in DbCM as revealed by Mellor et al. (72). Nevertheless, Xie et al. (73) found that OVE26 diabetic mice have reduced myocardial AMPK activity and autophagy [724]. Regarding autophagy in the pathophysiology of DbCM, no amiable agreement has been established (72). Dewanjee et al. (71) who recently reviewed autophagy in diabetic hearts demonstrated that autophagy might work in the form of a sword possessing double edges with the earlier activation aiding in the elimination of injured mitochondria, peroxisomes, along with proteins accrual, as well as enhancing antioxidant transcription factor in the same way as nuclear factor 2 linked to erythroid-2 (Nrf2). However, the cell's autophagy results in autodigestion, an increase in the production of reactive oxygen species (ROS), and heart damage.

Occasional publications pointed that miRNAs might control diabetes-stimulated autophagy. According to Chen et al. (74), individuals with DM had significantly lower levels of circulatory miRNA 30c. Cardiomyocytes and an animal diabetes model showed comparable outcomes. It was

miRNA 30c seen to directly control the expression of Beclin. Hence, miRNA 30c downregulation escalated autophagy by escalating proautophagic Beclin1 expression in diabetic hearts. Moreover, miRNA 30c directly controls Beclin1, hence regulating autophagy in DM (74).

Several studies have shown that lncRNAs have a part in DbCM. lncRNAs and Findings by Feng et al. (75) show that DCM-related factor (DCRF) expression in the DbCM was markedly increased in the diabetic mice model. By sponging miRNA-551-b-5p, they showed that DCRF stimulated cardiomyocyte autophagy by raising protocadherin (PCDH17) expression (75). DbCM showed lower levels of lncRNA H19 expression, as shown by Zhou et al. (76). They discovered that the production of lncRNA H19 inhibits DbCM autophagy by regulating the expression of the Di Ras3 (DIRAS3), a GTP-binding protein, which facilitates mTOR phosphorylation.

### **Epigenetics controlling of pyroptosis**

Pyroptosis, also known as inflammation-stimulated cell death, has been shown to accelerate the removal of cardiomyocyte cells in DbCM (77). miRNA 30d encouraged the pyroptosis of cardiomyocytes in hyperglycemic situations by suppressing Foxo3, and ARC, a protein linked with the cytoskeleton that regulates apoptosis, was its downstream effector activity suppressor that resulted in caspase1 activation and the escalation of proinflammatory molecule. Research by Jeyabal et al. (78) showed that miRNA 9 may have a role in the apoptosis that hyperglycemia stimulates in cardiomyocytes. They demonstrated reduced miRNA 9 expression in human diabetic hearts and *in vitro* hyperglycemia-treated cardiomyocytes. It has been established that the target protein of miRNA 9 is the inflammatory protein 1 that resembles ELAV (ELAVL1). Jeybal et al. (78) demonstrated that downregulation of ELAVL1 expression and overexpression of miRNA 9 alleviated hyperglycemia-stimulated cardiomyocyte pyroptosis, which indicates the diabetic heart's antiapoptotic function (78).

### **Epigenetics controlling of mitochondrial impairment in DbCM**

#### **(i) Role of miRNA**

Mitochondria possess a key part in the maintenance of metabolism and heart function. DbCM production is caused by the elimination of mitochondrial function (79). Adult cardiomyocyte mitochondria generate the majority of intracellular ATP by oxidative phosphorylation. When DM occurs, the mechanism for generating ATP switches from glucose oxidation in the mitochondria to free fatty acid (FFA) oxidation (80). ROS production is accelerated by defective oxidative phosphorylation (81). Apoptosis of cardiomyocytes was also a result of anomalies in Ca<sup>2+</sup> flux (82). This improperly managed Ca<sup>2+</sup> + flow causes the mitochondrial membrane to undergo increased autophagy (83).



