Diabetology

Extended Abstract

Effect of CoQ10 Supplementation on Oxidative Stress and Muscle Bioenergetics in Type II Diabetes: A Pilot Study - Joohee Sanders – Shippensburg University, USA

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Abstract

Objective

To compare oxidative stress, mitochondrial oxidative phosphorylation capacity, microvascular function, and exercise performance of type II diabetics (T2D) to that of control subjects and to determine whether Co-enzyme Q10 (CoQ10) supplementation has any effects on these measures.

Another factor contributing to impaired functional capacity in T2D is mitochondrial dysfunction. Studies have reported decreased oxidative phosphorylation activity [13,14], as well as mitochondrial DNA damage [15], in T2D. Moreover, defects in the capacity to metabolize glucose and fatty acids results in accumulation of fatty acids and triacylglycerol in non-adipose tissues, including skeletal muscle [16]. These accumulating fatty acids are prone to lipid peroxidation increasing ROS, a process thought to be one of the major causes of mitochondrial damage [17].

While hyperglycemia in T2D increase ROS production, it can also lead to glycation of antioxidant (AOX) enzymes thereby reducing AOX availability [18,19]. Thus, hyperglycemia upregulates ROS formation while down-regulating AOX formation leading to an even higher level of oxidative stress. For example, mitochondrial reducing equivalents, such as co-enzyme Q10 (CoQ10), have been found to be deficient in T2D [20,21]. This suggests that a quantitative and/or functional deficiency in CoQ10 may potentially occur in T2D, further diminishing metabolic efficiency and functional capacity.

CoQ10 is a potent antioxidant [22,23] and a component of the ETC which has been shown to improve mitochondrial [24,25] and vascular function [26,27]. Furthermore, CoQ10 has shown to reduce fasting plasma glucose in diabetes [23]. Thus, supplemental CoQ10 has the potential to improve functional capacity of T2D and possibly reduce the progression of disease. In the present study, we examined and compared these parameters of T2D patients to that of control subjects and how short-term dietary CoQ10 supplementation may alter these measures. We hypothesized that; 1) T2D patients would exhibit impaired mitochondrial and microvascular functions, and exercise performance when compared to age-matched control subjects and 2) T2D patients would show significant improvements in these measures after CoQ10 supplementation.

Methods

Fourteen older adults (7 T2D patients with mild peripheral arterial disease (PAD) (69.9 ± 5.1 years) and 7 age-matched controls (67.0 ± 8.9 years) participated in the study. Each participant went through 2 week placebo followed by 2 week CoQ10 supplementation trials. During each trial, participants performed plantar

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flexion exercise during which gastrocnemius phosphocreatine (PCr), pH, oxygen (O_2) saturation and BFindex were measured using 31P magnetic resonance spectroscopy (MRS) and near infrared spectroscopy (NIRS).

This study used a non-randomized, single blinded, cross-over design, where all T2D patients and control subjects received 2 weeks of placebo treatment first, followed by 2 weeks of CoQ10 treatment at 200 mg•day^{-1} (100 mg capsule, twice a day). The treatment order was not randomized due to a long wash out period of CoQ10. An oral, over-the-counter CoQ10 dietary supplement was used (Swanson Health Products, Inc., Fargo, ND). To account for a possible order effect, an initial baseline trial was conducted before the placebo trial.

Each subject was asked to report three times; 1) Baseline (visit 1); 2) 2 weeks post placebo (visit 2); and 3) 2 weeks post CoQ10 supplement (visit 3). Identical exercise testing was performed during each visit. Blood samples were drawn from the antecubital vein before and after exercise in all trials to measure changes in Malondialdehyde (MDA) level to estimate oxidative stress status.

Exercise protocol

All exercise protocols were performed in a 2 Tesla, 75 cm bore MRS magnet. Co-registration of 31P-MRS and NIRS (Cogniscope; NIM, Inc.) was performed to observe dynamic changes of phosphate (31P) metabolites, intracellular pH (ipH) and total hemoglobin/myoglobin-O_2 saturation (Hb/Mb-oxy) in the medial gastrocnemius at rest, during and after exercise. For exercise protocol, dynamic plantar flexion in supine position was performed, using workloads relative to pre-determined one repetition maximum (RM) (Figure 1). For T2D group, the leg that the patient was having the most pain was used throughout the study.

