Kaur et al. Scr Med. 2025 May-Jun;56(3):579-87. DOI:10.5937/scriptamed56-59599

REVIEW ARTICLE

Beneficial Effects of Propionyl L-Carnitine Therapy in Diabetic Cardiomyopathy

Khushman Kaur,[1] Lorrie Kirshenbaum,[1] Paramjit S Tappia,[2] Naranjan S Dhalla[1]

Abstract

In this review, the beneficial effects of metabolic therapy with propionyl L-carnitine (PPLC) on cardiovascular complications during the development of diabetic cardiomyopathy was evaluated. Since metabolic abnormalities due to mitochondrial dysfunction are invariably associated with deficiency of carnitine, accumulation of toxic long-chain derivatives of fatty acids and development of oxidative stress in the heart, it appears that the effects of PPLC therapy are related to the attenuation of these derangements. Particularly, the beneficial effects of PPLC therapy in improving cardiac function in chronic diabetes were associated with attenuation of increase in sarcolemmal Ca^{2+}-binding and Ca^{2+}-ecto ATPase activities. Furthermore, depressed sarcolemmal Na^{+}-K^{+} ATPase and Na^{+}-dependent Ca^{2+}-uptake as well as sarcoplasmic reticulum Ca^{2+}-pump activities in diabetic hearts were attenuated by PPLC therapy. These actions of PPLC therapy were accompanied by improvement in mitochondrial oxidative phosphorylation and attenuation of changes in the high energy phosphate stores in the diabetic heart. Since incubation of sarcolemma with PPLC was found to reduce the inhibitory actions of palmitoyl L-carnitine on Na^{+}-K^{+} ATPases and Na^{+}-dependent Ca^{2+}-uptake, it is suggested that PPLC therapy may attenuate cardiac abnormalities by antagonising the deleterious actions of accumulated long- chain lipids in diabetic cardiomyopathy.

Key words: Diabetic cardiomyopathies; Propionyl L-carnitine; Palmitoyl L-carnitine; Oxidative stress; Sarcolemma; Sarcoplasmic reticulum; Mitochondria.

1. Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Centre, Department of Physiology and Pathophysiology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada.
2. Asper Clinical Research Institute, St. Boniface Hospital, Winnipeg, Canada.

Citation:
Kaur K, Kirshenbaum L, Tappia PS, Dhalla NS. Beneficial effects of propionyl L-carnitine therapy in diabetic cardiomyopathy. Scr Med. 2025 May-Jun;56(3):579-87.

Corresponding author:
NARANJAN S DHALLA
T: (204) 235-3417
E: nsdhalla@sbrc.ca

Received: 18 June 2025
Revision received: 20 June 2025
Accepted: 21 June 2025

Introduction

Chronic diabetes is a major health hazard, which not only results in diabetic cardiomyopathy (in the absence of coronary disease) but is also a risk factor for the development of heart failure.[1-12] This complex disease is primarily caused by either insulin deficiency or insulin resistance and is generally associated with elevated levels of plasma glucose and lipids as well as reduced utilisation of glucose and increased utilisation of free fatty acids in the heart. Since several vasoactive hormones such as catecholamines, angiotensin II, vasopressin, serotonin and endothelin are elevated in diabetic subjects, these hormones are also considered to participate in inducing diabetes-associated cardiovascular disease, atherosclerosis and cardiac dysfunction.[13-16] Although, the exact mechanisms for the occurrence of diabetic cardiomyopathy are not clear, it has been suggested that the development of oxidative stress, inflammation, intracellular Ca^{2+}-overload and metabolic

alterations are intimately involved in its pathogenesis.[11, 12, 16-20] Furthermore, extensive studies have shown that cardiac dysfunction in diabetic cardiomyopathy may be a consequence of subcellular remodelling associated with excessive entry of Ca^{2+} through sarcolemma (SL), defects in sarcoplasmic reticulum (SR) for Ca^{2+}-handling and mitochondrial Ca^{2+}-overload for the impairment of energy production.[1, 2, 14, 16, 19-21] A wide variety of pharmacological interventions including antioxidants, blocking of renin-angiotensin system, Ca^{2+}-antagonists, adrenoreceptor antagonists and metabolic inhibitors have been shown to exert beneficial, but partial, effects in diabetic cardiomyopathy.[9, 15, 20, 21] It has now become clear that diabetic cardiomyopathy is a multifactorial disease and thus a detailed understanding of various target sites for identifying appropriate drug therapy is considered of critical importance. This article is therefore focused on the discussion for metabolic therapy of chronic diabetes with propionyl L-carnitine (PPLC), a highly active amphipathic derivative of L-carnitine, which has been used for the treatment of different cardiovascular diseases such as peripheral vascular disease, ischaemic heart disease, arrhythmias, atherosclerosis, diabetic cardiomyopathy and heart failure.[22-28]

