Review

# Prevention of diabetic cardiomyopathy through metabolic amendments of myocardium by melatonin: a role beyond antioxidative efficiency

**Adrita Banerjee[1, 2], Aindrila Chattopadhyay[2], Debasish Bandyopadhyay[1*]**

[1]Oxidative Stress and Free Radical Biology Laboratory, Department of Physiology, University of Calcutta, 92, APC Road, Kolkata-700009, India
[2]Department of Physiology, Vidyasagar College, 39, Sankar Ghosh Lane, Kolkata-700006, India
*Correspondence: debasish63@gmail.com, Tel: +91-9433072066

**Running Title:** Melatonin modulates metabolic pathways to prevent diabetic cardiomyopathy

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## ABSTRACT

The alarming rise in diabetes throughout the world brings the scientists at the brink of finding the suitable remedies which can impede glucotoxicity and insulin resistance involved in initiation and progression of diabetes. Either devoid of insulin or resistance to insulin makes the pancreatic tissue a most vulnerable target. However, cardiac tissue, is another target of hyperglycaemia. The remodelling of cardiac tissue in insulin resistant individuals often includes cardiac hypertrophy along with misaligned diastolic and systolic functions. All these amendments reduce cardiac contractility and cause heart failure. Both carbohydrate and fatty acid metabolism are altered in diabetes with declined glycolysis and elevated lipolysis leading to rise in fatty acid oxidation. Melatonin, as a potent antioxidant, reduces the excessive reactive oxygen species (ROS) generation induced by glucotoxicity, therefore, prevents diabetes associated cellular injury. The reduced ROS production, in turn, lowers both glucose and fatty acid accumulation by augmenting glycolysis and diminishing lipolysis. Melatonin also inhibits gluconeogenesis and glycogenesis pathways in diabetic myocardium. The regulation of important metabolic pathways by melatonin assists the myocardium to maintain energy balance, the primary need for heart contraction. Hence, this review focuses on metabolic modulatory actions of melatonin in diabetic myocardium, which may encourage its usage as a saviour for diabetic cardiomyopathy.

**Key words:** diabetic cardiomyopathy, carbohydrate metabolism, fatty acid metabolism, melatonin, cardiac function

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## 1. INTRODUCTION

Among metabolic disorders, diabetes mellitus (DM) is a leading cause of death worldwide (1). Pancreatic oxidative stress, high glucose intake, obesity- any of them or all in combination lead to glucose intolerance (2, 3). As a typical physiological response, pancreas secretes more insulin and manages to neutralize the hyperglycaemia (4). However, this long-lasting excessive insulin secretion makes the pancreatic tissue exhausted with mitochondrial

and endoplasmic reticulum stress (5, 6). On the other hand, the surplus of insulin secretion fails to ameliorate hyperglycaemia which is referred as insulin resistance (7). The prevalence and progression of diabetes give rise to various life-threatening disorders (8-10). The excessive blood glucose is the biomarker of diabetes; thus, red blood cells are the first to expose to high glucose (11) followed by cardiac tissue. As a result, the diabetic cardiac anomalies emerge as a primary cause of morbidity as well as the mortality (12). The alterations in cardiac structure and functions are collectively named as 'Diabetic Cardiomyopathy' (DCM) featured as left ventricular hypertrophy, fibrosis, changes in cardiac contractility, myocardial ischaemia, etc. (13, 14). These cardiac abnormalities other than those observed in coronary artery disease are signature marks of DCM which has been considered as a multifactorial disease.

Among the factors responsible for DCM, oxidative stress can be considered as one of the initial causes. High plasma glucose mediated excessive ROS generation is unavoidable for diabetic patients (15), especially in their myocardium (16). Under hyperglycaemia, the myocardium responds to reduction in glucose oxidation (17) and find the alternative source for ATP production. Insulin resistance in diabetes gives rise to excess of free fatty acids in plasma by accelerating the process of lipolysis (18). Thus, fatty acid becomes the central source of energy for diabetic myocardium and as a consequence, the rate of fatty acid oxidation surges with lipid accumulation (19, 20). Overload of fatty acids and escalation in beta-oxidation prompt mitochondrial ROS generation (21) and reduced contractility of cardiomyocytes (22). Moreover, the long chain free fatty acids can alter plasma membrane composition and fluidity which may cause release of cytochrome C from mitochondria with succeeding cellular death (23).