### (ii) Role of lncRNA

Occasional lncRNAs have been documented to control diabetes-stimulated OS. Downregulation of lncRNA H19 was illustrated in the diabetic rat hearts along with forced expression resulting in the amelioration of OS which in turn subsequently lessened LV impairment (57). Histone DNA deacetylases, one kind of epigenetic modulator, have been further observed to be implicated in OS- modulated pathophysiology of DbCM. Kumar et al. (98) revealed that dysfunction of SIRT1 and methyltransferases 3b (Dnmt3b) action caused escalated. Diabetes is caused by both CpG demethylation and histone H3 acetylation at the p66Shc (prooxidant adaptor protein) promoter stimulated vascular OS (96). Akin to that, Mortaza et al. (99) explored the modes of reduction of SIRT1 action along with the part of SIRT1 and FOXO3 in ROS-modulated stress (99).

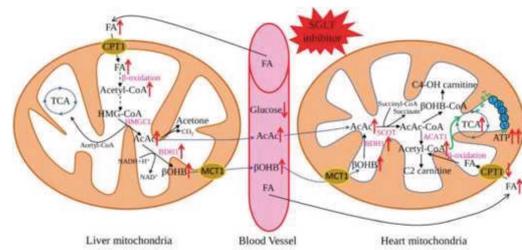
### Electrical remodeling along with its epigenetics controlling in the propagation of DbCM

Structural examples like cardiac remodeling (fibrosis and hypertrophy) result in functional aberrations (changed electrical activation) with final electrical remodeling hypertrophy of heart at the time of HF. The properties of electrical remodeling are compensatory or poor adaptability to ongoing ion channel disruptions that may be irreversible or reversible, respectively. Arrhythmias that cause mortality are thought to be caused by this remodeling, which involves the conduction system (100). Although several etiological variables delay the ventricular action potentials, repolarization is a typical type of electrical disturbance that is hypothesized to contribute to the development of CVD remodeling (100). Maximum electrophysiological investigations indicated that the K<sup>+</sup> currents had decreased possessing a crucial part in electrical remodeling (101). It has been confirmed experimentally that changes in the metabolism of glucose led to the modification of different channels in the ventricle in cardiomyocytes. It would be fascinating to understand more about how the K<sup>+</sup> channels are changed by DM. Insulin signalling and glucose uptake are both disturbed in cardiomyocytes from DbCM patients with upregulated K<sup>+</sup> channel activities. It was discovered that insulin therapy is appealing regarding the acquisition of typical transient outer currents in streptozocin (STZ)-induced diabetes in a mouse model (101).

In DbCM (stimulated by type 1 or type 2 DM), prolongation of QT interval is observed (102), escalating the risk of ventricular arrhythmias (103). The expansion of the action potential is primarily governed by the unregulated expression of various ion channel proteins and their characteristics (104).

### (i) Role of miRNA

Epigenetic regulators like miRNAs have more recently been found to be involved in the remodeling of the