Functional significance of L-carnitine derivatives

In view of the role of mitochondria in the generation of energy for cardiac function and the identification of mitochondrial defects in various cardiovascular diseases, these organelles are considered to serve as excellent targets for the development of different interventions to promote energy production in the diseased myocardium.[2, 11, 12, 18] In fact, there is increasing evidence that L-carnitine and its short-chain derivatives such as PPLC and acetyl L-carnitine, which promote the transport and oxidation of long-chain fatty acids for energy production in mitochondria, are most useful interventions for the treatment of heart disease.[23, 27-30] This view is supported by the fact that myocardial carnitine deficiency has been demonstrated to be associated with the occurrence of different heart diseases both in humans and experimental animals.[31-35] It is pointed out that a long chain acylderivative of L-carnitine, palmitoyl L-carnitine (PMLC), which is also formed by carnitine acyltransferases in mitochondria, is known to exert deleterious actions, unlike PPLC, on the myocardium and is considered to be involved in the pathogenesis of heart disease.[36-38] While L-carnitine, acetyl L-carnitine and PPLC did not show any *in vitro* effect on cardiac contractility and subcellular ATPase activities, PMLC was observed to depress contractile force development and myofibrillar Ca^{2+}-stimulated ATPase, mitochondrial Mg^{2+} ATPase, SR Ca^{2+}-pump ATPase as well as SL Ca^{2+}-pump ATPase and Na^{+}-K^{+} ATPase activities.[39-41] Furthermore, the beneficial actions of PPLC therapy are not only considered to be due to its effects on myocardial metabolism, but other actions such as antioxidant and Ca^{2+}-antagonism have also been documented in this regard.[42-45] It should be noted that therapy with L-carnitine, unlike that with PPLC or acetyl L-carnitine, was observed to reduce body mass of diabetic patients indicating differences in the mode of action among L-carnitine and its derivatives.[46]

PPLC therapy and diabetes-induced cardiovascular abnormalities

Not only is chronic diabetes associated with diabetic cardiomyopathy, but there also occurs several other organ pathologies such as angiopathy, arteriopathy, neuropathy, retinopathy and peripheral vasculopathy in patients with diabetes.[1, 47-50] Accordingly, it is generally considered that diabetes affects both blood vessels and cardiomyocytes and is intimately associated with the development of impaired microcirculation. In this regard, it was observed that PPLC therapy increased peripheral blood flow and improved symptoms related to microcirculation in diabetic patients with arterial disease and peripheral vasculopathy.[47, 48] The prevention of diabetic neuropathy and retinopathy upon PPLC therapy was mediated by the amelioration of changes in microcirculation and tissue carnitine content and thus resulting in an increase in fatty acid oxidation and shortening of the peak latencies in the oscillatory potentials in the electroretinogram.[50, 51] PPLC therapy also improved diabetic neuropathy by attenuating the delay in nerve conduction, decreased R-R variability and reduced sciatic nerve blood flow, in addition to increasing the nerve

tissue carnitine level and reducing the serum triglyceride level.[49] Furthermore, combination therapy of PPLC and 5-phosphodiesterase inhibitors such as sildenafil and vardenafil, was found to exert synergic effect in diabetic patients with erectile dysfunction by improving blood flow as a consequence of reduction in endothelial dysfunction, decrease in the levels of advanced glycation end products and depression in oxidative stress.[52-54]

Treatment of chronic diabetes with PPLC was found to overcome cardiac dysfunction because it increased myocardial carnitine content, improved lipid metabolism and lowered plasma lipids.[55, 56] The improvement in cardiac function by PPLC therapy was also observed to be associated with increases in ATP production as well as tricarboxylic acid cycle activity due to augmented glucose and palmitate utilisation.[57] Furthermore, the beneficial effects of PPLC therapy in diabetic cardiomyopathy were seen to be associated with attenuation of the impaired erythrocyte membrane phospholipid fatty acid turnover.[58] Since diabetic hearts are vulnerable to ischaemia- reperfusion injury during cardiac surgery, the effects of PPLC therapy were also evaluated in diabetic patients undergoing coronary bypass surgery.[59] It was found that PPLC administration improved hemodynamic changes, reduced the trans-cardiac endothelin difference and depressed the rapid hypoxanthine washout during reperfusion. Chronic PPLC treatment was also observed to show improved function of post ischaemic diabetic heart due to an increase in the oxidation of glucose and palmitate.[60] The improvement of cardiac function in diabetic ischaemia- reperfusion hearts by PPLC therapy was seen to be associated with enhanced mitochondrial oxidation of pyruvate and glutamate.[61] These observations indicate that PPLC therapy not only showed beneficial effects in diabetic cardiomyopathy, but also prevented the ischaemia- reperfusion induced alterations in cardiac function and myocardial metabolism in diabetic hearts.

PPLC therapy and diabetes-induced subcellular alterations

Extensive studies have revealed that cardiac dysfunction in diabetic cardiomyopathy is associated with remodelling of subcellular organelles such as SL, SR, mitochondria and myofibrils in the heart.[1, 2, 14, 15, 20, 21] It is now well known that the SL membrane is involved in Ca^{2+}-entry for excitation-contraction coupling whereas the SR membrane is related to the regulation of intracellular Ca^{2+} for the occurrence of cardiac contraction and relaxation processes. Furthermore, mitochondria are mainly concerned about the process of energy production whereas myofibrils are associated with the process of energy utilisation during cardiac contraction. By employing a rat model of streptozotocin- induced diabetic cardiomyopathy,[20, 21, 62, 63] we have observed that heart function was depressed. This defect was evident from depressions in the left ventricle developed pressure as well as in both positive and negative rates of contractile force development. Previously, PPLC therapy of animals with chronic diabetes was shown to prevent alterations in cardiac dysfunction.[20] Although myofibrillar Ca^{2+}-stimulated ATPase, which determines the strength of cardiac contractile force development, was depressed in diabetic cardiomyopathy, this activity was not improved by PPLC treatment.[64] On the other hand, Table 1 shows that ATP- independent Ca^{2+}-binding to predominantly right-sided out SL vesicles (heavy SL preparation) was depressed.