Since a fine weaving between excessive ROS generation and metabolic perturbation is prominent as aetiology of diabetes, a mitochondria-targeted stress reliever which can bring about normalcy in metabolic pathways can be the best preventive approach. Melatonin seems as such a reliever, by its virtue, acting as an antioxidant and also as a metabolic regulator (24, 25). The contribution of melatonin as an antioxidant in impediment of diabetes and associated disorders like DCM has been well documented but, its metabolic modulatory roles on this issue remains less cultivated. As to its metabolic activities, melatonin enhances the glucose uptake in adipose tissue by influencing the expression of GLUT(s) (Glucose transporter) to lower the plasma glucose load (26) and escalates the aerobic oxidative rate of glucose (27) as well as suppresses gluconeogenesis from non-carbohydrate sources (28). In addition, melatonin regulates fatty acid metabolism by interacting with enzymes which are involved in rate limiting steps of fatty acid synthesis (29). Therefore, melatonin reduces excessive fatty acid burden and assists the cells to rely upon carbohydrates instead of lipids as energy source under hyperglycaemia. These actions of melatonin in cardiac cells lower likelihood of ROS generation and facilitates cells to avert the fatty acid metabolism associated mitochondrial uncoupling (30). Hence, melatonin instigated preferential selection of energy source to avoid insulin resistance, mitochondrial uncoupling and excessive ROS generation, preserves the cardiac structure, function and the integral contractile nature of heart in diabetes patients.

## 2. DCM

The exclusive risk factors for DCM are independent for those in coronary arterial disease, hypertension, congenital heart disease or cardiac valvular disease (31). Hyperglycaemia and insulin resistance contribute equally in the progression of DCM, the alterations of vascular structure and metabolism (14, 32, 33). If not screened and diagnosed at appropriate time, especially in the asymptomatic type 2 diabetes, the gradual progression of disease leads to

heart failure (34, 35). Alterations in cardiac systolic and diastolic functions in diabetes are the primary causes behind such detrimental outcomes (33), where early-onset diastolic dysfunction followed by systolic dysfunction cause cardiac hypertrophy, and fibrosis, and finally failure (36). The early diastolic filling with escalated atrial filling is the biomarker of type 1 diabetes (37) whereas, left ventricular hypertrophy is the primary pathophysiology behind ventricular dysfunction in type 2 diabetes (38). The insulin resistance and enhanced left ventricular mass indicate a strong linkage between cardiac hypertrophy and heart failure (39, 40). Additionally, the action of insulin as a growth factor in cardiac tissue has been substantiated in type 2 diabetes where augmented insulin signalling participates in progression of cardiac hypertrophy (41). Interstitial and perivascular fibrosis are also the causative factors of cardiac hypertrophy (42). In type 2 diabetic patients with hyperinsulinemia, collagen, and especially collagen type III deposits in intramural vessels and myofibres, indicating fibrosis in diabetes (43). Hyperglycaemia also activates renin-angiotensin-aldosterone system and the resulted augmentation in angiotensin II level promotes cardiovascular proliferation and cardiac hypertrophy (44, 45). The occurrence of myocardial infarction, myocardial ischaemia and heart failure are often observed in both type 1 and 2 diabetes (46, 47). Moreover, defective cardiac insulin metabolic signalling strengths the correlation between hyperglycaemia and cardiac abnormalities, a leading cause of death among diabetic patients (48, 49).

Various factors, associated with diabetic cardiac incongruities have been identified. These include oxidative stress, inflammation, endoplasmic reticulum (ER) stress, mitochondrial structural and functional disorientation, advanced glycation end products (AGE) mediated extracellular matrix stiffness (48, 50) and all of these can cause myocardial infarction and heart failure (51, 52). The metabolic amendments involved in cardiac structural and functional modifications have been extensively studied (13, 53, 54). A disturbed homoeostasis of substrate utilisation and energy production has been considered as the key aetiology of DCM (54, 55). Declined energy level lowers efficiency of heart contractability and jeopardizes its diastolic and systolic functions (35). The inability of diabetic heart to utilise more glucose as substrate to generate ATP becomes the sole pathophysiological factor of initiation and progression of DCM (54). This low glucose oxidation makes the cardiac tissue less efficient in substrate use (56) and leads the myocardium to be more dependent on fatty acid oxidation (57, 58). This substrate shift alarmingly enhances the chance of malfunction in oxidative phosphorylation pathway with excess of proton leakage from mitochondria (48) which triggers ROS generation (59). The mitochondrial uncoupling further lowers ATP production and the ATP dependent contractile efficiency of cardiac cells (60, 61). This is a vicious cycle of high glucose instigated metabolic alterations and excess oxidative stress generation associated with DCM.