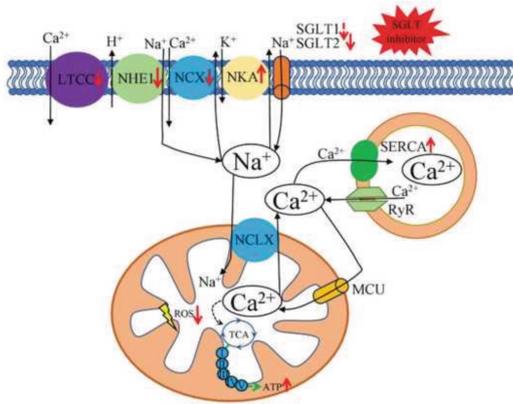


**FIGURE 4 |** Effect of SGLT2 inhibitors on ketone body metabolism, courtesy reference no. (125). By lowering plasma glucose levels and promoting adipose tissue lipolysis and FA synthesis, SGLT2 inhibitor therapy also increases the creation of ketone bodies. In the heart, ketone bodies are metabolized to acetyl- CoA more quickly than glucose or FA. SGLT2 inhibitors also promote the expression of critical genes involved in ketone oxidation, which causes the metabolism to switch using ketone bodies as a preferred substrate. The important metabolites and enzymes are indicated by red arrows, the primary metabolite fluxes are indicated by black arrows, and the synthesis of ATP by the mitochondrial oxidative phosphorylation system is indicated by green arrows. Fatty acids (FA), acetoacetyl CoA, 3-hydroxy-3-methylglutaryl-CoA, hydroxybutyrate, and the tricarboxylic acid cycle are examples of coenzymes. 3-hydroxy- 3-methylglutaryl-coenzyme A lyase is known as HMGCL. Mitochondrial-hydroxybutyrate dehydrogenase, also known as BDH1; adenosine triphosphate or ATP; acetyl-CoA acetyltransferase or ACAT1; acylcarnitine (C2-carnitine); hydroxybutyrylcarnitine (C4-OH carnitine); and succinyl-CoA:3-oxoacid-CoA transferase (CPT1) are examples of carnitine derivatives.

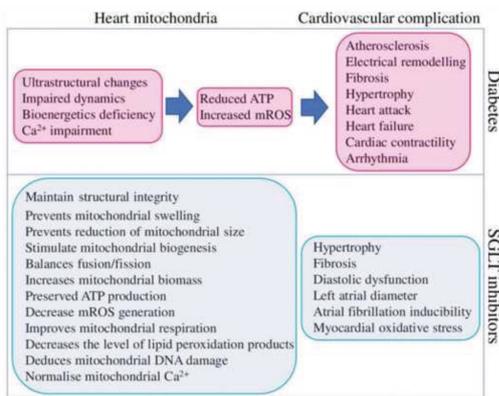
cardiac electrical system (1, 21). Diabetes miRNA-301a controls the expression of the voltage-gated potassium channel Kv4.2 (105). miRNA-29 overexpression caused structural cardiac damage in the diabetic mouse model (106). Increasing the amount of miRNA-141 has an impact on ATP generation by decreasing mitochondrial phosphate transport, as demonstrated by a mouse model of diabetes (91).

### (ii) Role of histone modifiers

The function of HDACs in the control of ion channel expression has been emphasized in several publications, although more research is still needed to determine their exact role. In a research, HDAC 5 was used to modulate the sodium-calcium exchanger (NCX)1. This NCX1 is involved in Ca<sup>2+</sup> + efflux out of the cells, and NK homeobox 5 regulates its expression (NK X2.5). It is connected to the recruitment of HDAC 5 to the promoter of the NCX gene (107). The acetylation of NK X2.5 escalated the crosstalk with HDAC 5, while the deacetylation of NK X2.5 enhanced its affinity toward the p300 complex, which was illustrated by a different study (108). Epigenetic controlling of HDAC 5 impacts Ca<sup>2+</sup> flux in the cardiomyocytes (109). Lehmann et al. (110) in this study revealed that the N terminal of HDAC 4 hampers myocyte enhancer factor 2 (MEF2). MEF2 action leads to a reduction in the hexosamine biogenerational pathway and is suppressed by nuclear orphan receptor NR4A expression (110). The porcine model of HF affecting the potassium showed the downregulation of HDAC 2 channels