Table 1: ATP- independent Ca^{2+}-binding and Ca^{2+}-ecto ATPase activities in a heavy sarcolemmal preparations from diabetic hearts with or without propionyl L-carnitine (PPLC) treatment

Parameters	Control	Diabetic	PPLC- treated diabetic
A. ATP- independent Ca^{2+}-binding (nmol/mg/5 min)			
1. In the presence of 0.05 mM Ca^{2+}	19.2 ± 1.32	11.5 ± 1.26*	16.05 ± 1.18†
2. In the presence of 1.25 mM Ca^{2+}	196.0 ± 7.61	86.0 ± 4.25*	158.0 ± 5.96†

B. Ca^{2+}-ecto ATPase activity (umol Pi/mg/h)			
1. In the presence of 1.25 mM Ca^{2+}	38.9 ± 3.6	51.2 ± 23*	42.4 ± 2.0†
2. In the presence of 4.0 mM Ca^{2+}	53.6 ± 3.9	66.5 ± 2.4*	56.1 ± 2.3†

*Values are means ± standard error (SE) of 6 experiments. 3 Days after the induction of diabetes with 65 mg/ kg streptozotocin, rats were treated with or without PPLC (250 mg/kg; daily) for 8 weeks. Sarcolemmal preparation with basement was isolated from the heart by hypotonic shock- LiBr treatment method and high or low affinities Ca^{2+}-binding and Ca^{2+}-ecto ATPase activities were determined as before (Kaneko et al[65] and Dhalla et al[66]). This preparation does not show Ca^{2+}- stimulated ATPase or ATP-dependent Ca^{2+}-uptake. *-p < 0.05 vs control; †- p < 0.05 vs diabetic.*

Table 2: Sarcolemmal Na^+-K^+ ATPase, Na^+-dependent Ca^{2+}-uptake and ATP-dependent Ca^{2+}-pump activities in diabetic rat hearts with or without propionyl L-carnitine (PPLC) treatment

Parameters	Control	Diabetic	PPLC- treated diabetic
A. Na^+-K^+ ATPase activity (µmol Pi/mg/h)	28.4 ± 1.91	16.2 ± 2.30*	24.5 ± 1.43†
B. Na^+-dependent Ca^{2+}-uptake (nmol/mg/15 s)	22.5 ± 1.52	11.6 ± 1.74*	17.9 ± 1.32†
C. ATP-dependent Ca^{2+}-uptake (nmol/mg/min)	21.0 ± 1.70	13.4 ± 0.84*	13.2 ± 1.26
D. Ca^{2+}-stimulated ATPase activity (µmol Pi/mg/h)	12.2 ± 0.86	7.2 ± 0.71*	7.9 ± 0.86

*Values are means ± S.E. of 4 experiments. Diabetes was induced by 65 mg/kg streptozotocin. 3 days after inducing diabetes, the animals were treated with or without PPLC (250 mg/kg/daily) for 8 weeks. Sarcolemmal vesicles were isolated by sucrose- gradient method and biochemical parameters were measured as described earlier (Makino et al[67] and Pierce et al[68]). *-p < 0.05 vs control; †- p < 0.05 vs diabetic.*

Table 3: Sarcoplasmic reticulum (SR) Ca^{2+}-uptake, Ca^{2+}-stimulated ATPase and Mg^{2+}-ATPase activities from control, diabetic and propionyl L-carnitine (PPLC) treated diabetic rat hearts

Parameters	Control	Diabetic	PPLC- treated diabetic
A. SR Ca^{2+}-uptake activity (nmol Ca^{2+}/mg/2 min)	110.0 ± 3.9	65.9 ± 4.1*	92.0 ± 3.7†
B. SR Ca^{2+}-stimulated ATPase activity (µmol Pi/ mg/5 min)	0.96 ± 0.12	0.56 ± 0.12*	0.82 ± 0.86†
C. SR Mg^{2+}-ATPase activity (µmol Pi/mg/5 min)	9.10 ± 0.36	4.56 ± 0.42*	6.54 ± 0.51†

*Values are means ± S.E. of 8 to 10 experiments. These data are based on the information described in our article Ferrari et al.[64] The diabetic rats 3 days after inducing diabetes with 6 mg/kg streptozotocin were treated with or without PPLC (250 mg/kg daily) for a period of 8 weeks. The activities of SR preparations were measured by the methods described by Ganguly et al[63] and Ferrari et al.[64] *-p < 0.05 vs control; †- p < 0.05 vs diabetic.*

Table 4: Mitochondrial respiration and oxidative phosphorylation as well as high energy phosphate stress in diabetic rat hearts with or without propionyl L-carnitine (PPLC) treatment

Parameters	Control	Diabetic	PPLC- treated diabetic
A. Mitochondrial oxidative phosphorylation			
1. State 3 respiration (natoms O/mg/min)	184 ± 7.52	137 ± 8.14*	162 ± 6.58†
2. Oxidative phosphorylation rate (state 3x ADP/O ratio)	536 ± 28	364 ± 31*	480 ± 36†
B. High energy phosphate stores			
1. Creatine phosphate (CP, µmol/g)	6.48 ± 0.42	3.52 ± 0.44*	5.33 ± 0.37†
2. Adenosine triphosphate (ATP, µmol/g)	4.26 ± 0.28	3.42 ± 0.22*	3.86 ± 0.28†

*Values are means ± S.E. Diabetes was induced by an injection of 65 mg/kg streptozotocin. 3 days after inducing diabetes, the animals were treated with or without 250 mg/kg PPLC daily for 8 weeks. Mitochondrial respiration and both CP and ATP content were determined according to the procedures described earlier in Tappia et al[71] *-p < 0.05 vs control; †- p < 0.05 vs diabetic.*

