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Impact of Caloric Restriction and Exercise on Trimethylamine N-oxide Metabolites in Women with Obesity

Daniel J. Battillo and Steven K. Malin, FACSM, Rutgers University, New Brunswick, NJ 08901

Trimethylamine N-oxide (TMAO) has been linked to cardiovascular disease (CVD) through, in part, arterial stiffness and altered central hemodynamics. While a low-calorie diet (LCD) is considered primary in lowering plasma TMAO, the impact of exercise is unclear. **PURPOSE:** Examine if LCD+interval exercise (LCD+INT) reduces TMAO more than LCD in relation to hemodynamics, prior to clinical weight loss. **METHODS:** Women with obesity ($n=23$; 48.0 ± 2.4 y; 37.9 ± 1.4 kg/m²) were randomized to either LCD ($n=12$; mixed meals of ~ 1200 kcal/d) or LCD+INT ($n=11$; 60 min/d supervised INT at 90% HR_{peak} for 3 min and 50% HR_{peak} for 3 min) for 2-wks. A 350kcal shake was provided post-INT to equate energy availability between groups. A 180min 75g OGTT was performed pre- and post-intervention to assess fasting TMAO and precursors (carnitine, choline, betaine, and trimethylamine (TMA)). Pulse wave analysis (applanation tonometry) including augmentation index (AIx75), brachial (bBP) and central blood pressure (cBP), pulse pressure amplification (PPA), forward (Pf) and backward pressure (Pb) waveforms, and reflection magnitude (RM) at 0, 60, 120, and 180min was also analyzed. Subgroup analysis was performed on responders and non-responders to treatments. **RESULTS:** LCD and LCD+INT comparably reduced weight ($P<0.01$), fasting insulin ($P=0.03$), glucose ($P=0.05$), and choline ($P<0.01$), as well as Pf ($P=0.04$). Only LCD+INT increased VO_{2peak} ($P=0.03$). Despite no overall treatment effect, higher baseline choline and TMAO associated with greater reductions in choline ($r=-0.63$, $P<0.01$) and TMAO ($r=-0.45$, $P=0.03$). As such, LCD and LCD+INT responders comparably reduced TMAO ($P=0.03$), TMA ($P<0.01$), carnitine ($P<0.01$), choline ($P<0.01$), and betaine ($P<0.01$). Reduced TMAO associated with increased PPA ($r=-0.48$, $P=0.03$). Reductions in TMA correlated with reduced 120min Pf ($r=0.68$, $P<0.01$) and greater 0min RM ($r=-0.64$, $P<0.01$). Similarly, reduced carnitine related to lowered 120min Pf ($r=0.68$, $P<0.01$) and increased 0min RM ($r=-0.59$, $P<0.01$). **CONCLUSION:** LCD and LCD+INT did not differentially improve TMAO and related precursors. Yet, reduction in TMAO metabolites favored aortic waveforms. This highlights caloric restriction as a key mechanism impacting TMAO metabolism.

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