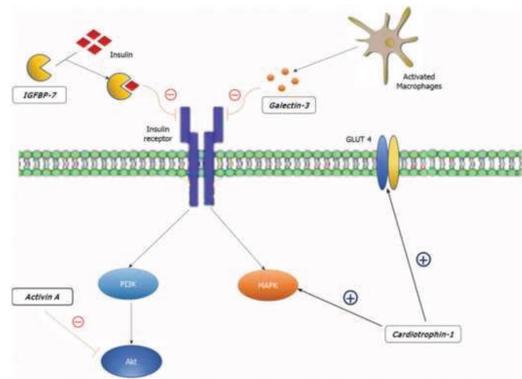


**FIGURE 5** | Red arrows point to essential metabolites and enzymes, black arrows point to main metabolite fluxes, and green arrows point to the mitochondrial oxidative phosphorylation system, which produces ATP. Examples of coenzymes include fatty acids (FA), acetoacetyl CoA, 3-hydroxy-3-methylglutaryl-CoA, hydroxybutyrate, the tricarboxylic acid cycle, and 3-hydroxy-3-methylglutaryl-coenzyme. The name HMGCL denotes a lyase. Acylcarnitine (C2-carnitine), hydroxybutyrylcarnitine (C4-OH carnitine), and succinyl-CoA:3-oxoacid-CoA transferase (CPT1) are a few examples of carnitine derivatives. Mitochondrial hydroxybutyrate dehydrogenase, also known as BDH1, acetyl CoA acetyltransferase or ATP. NCLX's effectiveness, however, is inferior to the MCU's absorption of Ca<sup>2+</sup>. The Ca<sup>2+</sup> absorption by SERCA and the leaking from the SR RyR receptors both have an impact on [Ca<sup>2+</sup>]<sub>i</sub> level. TCA cycle dehydrogenases are controlled by [Ca<sup>2+</sup>]<sub>i</sub> concentration, which leads to more ATP and less ROS being produced. The major transporters are indicated by red arrows, the fluxes of the ions are indicated by black arrows, and the synthesis of ATP by the mitochondrial oxidative phosphorylation system is indicated by green arrows. Sarcolemmal Na<sup>+</sup>/H<sup>+</sup>-exchanger NHE, voltage-dependent L-type calcium channel LTCC, mitochondrial Ca<sup>2+</sup> uniporter MCU, sarcolemmal Na<sup>+</sup>/Ca<sup>2+</sup> exchanger NCX, Na<sup>+</sup>/K<sup>+</sup>-ATPase NKA, ryanodine receptor RyR, and sarcoplasmic reticulum Ca<sup>2+</sup>-ATPase SERCA are some of the other proteins.

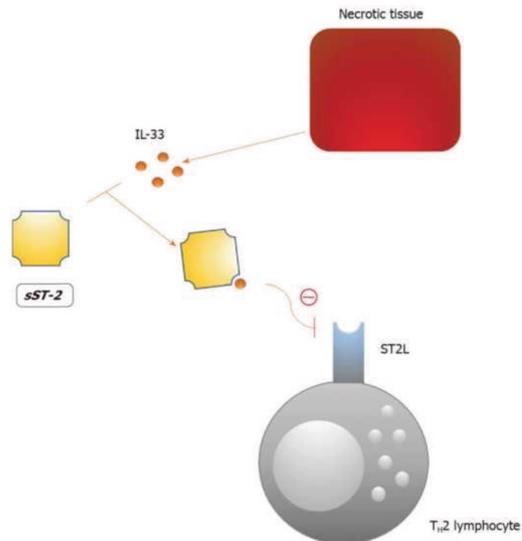


**FIGURE 6** | Courtesy reference no (125). Beneficial effects of SGLT2 inhibitors on mitochondrial function and the cardiovascular system and the role of diabetes in the development of cardiovascular problems (magenta) (blue).

along with QT interval prolongation (111), resulting in the hampering of HDAC 2 along with the influencing action potential. Hampering of HDACs with the utilization of class



**FIGURE 7** | Courtesy reference no. (127). Molecular targets of the diabetic cardiomyopathy biomarkers in cardiomyocytes. MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase-protein kinase B; IGFBP7, insulin-like growth factor binding protein 7; GLUT4, glucose transporter type 4.

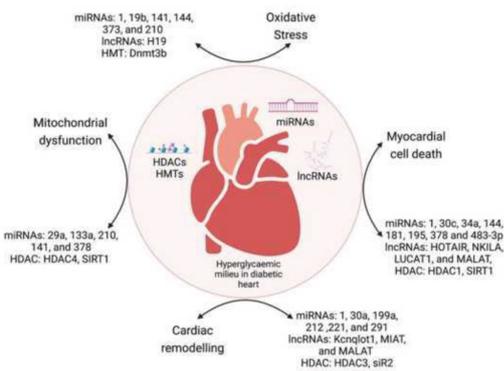


**FIGURE 8** | Courtesy reference no. (127). Molecular target of the soluble form of suppression of tumorigenicity 2. sST2, soluble form of suppression of tumorigenicity 2; IL-33, interleukin-33; ST2L, Suppression of tumorigenicity 2 ligand; T<sub>H</sub>2, T helper lymphocyte type 2.