However, the activity of Ca^{2+}-ecto ATPase, which is considered to serve as a Ca^{2+}-gating mechanism, was increased in diabetic cardiomyopathy. These alterations were partially prevented by PPLC therapy.[65, 66] The SL Na^+-K^+ ATPase and SL Na^+-dependent Ca^{2+}- uptake as well as SL Ca^{2+}-pump (ATP- dependent Ca^{2+}-uptake and Ca^{2+}-stimulated ATPase) activities in the inside out SL preparations were decreased in diabetic cardiomyopathy (Table 2).[67, 68] Treatment of diabetic animals with PPLC was observed to attenuate changes in both SL Na^+-K^+ ATPase and Na^+- dependent Ca^{2+}-uptake activities without affecting the SL vesicle Ca^{2+}-pump activities (Table 2).[67, 68] Although SL Na^+-H^+

activity was depressed in the diabetic cardiomyopathy, this change was also not affected by PPLC treatment.[68] Likewise, SL N-methylation, which is known to regulate SL Ca^{2+}-transport activities, was observed to be depressed in chronic diabetes and this change was also not attenuated by PPLC treatment.[69]

The effects of PPLC treatment were also examined on the diabetes-induced alterations in the SR Ca^{2+}-transport and mitochondrial energy production parameters. The results shown in Table 3 reveal that depressions in the SR Ca^{2+}-uptake and SR Ca^{2+}-stimulated activities (SR Ca^{2+}-pump activities) as well as SR Mg^{2+}-ATPase activity were depressed in diabetic cardiomyopathy and these changes were attenuated by PPLC therapy. Likewise, mitochondrial function, as evidenced from mitochondrial state 3 respiration and oxidative phosphorylation rate, was depressed in the diabetic heart and these alterations were attenuated by PPLC treatment (Table 4).[21] The observed alterations in mitochondrial function are supported by the fact that high energy phosphates such as creatine phosphate (CP) and adenosine triphosphate (ATP) levels were decreased in the diabetic heart and these changes were attenuated by PPLC treatment (Table 4). From the overall observations on subcellular changes in diabetic cardiomyopathy, it is evident that the improvement of cardiac function by PPLC therapy may be related to its beneficial effects in attenuating the depressions in SL Na^+-K^+ ATPase, SL Na^+-dependent Ca^{2+} uptake, SR Ca^{2+}-pump activities and mitochondrial energy production.

Mechanisms of beneficial effects of PPLC

Previously, it was described that oxidative stress plays an important role in the pathogenesis of cardiac dysfunction as well as in metabolic and subcellular abnormalities during the development of diabetic cardiomyopathy.[2, 14, 20] This view is supported by the findings that different antioxidants were shown to attenuate the diabetes-induced changes in the heart.[15, 20] Since PPLC is a highly permeable agent in cardiac membranes and is considered to antagonise the deleterious actions of different cytotoxic metabolites such as PMLC and accumulate during the development of diabetic cardiomyopathy,[36-38] some experiments were carried out to examine if the adverse effect of PMLC are antagonised directly by PPLC. For this purpose, the effects of PMLC were studied

Table 5: Modification of palmitoyl L-carnitine (PMLC)-induced depression in rat heart sarcolemmal Na^+-K^+ ATPase activity by propionyl L-carnitine (PPLC) at different concentrations of ATP in vitro

Concentrations of ATP (mM)	Na^+-K^+-ATPase activity (µmol Pi/mg/h)		
	Control	PMLC	PPLC (10 µM) + PMLC (10 µM)
0.25	8.2 ± 0.38	3.9 ± 0.28*	6.7 ± 0.14†
0.50	11.3 ± 0.58	5.1 ± 0.33*	9.2 ± 0.36†
0.75	15.0 ± 0.76	7.8 ± 0.39*	12.5 ± 0.57†
1.00	19.6 ± 0.84	9.6 ± 0.55*	16.2 ± 0.76†
2.00	24.5 ± 0.98	11.8 ± 0.53*	19.4 ± 0.85†
3.00	26.2 ± 1.04	12.9 ± 0.62*	20.8 ± 0.76†
4.00	26.4 ± 1.02	13.1 ± 0.58*	20.8 ± 0.65†

*Values are mean ± SE of 3 experiments. Sarcolemmal membranes were incubated with or without 10 µM PPLC for 5 min before adding 10 µM PMLC for 5 min and then Na^+-K^+ ATPase reaction was initiated with different concentrations of ATP as described by Makino et al.70 Values for PPLC group were not different from the control group and thus are not shown in the Table. *-$p < 0.05$ vs control; †- $p < 0.05$ vs PMLC. The lineweaver- Burke plot of data for control, PMLC and PPLC + PMLC preparations showed Vmax values as 31.43, 15.82 and 25.01 (umol Pi/mg/h) and Km vlues as 0.7421, 0.8077 and 0.7153 (mM ATP), respectively.*

Table 6: Modification of palmitoyl L-carnitine (PMLC)-induced depression in rat heart sarcolemmal Na+-dependent Ca^{2+}-uptake activity by propionyl L-carnitine (PPLC) at different concentrations of Ca^{2+} in vitro

Concentrations Ca^{2+}(μM)	Na^+-dependent Ca^{2+}-uptake (nmol Ca^{2+}/mg/2 s)		
	Control	PMLC	PPLC (10 μM) + PMLC (10 μM)
5.00	1.20 ± 0.08	0.74 ± 0.13*	1.08 ± 0.07†
10.00	2.84 ± 0.26	0.74 ± 0.13*	2.56 ± 0.23†
20.00	5.92 ± 0.87	2.63 ± 0.49*	3.76 ± 0.26†
40.00	7.34 ± 1.05	4.12 ± 0.57*	6.74 ± 0.40†
80.00	7.34 ± 1.05	5.27 ± 0.64*	7.86 ± 0.43†
160.00	8.64 ± 0.86	6.32 ± 0.39*	7.83 ± 0.38†