## 3. DCM AND ALTERED CARDIAC METABOLISM

### 3.1. Substrate shifting in DCM.

The substrate switching of diabetic heart was highlighted as a major concern for cardiac morphological as well as pathophysiological alterations even though the preferential switching of normal cardiac tissue from glucose to fatty acid occurs just after birth depending on the plasma fatty acid content (61, 62). However, hyperglycaemia makes cardiac tissue to use fatty acid as the exclusive substrate for energy generation in diabetes (58, 63) where insulin resistance acts as the signal for such biased shifting (64, 65) and thus, β-oxidation of free fatty acids becomes the sole ATP generating pathway of diabetic heart (57). Two

possible factors may relate to this metabolic amendment. First, less glucose has been uptaken by cardiac cells and second, excessive fatty acid accumulated within cardiac cells which might drive the tissue to restrict its energy generation from fatty acid oxidation.

### 3.2. Alterations in carbohydrate metabolism.

The myocardial metabolic substrate shift in diabetes has been attributed to insulin mediated reduction in glucose uptake (66). The insulin instigated depletion of glucose transporter protein type 4 (GLUT4) in diabetic myocardium is responsible for its lower uptake from plasma (67). Along with GLUT4, glucose transporter protein type 1 (GLUT1) expression was also abated in diabetic cardiac tissue (68). Apart from low GLUT content of myocardial cells, the abated translocation of GLUT4 to the sarcolemma in hyperglycaemia, makes cardiomyocytes more averted from plasma glucose (69). A clinical trial showed a significant downregulation of GLUT4 expression in diabetic patients with cardiac ailments (70). The non-availability of glucose causes suppression of glycolytic cycle (32) leading to a drastic decline in glucose oxidation. The depressed glucose oxidation level in type1 diabetic patients has also been observed (17, 61, 71) as in type2 diabetes (72, 73), which may be due to the reduction in pyruvate dehydrogenase (PDH) flux toward mitochondria (74).

### 3.3. Modifications of lipid metabolism.

On other hand, in hyperglycaemia, an increase in free fatty acid content (75) and subsequent augmentation of its flux in cardiomyocytes (61) compel myocardium to utilize fatty acid over glucose. This excessive fatty acid uptake has been observed in both type1 (22, 76) and 2 (17) diabetic patients. Insulin resistance in diabetes induces excessive lipolysis of adipose tissue. The accumulation of free fatty acids and triglycerides (19, 74) become high cardiac risk factor in type1 diabetic patients (77). Moreover, the free fatty acid uptake into cardiomyocytes is a dynamic process with several routes. These include passive diffusion, through fatty acid translocase and/or fatty acid binding protein (FABP) mediated translocation which provide the lipid entry into myocardium a supremacy over glucose (78). The preference of cardiomyocytes for fatty acids is more obvious when the expressions of FABP4 and FABP5 augment in type2 diabetes with cardiovascular abnormalities (79, 80) and this has been substantiated in animal studies (81, 35). Free fatty acids of plasma not only compete with glucose entry to myocardium, but also hinders glucose oxidation by impeding the action of PDH, a crucial enzyme for glucose metabolism (82, 83). Excess fatty acid oxidation increases the ratio of acetyl coA/coA with a concomitant rise in $NAD^+$ cofactor, which in turn impedes the action of PDH and hampers glucose oxidation (84). Additionally, the ascended expression of peroxisome proliferator-activated receptor-gamma coactivator-1 α (PGC-1α) (85) in diabetic heart in turn elevates the expression of peroxisome proliferator-activated receptor α (PPARα) (86), a transcriptional factor accountable for induction of enzymes involved in beta oxidation (87, 88). PPARα not only positively regulates fatty acid oxidation, but also elevates the rate of beta oxidation by hindering glucose oxidation through pyruvate dehydrogenase kinase (PDK4) actuation, responsible for PDH inactivation (35, 12).

