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File: ■ Cocoa (*Theobroma cacao*)
■ Heart Failure
■ Type 2 Diabetes Mellitus
■ Skeletal Muscle Function

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RE: Cocoa Consumption Improves Skeletal Muscle Structure in Patients with Heart Failure and Type 2 Diabetes

Taub PR, Ramirez-Sanchez I, Ciaraldi TP, et al. Perturbations in skeletal muscle sarcomere structure in patients with heart failure and type 2 diabetes: restorative effects of (-)-epicatechin-rich cocoa. *Clin Sci (Lond)*. 2013;125(8):383-389.

Patients with heart failure (HF) often suffer from fatigability. Skeletal muscle (SkM) atrophy, including reductions in mitochondrial volume, cristae abundance, and myosin fiber content, can lead to loss of function. In patients with type 2 diabetes mellitus, perturbations in SkM are also observed. Because HF and type 2 diabetes often coexist, together they may cause increased alterations in SkM. Exercise can improve HF or diabetes-induced changes in SkM structure and function; however, patients with HF tend to be older and have restricted mobility. Alternative safe and effective therapeutic interventions are needed.

The authors previously demonstrated that administering the flavanol epicatechin to mice led to improvements in exercise capacity correlating with increased mitochondrial volume, cristae abundance, and capillarity in SkM and myocardium.[1] They further conducted a pilot study of 5 patients with HF and type 2 diabetes using epicatechin-rich cocoa (ERC; *Theobroma cacao*) for 3 months.[2] In that study, the consumption of ERC led to "a notable recovery of SkM markers of mitochondrial biogenesis and of cristae abundance, indicating improved microstructure and possibly, bioenergetics," write the authors, further hypothesizing that improvements in mitochondrial microstructure may allow myofibers to regenerate and have more normal architecture. From that pilot study, the authors performed a subanalysis of samples to search for changes in sarcomere microstructure, members of the dystrophin-associated protein complex (DAPC) essential for maintaining SkM structure and function, and regulators of SkM growth and regeneration. They compared those measures before and after ERC intervention and to those of healthy control muscle.

For the pilot study, the authors recruited 5 men from the San Diego Veterans Administration Center in San Diego, California, who had been diagnosed with stage II/III

HF (as defined by the New York Heart Association guidelines) and non-insulin-dependent type 2 diabetes. All patients were being treated with standard therapy for those conditions, with stable medical management for at least 6 months.

The patients consumed Hershey's Extra Dark 60% cacao chocolate and cocoa beverages containing 18 g of natural cocoa powder (Hershey, Inc.; Hershey, Pennsylvania) for 3 months (daily total of 100 mg epicatechin, with 390 calories and 18 g fat). The patients underwent muscle biopsies from their quadriceps femoris before and after ERC consumption. For comparison, 3 SkM biopsy samples were obtained from healthy men aged 50 to 53 years.

During the 3-month study, significant improvements were noted in high-density lipoprotein cholesterol (from 38.2 ± 7.2 mg/dL to 44 ± 7.4 mg/dL) and a trend in brain natriuretic peptide levels (used to determine HF) (from 218.9 ± 206.2 pg/mL to 107.4 ± 94.7 pg/mL), while no major changes were noted in total cholesterol, low-density lipoprotein cholesterol, triglycerides, or hemoglobin A1c. Plasma epicatechin concentrations increased on average 1.06 ± 0.3 µM after 3 months of ERC consumption.

Treadmill testing was used to measure maximum oxygen consumption (VO_2 max) levels. At the end of 3 months, VO_2 max levels had increased, though not statistically significantly, by 24%.

At baseline, significant decreases were observed in the α-, β-, δ-sarcoglycan (SG) transmembrane proteins and in dystrophin and utrophin expression (compared with those of the healthy control subjects); those were restored by the ERC. Reductions in DAPC, particularly dystrophin, can greatly affect muscular function. "Given the magnitude of dystrophin loss and sarcomere perturbations observed at baseline, the SkM of these patients could be described as in a state of 'acquired muscular dystrophy,'" write the authors. Though not significantly decreased at baseline, levels of the proteins γ-SG, β-dystroglycan, and dysferlin increased with ERC.

High at baseline, the myostatin levels were significantly reduced by ERC consumption but remained higher than those of the healthy control subjects. On the other hand, reduced levels of follistatin at baseline increased above those of the healthy controls after treatment. The plasma follistatin/myostatin ratio increased significantly with treatment (P=0.01). The authors explain, "Myostatin and follistatin negatively and positively modulate SkM growth respectively."

After 3 months of ERC consumption, significant increases were observed in these markers of SkM growth and regeneration: myocyte enhancer factor 2 (MEF2; P=0.022), myogenic regulatory factor 5 (Myf5; P=0.0077), myogenic differentiation (MyoD; P=0.002), and myogenin (P=0.017) levels.

The authors conclude that a severe perturbation of sarcomere microstructure at baseline was strikingly restored with treatment. "Altogether, a coherent signature of molecular events was documented, supporting ERC-induced improved microstructure," they write, further offering this explanation of the underlying mechanisms responsible for the recovery of muscle microstructure: "It is possible that at baseline a state of catabolism predominated and that following ERC treatment as mitochondria partially recovered, a more 'normal' metabolic state ensued allowing for muscle regeneration to take place."

Although ERC or pure epicatechin may be effective in treating muscle-wasting conditions, the authors caution that it should not replace exercise as a proven beneficial intervention. Further research is needed on the combined effects of the 2 interventions.

—Shari Henson

References

[1]Nogueira L, Ramirez-Sanchez I, Perkins GA, et al. (-)-Epicatechin enhances fatigue resistance and oxidative capacity in mouse muscle. *J Physiol*. 2011;589(Pt 18):4615-4631.

[2]Taub P, Ramirez-Sanchez I, Ciaraldi TP, et al. Alterations in skeletal muscle indicators of mitochondrial structure and biogenesis in patients with type 2 diabetes and heart failure: effects of epicatechin rich cocoa. *Clin Transl Sci*. 2012;5(1):43-47.

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