*Values are mean ± SE of 3 experiments. Preloaded sarcolemmal vesicles with NaCl were incubated with or without 10 μM PPLC for 5 min before adding PMLC for 5 min and then determination of Na^+-dependent Ca^{2+}- uptake activity according to the method of Makino et al.[67] Since PPLC showed no effect on Na^+-dependent Ca^{2+}- uptake, the value for this group is shown in the table. *-$p < 0.05$ vs control; †- $p < 0.05$ vs PMLC. The lineweaver plot of data showed B_{max} values for control, PMLC and PPLC + PMLC groups were 9.85, 6.74 and 8.23 (nmol Ca^{2+}/mg/2 s whereas K_α values were 18.31, 20.26 and 18.54 (μM Ca^{2+}), respectively.*

on the SL Na^+-K^+ ATPase and SL Na^+-dependent Ca^{2+}- uptake by incubating the SL preparations under in vitro conditions in the absence or presence of PPLC.[70, 71] The results in Table 5 indicate that the suppressive actions of PMLC on SL the Na^+-K^+ ATPase activity in the presence of different concentrations of ATP was inhibited by PPLC. Likewise, the Na^+- dependent Ca^{2+}-uptake activity in the presence of different concentrations of Ca^{2+} was inhibited by PMLC and this inhibitory effect of PMLC was attenuated by the presence of PPLC in the incubation medium (Table 6). These observations indicate PPLC may also produce beneficial effects in diabetic cardiomyopathy by directly antagonising the deleterious effects of some long-chain acyl metabolites such as PMLC.

Conclusion

The beneficial effects of metabolic therapy with PPLC were evaluated, which is known to promote the oxidation of fatty acids in mitochondria and increase the utilisation of glucose for energy production in the heart. From the information provided in this article, it is evident that PPLC therapy not only improves cardiac function but also attenuates subcellular remodelling for promoting Ca^{2+}-handling and energy production in diabetic cardiomyopathy. These beneficial effects of PPLC therapy seem to be related to a direct action of PPLC in antagonising the deleterious actions of long-chain fatty acid metabolites, which become accumulated in the myocardium in chronic diabetes. Such a proposed mechanism is complimentary to antioxidant and lipid lowering actions of this intervention.

Ethics

This study was a secondary analysis and did not directly involve human participants. Therefore, ethics approval was not required for this work.

Acknowledgement

The infrastructural support for the preparation of this article was provided by the St. Boniface Hospital Albrechtsen Research Centre.

Conflicts of interest

The authors declare that there is no conflict of interest.

Funding

This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

Author ORCID numbers

Khushman Kaur (KK):
0009-0002-7013-3231
Lorrie Kirshenbaum (LK):
0000-0002-9617-5803
Paramjit S Tappia (PST):
0000-0001-8307-2760
Naranjan S Dhalla (NSD):
0000-0002-4894-4727

Author contributions

Conceptualisation: NSD, LK
Validation: PST, KK
Data curation: PST, KK
Writing-original draft: KK, PST
Writing-review and editing: NSD, LK

References

1. Dhalla NS, Pierce GN, Innes IR, Beamish RE. Pathogenesis of cardiac dysfunction in diabetes mellitus. Can J Cardiol. 1985;1(4):263-281. PMID: 3850773.
2. Dhalla NS, Liu X, Panagia V, Takeda N. Subcellular remodeling and heart dysfunction in chronic diabetes. Cardiovasc Res. 1998;40(2):239-47. doi:10.1016/s0008-6363(98)00186-2.
3. Candido R, Srivastava P, Cooper ME, Burrell LM. Diabetes mellitus: a cardiovascular disease. Curr Opin Investig Drugs. 2003;4(9):1088-94. PMID: 14582453.
4. Asghar O, Al-Sunni A, Khavandi K, Khavandi A, Withers S, Greenstein A, Heagerty AM, Malik RA. Diabetic cardiomyopathy. Clin Sci (Lond). 2009;116(10):741-60. doi: 10.1042/CS20080500.
5. Watanabe K, Thandavarayan RA, Harima M, Sari FR, Gurusamy N, Veeraveedu PT, et al. Role of differential signaling pathways and oxidative stress in diabetic cardiomyopathy. Curr Cardiol Rev. 2010;6(4):280-90. doi: 10.2174/157340310793566145.
6. Sharma A, Tate M, Mathew G, Vince JE, Ritchie RH, de Haan JB. Oxidative stress and NLRP3-inflammasome activity as significant drivers of diabetic cardiovascular complications: therapeutic implications. Front Physiol. 2018;9:114. doi: 10.3389/fphys.2018.00114.
7. Ganguly PK, Pierce GN, Dhalla NS. Diabetic cardiomyopathy: membrane dysfunction and therapeutic strategies. J Appl Cardiol. 1987;2(4):323-38.
8. Karan A, Bhakkiyalakshmi E, Jayasuriya R, Sarada DVL, Ramkumar KM. The pivotal role of nuclear factor erythroid 2-related factor 2 in diabetes-induced endothelial dysfunction. Pharmacol Res. 2020;153:104601. PMID: 31838079.
9. De Blasio MJ, Huynh K, Qin C, Rosli S, Kiriazis H, Ayer A, et al. Therapeutic targeting of oxidative stress with coenzyme Q10 counteracts exaggerated diabetic cardiomyopathy in a mouse model of diabetes with diminished PI3K(p110α) signaling. Free Radic Biol Med. 2015;87:137-47. doi: 10.1016/j.freeradbiomed.2015.04.028.
10. Packer M. Differential pathophysiological mechanisms in heart failure with a reduced or preserved ejection fraction in diabetes. JACC Heart Fail. 2021;9(8):535-549. doi: 10.1016/j.jchf.2021.05.019.
11. Stanley WC, Lopaschuk GD, McCormack JG. Regulation of energy substrate metabolism in the diabetic heart. Cardiovasc Res. 1997;34(1):25-33. doi: 10.1016/s0008-6363(97)00047-3.
12. Lopaschuk GD, Ussher JR, Folmes CD, Jaswal JS, Stanley WC. Myocardial fatty acid metabolism in health and disease. Physiol Rev. 2010;90(1):207-58. doi: 10.1152/physrev.00015.2009.
13. Adameova A and Dhalla NS. Role of microangiopathy in diabetic cardiomyopathy. Heart Fail Rev. 2014; 19:25-33. doi: 10.1007/s10741-013-9378-7.
14. Dhalla NS, Takeda N, Rodriguez-Leyva D, Elimban V. Mechanisms of subcellular remodeling in heart failure due to diabetes. Heart Fail Rev. 2014;19(1):87-99. doi: 10.1007/s10741-013-9385-8.
15. Xu YJ, Tappia PS, Neki NS, Dhalla NS. Prevention of diabetes-induced cardiovascular complications upon treatment with antioxidants. Heart Fail Rev. 2014 ;19(1):113-21. doi: 10.1007/s10741-013-9379-6.
16. Shaffer SW. Cardiomyopathy associated with non-insulin-dependent diabetes. Mol Cell Biochem. 1991;107:1-20. doi: 10.1007/BF02424571.
17. Varga ZV, Giricz Z, Liaudet L, Haskó G, Ferdinandy P, Pacher P. Interplay of oxidative, nitrosative/nitrative stress, inflammation, cell death and autophagy in diabetic cardiomyopathy. Biochim Biophys Acta. 2015;1852(2):232-42. doi: 10.1016/j.bbadis.2014.06.030.
18. Verma SK, Garikipati VNS, Kishore R. Mitochondrial dysfunction and its impact on diabetic heart. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1098-05. doi: 10.1016/j.bbadis.2016.08.021.
19. Roul D, Recchia FA. Metabolic alterations induce oxidative stress in diabetic and failing hearts: different pathways, same outcome. Antioxid Redox Signal. 2015 Jun ;22(17):1502-14. doi: 10.1089/ars.2015.6311.
20. Dhalla NS, Shah AK, Tappia PS. Role of oxidative stress in metabolic and subcellular abnormalities in diabetic cardiomyopathy. Int J Mol Sci. 2020;21(7):2413. doi: 10.3390/ijms21072413.
21. Tappia PS, Elimban V, Shah AK, Goyal RK, Dhalla NS. Improvement of cardiac function and subcellular defects due to chronic diabetes upon treatment with sarpogrelate. J Cardiovasc Dev Dis. 2024;11(7):215. doi: 10.3390/jcdd11070215.