The selection of fatty acid as the major energy source by diabetic myocardium makes its uptake over its oxidising capacity (89- 91) with fatty acid accumulation, leading to cardiac lipotoxicity (92-94). Overload of fatty acid also triggers synthesis and further cumulation of a potent cardiotoxin ceramide, (32, 95, 96) which induces myocardial apoptosis in diabetic patients (95, 97). Thus, this lipotoxicity induced lipoapoptosis (98, 61) triggers morphological (99-101) and functional (102-104) alterations of cardiac tissue. The

suppressed contractility (99) and hindered myocardial performance (105) are the consequences of the altered lipid metabolism under the state of hyperglycaemia in diabetes (19, 105, 106).

## 4. LIPID METABOLISM INVOLVED OXIDATIVE STRESS IN DCM

Oxidative stress has been identified as a keynote factor behind occurrence of hyperglycaemia (107, 108) and this excessive ROS is detrimental for diabetic myocardium (109-111). Oxidative stress alters metabolism and morpho-functions in the myocardium (55, 111-114). In addition to insulin resistance, high glucose is considered as the principal metabolic anomaly to cause most pernicious outcome of diabetes, i.e., DCM. The accumulation and oxidation of fatty acid is another important factor behind redox imbalance in cardiac tissue of diabetes (99, 115, 116). The hindrance of glucose utilization in diabetic myocardium causes excess fatty acid oxidation (69) and lipid accumulation with subsequent stress in DCM. Hence, lowering lipid and subsequent stress level has been recommended as a therapeutic measure for DCM (36). Mitochondria are the major site of ROS generation. The morphologically altered and malfunctional mitochondria have been reported in the DCM (117, 118). Overexpression of mitochondrial superoxide dismutase (MnSOD) provides protection to DCM (119). In patients with diabetes, the augmented fatty acid mediated excessive mitochondrial ROS generation are supportive to cardiac lipid metabolism involved oxidative stress (120, 121). In diabetic heart, metabolic substrate switching and subsequent excessive fatty acid oxidation leads to hampered oxidative phosphorylation with excessive free radical generation (120, 122). The excessive β-oxidation causes electron leakage in mitochondria to produce superoxide anion radical (123), the hydrogen peroxide and hydroxyl radical (124). Moreover, fatty acid induced mitochondrial uncoupling causes less ATP production and incomplete reduction and thus it indicates lipid metabolism related declined cardiac efficiency (12, 125-127). The escalation of uncoupling has been reported in diabetic myocardial cells of mice with overloaded ROS and lipid peroxides (20, 128).

## 5. MELATONIN: A METABOLIC REGULATOR

Melatonin, a naturally occurring molecule, has been drawn a great attention due to its ability to redeem multiple arrays of metabolic hazards and disorders (24, 129). The antioxidant property of melatonin takes the ascendancy over its other properties in providing protective effects to stress stricken morpho-functionally altered tissues and/or cells. Not only its antioxidative activity, but also its anti-inflammatory and anti-apoptotic properties render this molecule as one of the best remedies for metabolic syndrome (130, 131).

Randomized control and double-blind clinical studies have authenticated the harmonizing effects of melatonin on metabolic syndrome components like fasting glucose, blood pressure, cholesterol level etc (132, 133). Diabetes is the most prevalent metabolic disorder with imbalance in plasma glucose and insulin level (134, 135). Melatonin exhibits anti-hyperglycaemic property with the potency to balance both insulin and glucose levels via endocrine signalling and metabolic modifications. Apart from protecting cells/tissues from high glucose stress and insulin resistance (136), melatonin shows enormous effects on carbohydrate metabolism by controlling the blood glucose and maintaining energy homoeostasis (24). Melatonin enhances the glucose uptake both in adipocytes and skeletal muscle to lower blood glucose load (137, 138). It also inhibits the rate of hepatic gluconeogenesis (28) through silent information regulator 1 (SIRT1) activation (139). Pinealectomy in rats abated GLUT4 expression and increased insulin resistance and this can

be rescued by melatonin administration (140, 141). In alloxan induced diabetic rats, melatonin steers the glucose metabolism toward aerobic mode by decreasing the activity of lactate dehydrogenase (LDH) (142). A more favourable action of melatonin toward energy balance comes through normalization of the activity of glucose-6-phosphate-dehydrogenase (G6PDH) in diabetic kidney, which leads to escalation in level of reduced nicotinamide adenine di-nucleotide phosphate ($NADPH_2$), an integral factor of aerobic oxidation of glucose (143).