Hampering agent entinostat might be a feasible therapeutic strategy for HF with the reduction of electrical remodeling besides structural remodeling in HF (112).

### Histone deacetylases hampering agent: future therapeutic strategy For DbCM

Histone deacetylases (HDAC) represent the molecules possessing the capacity of pleiotropic functions that are implicated in key homeostasis events like proliferation and cell cycle along with cell demise. HDAC hampering agents (HDACis) in particular block Zn<sup>2+</sup> based HDAC



**FIGURE 9** | Courtesy reference no. (8). The interaction between several DbCM systems and epigenetic modulators. Long non-coding RNAs, histone deacetylases, histone methyltransferases, microRNAs, lncRNAs, and DNA methyltransferases are few examples.

enzymes are implicated in histone acetylation. The USFDA recently approved HDACis for cancer therapy in clinical scenario (113). Furthermore, occasional publications pointed that histone acetylation might be an attractive therapeutic modality for the treatment of CVD in the preclinical model (114).

HDACis are classified into 5 categories depending on their structure:

- (i) Derivatives of hydroxamic acid, such as panobinostat and trichostatin A
- (ii) Short chain fatty (aliphatic) acids, such as sodium butyrate and valproic acid (VPA)
- (iii) Cycle-based peptides (like romedepsin)
- (iv) Benzamides I (like entinostat)
- (v) Sirtuin hampering agents.

These HDACis received the USFDA approval (115). Till date, HDACis utilization has not been done in clinical trials regarding fibrotic diseases; however, the utilization was made for cardiac along with lung fibrosis (116). The biggest actor implicated in this fibrotic situation is the fibroblasts' transformation into myofibroblasts (117). Studies pointing to HDACis achieving reversion of myofibroblasts activation in animal models have been illustrated. In hypertension, murine model fibrosis was ameliorated by VPA by controlling the acetylation of the corticoid receptor (118). When pressure overload occurred in a mouse model, VPA improved heart remodeling (119). Additionally, VPA reduced cardiac fibrosis via regulating ERK1/2 phosphorylation (120). According to a recent research, VPA reduced the remodeling event, which led to the establishment of atrial fibrillation (121). Similar to how HDACis showed anti-fibrotic effects, MPT0E014 also caused a decrease in Ang II and TGF-receptor expression in a mouse model of cardiomyopathy (122). By increasing the apoptosis and decreasing the phenotype of Ang II myofibroblasts, mocetinostat caused the expression of

HDACs to be downregulated in an HF model (123). HDAC 6 silencing or hampering with the utilization of tubacin resulted in the reduction of the expression of TGF-3, hence the reduction of cardiac fibrosis (124). A requirement for greater exhaustive studies is probing into the probability of selective HDACis for the therapy of DbCM.

### (i) Role of sodium-glucose cotransporter 2 (SGLT2) inhibitors

Furthermore, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been observed to be efficacious in the therapy of DbCM (see Figures 4–6 for modes of action apart from epigenetic modes) [rev in Ref. (125)].