22. Siliprandi N, Di Lisa F, Menabo R. Propionyl -L-Carnitine: biochemical significance and possible role in cardiac metabolism. 1991: 5(Suppl 1):11-5. doi: 10.1007/BF00128238.
23. Arsenian MA. Carnitine and its derivatives in cardiovascular disease. Prog Cardiovasc Dis. 1997;40(3):265-86. doi: 10.1016/s0033-0620(97)80037-0.
24. Retter AS. Carnitine and its role in cardiovascular disease. Heart Dis. 1999;1(2):108-13. PMID: 11720611.
25. Calvani M, Reda E, Arrigoni-Martelli E. Regulation by carnitine of myocardial fatty acid and carbohydrate metabolism under normal and pathological conditions. Basic Res Cardiol. 2000;95(2):75-83. doi: 10.1007/s003950050167.
26. Vargiu R, Licheri D, Carcassi AM, Naimi S, Collu M, Littarru GP, et al. Enhancement of muscular performance by a coformulation of propionyl-L-carnitine, coenzyme Q10, nicotinamide, riboflavin and pantothenic acid in the rat. Physiol Behav. 2002;76(2):257- 63. doi: 10.1016/s0031-9384(02)00717-5.
27. Mingorance C, Rodríguez-Rodríguez R, Justo ML, de Sotomayor AM, Herrera MD. Critical update for the clinical use of L-carnitine analogs in cardiometabolic disorders. Vasc Health Risk Manag. 2011;7:169-76. doi: 10.2147/VHRM.S14356.
28. Marcovina SM, Sirtori C, Peracino A, Gheorghiade M, Borum P, Remuzzi G, et al. Translating the basic knowledge of mitochondrial functions to metabolic therapy: role of L-carnitine. Transl Res. 2013;161(2):73-84. doi: 10.1016/j.trsl.2012.10.006.
29. Ferrari R, Merli E, Cicchitelli G, Mele D, Fucili A, Ceconi C. Therapeutic effects of L-carnitine and propionyl-L-carnitine on cardiovascular diseases: a review. Ann N Y Acad Sci. 2004;1033:79-91. doi: 10.1196/annals.1320.007.
30. Mingorance C, Rodriguez-Rodriguez R, Justo ML, Herrera MD, de Sotomayor AM. Pharmacological effects and clinical applications of propionyl-L-carnitine. Nutr Rev. 2011;69(5):279-90. doi: 10.1111/j.1753-4887.2011.00387.x.
31. Tripp ME, Katcher ML, Peters HA, Gilbert EF, Arya S, Hodach RJ, et al. Systemic carnitine deficiency presenting as familial endocardial fibroelastosis: a treatable cardiomyopathy. N Engl J Med. 1981;305(7):385-90. doi: 10.1056/NEJM198108133050707.
32. Kondrup J and Mortensen SA. Endomyocardial levels of free and total carnitine in patients with cardiomyopathy. Heart Failure. 1989;5:37-40.
33. Borum PR, Park JH, Law PK, Roelofs RI. Altered tissue carnitine levels in animals with hereditary muscular dystrophy. J Neurol Sci. 1978; 38:113-21. Doi: 10.1016/0022-510X(78)90251-4.
34. Reibel DK, Uboh CE, Kent RL. Altered coenzyme A and carnitine metabolism in pressure-overload hypertrophied hearts. Am J Physiol. 1983;244(6):H839-43. doi: 10.1152/ajpheart.1983.244.6.H839.
35. Fatani AG, Darweesh AQ, Rizwan L, Aleisa AM, Al-Shabanah OA, Sayed-Ahmed MM. Carnitine deficiency aggravates cyclophosphamide-induced cardiotoxicity in rats. Chemotherapy.2010;56(1):71-81.doi:10.1159/000298822.
36. Corr PB, Gross RW, Sobel BE. Amphipathic metabolites and membrane dysfunction in ischemic myocardium. Circ Res. 1984;55(2):135-54. doi: 10.1161/01.res.55.2.135.
37. Hara A, Hashizume H, Abiko Y. Dilazep and its derivative, K-7259, attenuate mechanical derangement induced by palmitoyl-L-carnitine in the isolated, perfused rat heart. J Pharmacol Exp Ther. 1996;279(1):32-8. PMID: 8858972.
38. Liedtke AJ. Lipid burden in ischemic myocardium. J Mol Cell Cardiol. 1988;20:65-74. doi: 10.1016/0022-2828(88)90333-1.
