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REVIEW ARTICLE

# Beneficial Effects of Propionyl L-Carnitine Therapy in Diabetic Cardiomyopathy

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## 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.

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## 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* | 3.9 ± 0.28* |
| 0.50 | 11.3 ± 0.58 | 5.1 ± 0.33* | 5.1 ± 0.33* |
| 0.75 | 15.0 ± 0.76 | 7.8 ± 0.39* | 7.8 ± 0.39* |
| 1.00 | 19.6 ± 0.84 | 9.6 ± 0.55* | 9.6 ± 0.55* |
| 2.00 | 24.5 ± 0.98 | 11.8 ± 0.53* | 11.8 ± 0.53* |
| 3.00 | 26.2 ± 1.04 | 12.9 ± 0.62* | 12.9 ± 0.62* |
| 4.00 | 26.4 ± 1.02 | 13.1 ± 0.58* | 13.1 ± 0.58* |

*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 $K_\alpha$ 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.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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## Data access

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

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