Results

Comparing T2D to controls, significant differences were observed in PCrre (22.3 ± 13.4 vs. 49.4 ± 36.6 mM·kg^{-1}·min^{-1}) and BFindex (5.3 ± 2.9 vs. 9.7 ± 2.9%·s-1) ($p = 0.03$). Moreover, O_2 saturation recovery was significantly longer for T2D (70.9 ± 52.1 vs. 31.8 ± 8.4 s; $p < 0.01$). When comparing placebo trial to CoQ10 trial, significant reduction in Malondialdehyde (MDA), after CoQ10 trial, was observed in controls (1.29 ± 0.41 vs. 0.88 ± 0.35 uM, $p < 0.05$) but not in T2D (1.31 ± 0.19 vs. 1.47 ± 0.36 uM, $p > 0.05$). With the CoQ10 trial, a trend of improved PCr/Pi in T2D patients at rest was seen (6.87 ± 1.2 to 8.59 ± 2.7). However, no other significant changes were observed with CoQ10 supplementation for either group, including pH, PCr recovery (T2D: 22.3 ± 13.4 vs. 23.2 ± 11.4 mM·kg^{-1}·min^{-1}; CON: 49.4 ± 36.6 vs. 43.7 ± 33.3 mM·kg^{-1}·min^{-1}, $p = 0.9$), and BFindex (T2D: 5.3 ± 2.9 vs. 3.9 ± 2.2%·s-1; CON: 9.7 ± 2.9 vs. 9.2 ± 2.4%·s-1, $p = 0.5$).

Conclusion

Noted reduction in MDA seen in healthy, older individuals suggests a positive antioxidant effect of CoQ10 supplementation. However, when PAD is present, as can be the case of T2D, two weeks of CoQ10 supplementation at 200 mg•day^{-1} may not be long enough or potent enough to produce similar effects.

Resting response: This study found a significantly lower PCr, PCr/Pi and higher Pi in T2D when compared to control subjects. Studies have reported abnormal resting Pi metabolites and/or ratios in different diseases. For example, lower PCr/Pi has been reported in mitochondrial [29] and COPD patients [30], while higher Pi/PCr has been associated with T2D [31,32]. Under the condition of constant pH, PCr/Pi is interpreted as phosphorylation potential, one of the main activators in cellular respiration [33,34]. Thus, lower resting PCr/Pi observed in T2D suggests a state

of constant metabolic stress even at rest and a reduced phosphorylation potential. Under ischemic conditions, this reduced phosphorylation potential results not only in over delivered electrons (e-) and subsequent over production of ROS but also accumulation of other metabolites, such as H^+, Pi, and ADP, which negatively impact cellular respiration and further stress the mitochondrial respiratory system.

Exercise and recovery responses: One of the research questions in this study was whether T2D patients have impaired skeletal muscle blood flow, mitochondrial function and exercise performance when compared to control subjects. To compare groups, this study used the same relative workloads for all subjects to keep the metabolic rate equivalent. During this state, PCrre was significantly less in T2D suggesting compromised mitochondrial oxidative phosphorylation capacity. Delayed PCrre can occur when mitochondria is not functioning properly. Delayed PCrre can also occur when there is an insufficient O_2 supply to the mitochondria as evidenced by a significant relationship between O_2 recovery and PCr recovery ($p < 0.01$) seen in this study. These observations are in agreement with other studies reporting delayed PCr recovery after exercise under ischemic condition [35,36]. Insufficient O_2 supply to the mitochondria impairs e- flow in the ETC and, as a result, ATP production is reduced. Furthermore, insufficient O_2 delivery while the mitochondria is fully activated during exercise can lead to overflow of e- within the mitochondria increasing redox potential that favors ROS production.

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