39. Dhalla NS, Kolár F, Shah KR, Ferrari R. Effects of some L-carnitine derivatives on heart membrane ATPases. Cardiovasc Drugs Ther. 1991;5:25-30. doi: 10.1007/BF00128240.
40. 43. Ferrari R, Pasini E, Condorelli E, Boraso A, Lisciani R, Marzo A, et al. Effect of propinoyl-L-carnitine on mechanical function of isolated rabbit heart. 1991; 5:17-23. doi: 10.1007/BF00128239.
41. Ferrari R, Di Lisa F, de Jong JW, Ceconi C, Pasini E, Barbato R, et al. Prolonged propionyl -L-carnitine pre-treatment of rabbit: biochemical, hemodynamic and electrophysiological effects on myocardium. J Mol Cell Cardiol. 1992;24(3):219-32. doi: 10.1016/0022-2828(92)93160-1.
42. Russell RR 3rd, Mommessin JI, Taegtmeyer H. Propionyl-L-carnitine-mediated improvement in contractile function of rat hearts oxidizing acetoacetate. Am J Physiol. 1995;268(1 Pt 2):H441-7. doi: 10.1152/ajpheart.1995.268.1.H441.
43. Cevese A, Schena F, Cerutti G. Short-term hemodynamic effects of intravenous propionyl-L-carnitine in anesthetized dogs. Cardiovasc Drugs Ther. 1991; 5:45-56. doi: 10.1007/BF00128243.
44. Bevilacqua M, Vago T, Norbiato G. Effect of propionyl-L-carnitine on L-type calcium channels in human heart sarcolemma. Cardiovasc Drugs Ther. 1991, 5:31-5. doi: 10.1007/BF00128241.
45. Ferrari R, Ciampalini G, Agnoletti G, Cargnoni A, Ceconi C, Visioli O. Effect of L-carnitine derivatives on heart mitochondrial damage induced by lipid peroxidation. Pharmacol Res Commun. 1988 ;20(2):125-32. doi: 10.1016/s0031-6989(88)80005-5.
46. Wang DD, Wang TY, Yang Y, He SM, Wang YM. The effects of L-carnitine, acetyl-L-carnitine, and propionyl-L-carnitine on body mass in type 2 diabetes mellitus patients. Front Nutr. 2021;8:748075. doi: 10.3389/fnut.2021.748075.
47. Greco AV, Mingrone G, Bianchi M, Ghirlanda G. Effect of propionyl -L-carnitine in the treatment of diabetic angiopathy: controlled doubled blind trail versus placebo. Clin Trial Drugs Exp Clin Res. 1992;18(2):69-80. PMID: 1644013.
48. Riccioni C, Sarcinella R, Palermo G, Izzo A, Liguori M, Koverech A, et al. Evaluation of the efficacy of propionyl-L-carnitine versus pulsed muscular compressions in diabetic and non-diabetic patients affected by obliterating arteriopathy Leriche stage II. Int Angiol. 2008;27(3):253-9. PMID: 18506129.
49. Hotta N, Koh N, Sakakibara F, Nakamura J, Hamada Y, Wakao T, et al. Effect of propionyl-L-carnitine on motor nerve conduction, autonomic cardiac function, and nerve blood flow in rats with streptozotocin-induced diabetes: comparison with an aldose reductase inhibitor. J Pharmacol Exp Ther. 1996;276(1):49-55. PMID: 8558455.
50. Hotta N, Koh N, Sakakibara F, Nakamura J, Hamada Y, Hara T, et al. Effect of propionyl-L-carnitine on oscillatory potentials in electroretinogram in streptozotocin-diabetic rats. Eur J Pharmacol. 1996;311(2-3):199-206. doi: 10.1016/0014-2999(96)00420-7.
51. Hotta N, Koh N, Sakakibara F, Nakamura J, Hamara Y, Hara T, et al. Effects of propionyl-L-carnitine and insulin on the electroretinogram, nerve conduction and nerve blood flow in rats with streptozotocin-induced diabetes. Pflugers Arch. 1996;431(4):564-70. doi: 10.1007/BF02191904.
52. Morano S, Mandosi E, Fallarino M, Gatti A, Tiberti C, Sensi M, et al. Antioxidant treatment associated with sildenafil reduces monocyte activation and markers of endothelial damage in patients with diabetic erectile dysfunction: a double-blind, placebo-controlled study. Eur Urol. 2007;52(6):1768-74. doi: 10.1016/j.eururo.2007.04.042.