The modulatory activity of melatonin has not only been evidenced in carbohydrate metabolism, but also in fatty acid metabolism (144). Long term melatonin administration influences the fatty acid metabolism along with alterations of lipid profile in type 2 diabetic rats (145). In DCM, the overload of fatty acids drives the cellular metabolic load toward beta oxidative pathway, as evidenced while melatonin hinders the synthesis of fatty acids directly to rescue cells from lipid burden. Melatonin impedes activities of acetyl-CoA carboxylase and fatty acid synthase in hyperlipidemic hamsters causing retardation in fatty acid production and concomitant decrease in triglyceride and cholesterol levels (29, 146). This has also been observed in *in vitro* condition. Alterations of lipid content in high concentration oleic acid exposed HepG2 has been prevented with melatonin pre-treatment where it acts by inhibiting acetyl-CoA carboxylase and other enzymes, involved in lipogenesis (147).

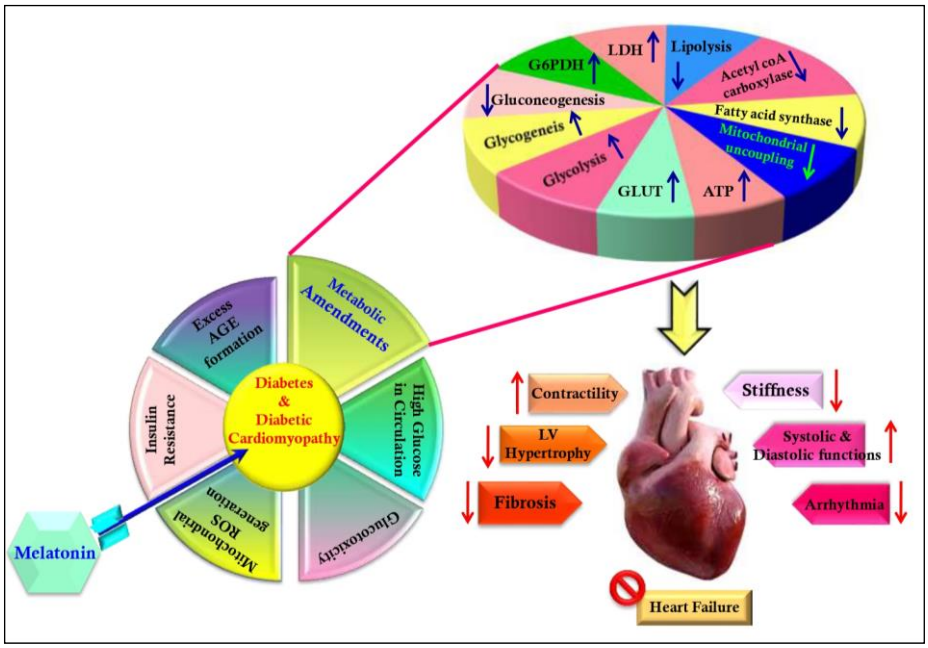


**Fig.1. The potentially protective mechanisms of melatonin on DCM.**

*The protective effects of melatonin on diabetes and DCM are to reduce many of severe symptoms among which metabolic amendment is a major one. Both carbohydrate and fatty acid metabolism pathways have drastically affected in diabetic heart, where melatonin rescues from those alterations to maintain convention in ATP level in order to normalize cardiac structure and function.*

## 6. MELATONIN DEFICIENCY AND DISORGANISED METABOLISM

A strong correlation between compromised melatonin synthesis and hyperglycaemia (148, 149) has put forward the goal for scientists to inspect the involvement of biorhythm and pineal gland function behind disastrous ailments of diabetes. The disarray in circadian rhythm