As mentioned earlier in diabetic nephropathy, SGLT2 inhibitors might have part of epigenetic changes in these modes which need further evaluation (126). SGLT2 inhibitors escalate plasma in addition to tissue amounts of ketone-3 hydroxy butyric acid that stimulated  $\beta$  hydroxy butylation of H3 at Lys 9 of the adiponectin gene in adipocytes, which identifies that a novel histone posttranslational alteration important to the therapeutic activity of SGLT2 inhibitors (52) is independent of their methylation or acetylation. Even if there is limited understanding of DNA methylation, histone epigenetics, or both, there is some knowledge about miRNAs. In an open-label trial, 40 diabetic patients were compared with thiazides or dapagliflozin for their treatment, and miR30e-5p levels were measured as upregulated whereas miR199 a -3p downregulated in dapagliflozin treatment patients [135, rev in ref (12)]. This study points out that SGLT2 inhibitors might manipulate epigenetic controllers. Moreover, of the different biomarkers Kumric et al. (127) evaluated, lncRNAs, soluble form of suppression of tumorigenicity 2 along with galectin 3 apparently were of maximum advantages regarding DbCM pickup. Combination of comparatively economical along with precise speckle tracking echocardiography with certain emphasized biomarkers would be an attractive screening approach for the newly diagnosed T2DM. The idea of screening examination would be to guide the influenced patients to more particular corroborating test with the present guidelines which highlight the significance (127) (see Figures 7, 8).

## Conclusions and future directions

Diabetic cardiomyopathy represents a pleiotropic metabolic disease with complicated etiopathogenesis besides accumulated interactions among genetic and epigenetic factors. In the diabetic environment, there are various cardiomyopathy-inducing factors like ROS-modulated OS hyperglycemic situations, cytokines- modulated inflammation, cell demise (apoptosis, pyroptosis, and autophagy), and epigenetic controlling of dyscontrolled molecular pathways that are stimulated by these

mediators. The variations in epigenetic modifications including lncRNAs (miRNA along with lncRNAs), histone modification (methylation and acetylation), and DNA promoter methylation regulate the production of important molecules via many processes that modulate DbCM. In summary, earlier research has shown that genetic, environmental, and epigenetic interactions strongly influence the pathogenesis of DbCM through changes in the cellular signaling system (Figure 9).

The past decade has illustrated that miRNA along with lncRNAs are significant controllers of the main molecular pathways like cell demise, mitochondrial impairment, and electrical remodeling. Cardiac fibrosis is a significant event regarding cardiac remodeling event in DbCM. Considerable proof exists regarding the part of epigenetics in diabetic correlated cell demise. Epigenetic controlling modes like histone alterations, DNA methylation, and miRNA along with lncRNAs control cardiac cell demise in the diabetic environment. Akin to that, other modes like mitochondrial impairment and OS are controlled by miRNA along with lncRNAs. Finding these modes has given the provision of generation and formation of innovative therapy approaches for DbCM. miRNAs along with lncRNAs have illustrated translational capacity in the form of diagnostic and prognostic biomarkers, besides therapeutic approaches for DbCM. It was further illustrated that HDACs are significant controllers of the pathophysiology of DbCM. Hampering HDAC with the utilization of hampering agent has demonstrated attractive outcomes regarding cardiac fibrosis. Still the need is present to evaluate controlling modes like chromatin modifications along with circRNAs as ones aiding in the generation of DbCM. Advancements in genomics and molecular biology technologies like transposase accessible chromatin (ATAC) sequences deep sequencing, ChIP sequencing, and high throughput data on DNA methylomes can be made. Provision of a more exhaustive picture of DbCM with this genome-wide data would be feasible. Acquisition of this knowledge will aid in getting insight regarding the part of epigenetic modulators. Furthermore, we already have knowledge regarding the benefits of sodium-glucose cotransporter 2 (SGLT2) hampering agents in the therapy of DbCM. As mentioned earlier in diabetic nephropathy, SGLT2 inhibitors might have part of epigenetic changes in these modes that need further evaluation. SGLT2 inhibitors escalate plasma in addition to tissue amounts of ketone-3 hydroxy butyric acid that stimulated  $\alpha$ -hydroxy butylation of H3 at Lys 9 of the adiponectin gene in adipocytes independent of their methylation or acetylation that isolates a new histone posttranslational modifications significant to the therapeutic action of SGLT2 inhibitors. This study points out that SGLT2 inhibitors might manipulate epigenetic controllers. Moreover, the role of lncRNAs might be of advantage for the early diagnosis of DbCM.

## Author contributions

KK and GA reviewed the references. MS finally approved the main draft of the work by KK with mutual agreement.

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