53. Gentile V, Antonini G, Bertozzi AM, Dinelli N, Rizzo C, Virmani AM, et al. Effect of propionyl-L-carnitine, L-arginine and nicotinic acid on the efficacy of vardenafil in the treatment of erectile dysfunction in diabetes. Curr Med Res Opin. 2009;25(9):2223-8. doi: 10.1185/03007990903138416.
54. Gentile V, Vicini P, Prigiotti G, Koverech A, Di Silverio F. Preliminary observations on the use of propionyl-L-carnitine in combination with sildenafil in patients with erectile dysfunction and diabetes. Curr Med Res Opin. 2004;20(9):1377-84. doi: 10.1185/030079904X2394.
55. Terada R, Matsubara T, Koh N, Nakamura J, Hotta N. Effects of propionyl-L-carnitine on cardiac dysfunction in streptozotocin- diabetic rats. Eur J Pharmacol. 1998; 357(2-3):185-91. doi: 10.1016/s0014-2999(98)00539-1.
56. Pasini E, Comini L, Ferrari R, de Giuli F, Menotti A, Dhalla NS. Effect of propionyl-L-carnitine on experimental induced cardiomyopathy in rats. Am J Cardiovasc Pathol. 1992;4(3):216-22. PMID: 1298298.
57. Broderick TL. ATP production and TCA activity are stimulated by propionyl-L-carnitine in the diabetic rat heart. Drugs R D. 2008;9(2):83-91. doi: 10.2165/00126839-200809020-00003.
58. Arduini A, Dottori S, Sciarroni AF, Corsico N, Morabito E, Arrigoni-Martelli E, et al. Effect of propionyl-L-carnitine treatment on membrane phospholipid fatty acid turnover in diabetic rat erythrocytes. Mol Cell Biochem. 1995;152(1):31-7. doi: 10.1007/BF01076461.
59. Lango R, Smoleński RT, Rogowski J, Siebert J, Wujtewicz M, Słomińska EM, et al. Propionyl-L-carnitine improves hemodynamics and metabolic markers of cardiac perfusion during coronary surgery in diabetic patients. Cardiovasc Drugs Ther. 2005;19(4):267-75. doi: 10.1007/s10557-005-3349-8.
60. Broderick TL, Driedzic W, Paulson DJ. Propionyl-L-carnitine effects on postischemic recovery of heart function and substrate oxidation in the diabetic rat. Mol Cell Biochem. 2000;206(1-2):151-7. doi: 10.1023/a:1007022114594.
61. Felix C, Gillis M, Driedzic WR, Paulson DJ, Broderick TL. Effects of propionyl-L-carnitine on isolated mitochondrial function in the reperfused diabetic rat heart. Diabetes Res Clin Pract. 2001;53(1):17-24. doi: 10.1016/s0168-8227(01)00240-6.
62. Pierce GN, Kutryk MJ, Dhalla NS. Alterations in Ca2+ binding by and composition of the cardiac sarcolemmal membrane in chronic diabetes. Proc Natl Acad Sci USA. 1983;80(17):5412-6. doi: 10.1073/pnas.80.17.5412.
63. Ganguly PK, Pierce GN, Dhalla KS, Dhalla NS. Defective sarcoplasmic reticular calcium transport in diabetic cardiomyopathy. Am J Physiol. 1983;244(6):E528-35. doi: 10.1152/ajpendo.1983.244.6.E528.
64. Ferrari R, Shah KR, Hata T, Beamish RE, Dhalla, NS. Subcellular defects in diabetic myocardium: influence of propionyl L-carnitine on Ca2+-transport. In: Nagano M, Dhalla NS, eeds. The Diabetic Heart. New York: Raven Press Ltd, 1991; pp. 167-81.
65. Kaneko M, Singal PK, Dhalla NS. Alterations in heart sarcolemmal Ca2+-ATPase and Ca2+-binding activities due to oxygen free radicals. Basic Res Cardiol. 1990;85(1):45-54. doi: 10.1007/BF01907013.
66. Dhalla NS, Smith CI, Pierce GN, Elimban V, Makino N, Khatter JC. Heart sarcolemmal cation pumps and binding sites. In: Trupp H, ed. The Regulation of Heart Function. New York, 1986; pp. 121-36.
67. Makino N, Dhalla KS, Elimban V, Dhalla NS. Sarcolemmal Ca2+ transport in streptozotocin-induced diabetic cardiomyopathy in rats. Am J Physiol. 1987;253:E202-7. doi: 10.1152/ajpendo.1987.253.2.E202.
68. Pierce GN, Ramjiawan B, Dhalla NS, Ferrari R. Na+-H+ exchange in cardiac sarcolemmal vesicles isolated from diabetic rats. Am J Physiol. 1990;258(1 Pt 2):H255-61. doi: 10.1152/ajpheart.1990.258.1.H255.
69. Ou C, Majumder S, Dai J, Panagia V, Dhalla NS, Ferrari R. Cardiac phosphatidylethanolamine N-methylation in normal and diabetic rats treated with L- propionyl-carnitine. In: Korecky B, Dhalla NS, Eds. Subcellular Basis of Contractile Failure. Developments in Cardiovascular Medicine. Boston, MA: Springer, 1990; pp. 219-34. doi: 10.1007/978-1-4613-1513-1_14.
70. Golfman L, Hata T, Netticadan T, Panagia V, Dhalla NS. Modification of cardiac sarcolemmal Na+-Ca2+ exchange activity by lysophosphatidylcholine and palmitoylcarnitine. Cardiovasc Pathobiol. 1998;2:181-5. PMID- 9434141.
71. Netticadan T, Yu L, Dhalla NS, Panagia V. Palmitoyl carnitine increases intracellular calcium in adult rat cardiomyocytes. J Mol Cell Cardiol. 1999;31(7):1357-67. doi: 10.1006/jmcc.1999.0968.