remains excused for long as a responsible factor behind metabolic alterations associated with hyperglycaemia. The disturbed biorhythm has been considered experimentally as a causative factor behind the development of metabolic syndrome (150) such as in type 2 diabetes (143). Thus, targeting the circadian rhythm becomes a potential approach to treat diabetes (151). It was shown that a fine harmony between biorhythmic melatonin and insulin secretion is a protective measure for diabetes (152, 153). The maintenance of circadian rhythm entrained metabolic pathways is also equally considerable in terms of a preventive measure towards development of hyperglycaemia (154, 155). The correlation between circadian rhythm misalignment and disturbed plasma glucose level comprehensibly indicates their association with glucose intolerance (154), such as in the shift workers (150). Advancement toward type 2 diabetes in patients with sleep deprivation, disrupted circadian rhythm also suggested this crucial association (156, 157). For example, pinealectomy with circulatory melatonin deficiency leads to night-time high blood glucose concentration (158) which induces surged insulin resistance and glucose intolerance (159, 160). Those metabolic amendments toward glucose overload and ensuing glucose intolerance have also been noted in melatonin receptor knockout mouse model (161) which again substantiates crucial involvement of the pineal indole in metabolic regulations. The decline in the level of melatonin with night time light exposure was also found responsible for metabolic disturbances (162), specifically, increase in the rate of gluconeogenesis (163). Melatonin supplementation maintained the glucose homoeostasis (164) which improves metabolic status of obesity associated pre-diabetic rat heart and impedes occurrence of myocardial ischaemia (165). The relevance of melatonin biorhythm in preserving metabolic status in normalcy became more prominent with 24 hour rhythmic melatonin exposure on primary adipocytes *in vitro* (166). Here, melatonin administration has shown to keep balance in fatty acid level by enhancing free fatty acid incorporation within adipocytes along with reduction in lipolysis rate. An association between melatonin rhythm disruption and occurrence of diabetic autonomic neuropathy also endorsed the effective role of pineal indole in retarding the development of diabetic symptoms (167). Hence, in addition to its antioxidative activity, melatonin biorhythm and associated metabolic modulations in high glucose system have enlightened the effect of this indolamine on both carbohydrate and lipid metabolism (158, 168, 169).

## 7. ALLEVIATION OF METABOLIC PERTURBATIONS IN DCM BY MELATONIN

The metabolic modulatory actions of melatonin add some feathers to its highly potent antioxidative role in amelioration of diabetes and associated disorders. Since, both metabolic pathways and oxidative stress are related to mitochondria, functional mitochondria are essential in mitigating metabolic disarray caused by glucotoxicty. Melatonin preserves stress stricken mitochondrial structure and thus revives functional status of cardiac mitochondria in DCM patients (170), otherwise, dysfunctional mitochondria in myocardium drastically lower functional mitochondrial content and energy production (171). Melatonin hinders the development of DCM (130) in multitudinous ways (172). Melatonin pre-treatment reduces glucose load by scavenging ROS (165, 173) and it also can rescue from the deleterious outcomes of diabetes by obstructing advancements of the disease toward heart failure (131).

Melatonin stimulates PGC-1α to increase SIRT3 level of diabetic cardiac tissue which contributes in mitochondrial biogenesis with an obvious rise in activities at complex I, III and IV (174). Hence, melatonin keeps energy balance by preserving oxidative phosphorylation. Melatonin also contributes in arresting excessive fatty acid oxidation and facilitates the cellular environment to rely upon glucose oxidation pathways (175). Fatty acid overload in myocardium of hyperglycaemics with insulin resistance is due to excessive fatty acid uptake.

This is mediated by PPARα, the transcription factor responsible for activation of enzymes related to β-oxidative pathway (176). Melatonin upregulates the expression of PPARα mRNA in hepatic and adipose tissue and accelerates fatty acid metabolism in those tissues to lower free fatty acid load (177, 178). These protective activities may be mediated by its receptor since mutated *MTNR1B* (Melatonin receptor 1B) gene is associated with diabetes (179, 180). The downregulation of melatonin nuclear receptor, RORα, is correlated with progression of DCM while melatonin application reduces cardiac hypertrophy and fibrosis associated with diabetes (181).

Hence, apart from the antioxidative and mitochondria preserving actions, the modulation of cardiac metabolism by melatonin effectively retards the occurrence of DCM. The key metabolic improvement by melatonin is to decrease glucose level and fatty acid load and lipolysis. The potency of melatonin to keep metabolic balance is the prime factor behind maintenance of non-oxidative environment in myocardial tissue. Thus, the role of melatonin particularly in carbohydrate and fatty acid metabolism regulation of diabetic myocardium is nothing but an indication of fostering the usage of melatonin as an aid for DCM.

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## CONFLICT INTEREST

The author(s) declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

## AUTHORSHIP

DB contributed to the conception. AB drafted the first version of the manuscript and figures and performed editing works. AC and DB critically reviewed the manuscript and approved it.

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