Oral Carnitine Therapy and Insulin Resistance

To the Editor:

Ruggenenti et al\(^1\) report that oral administration of acetyl-L-carnitine results in a substantial, sustained, and simultaneous improvement in insulin sensitivity and blood pressure in insulin-resistant individuals. Carnitine is essential for mitochondrial import and subsequent $\beta$-oxidation of long-chain fatty acids and in the sequestration and mitochondrial export of inhibitory acetyl-coenzyme A units as acetyl-carnitine, actions that favor glucose oxidation. Mitochondrial dysfunction associated with incomplete $\beta$-oxidation and accumulation of intramyocellular lipids may contribute to insulin resistance. In this context, the proposed rationale to study the effects of oral carnitine therapy on insulin sensitivity is seemingly plausible.

Cited studies\(^2,3\) in this report demonstrating insulin-sensitizing effects of L-carnitine have all been observed during conditions of hypercarnitiniemia (plasma carnitine $\approx 600$ $\mu$mol/L) and hyperinsulinemia. Hyperinsulinemia ($\approx 700$ pM) increases skeletal muscle carnitine levels ($\approx 15\%$) by stimulating carnitine uptake through the organic cation transporter, OCTN2.\(^4\) Extant data suggest that skeletal muscle carnitine concentration (typically in the low millimolar range) is not increased by chronic oral carnitine supplementation. Poor bioavailability (10% to 20%), rapid renal clearance, and the saturating kinetics of muscle carnitine transport systems (Michaelis constant $\approx 5$ $\mu$mol/L for OCTN2; basal plasma carnitine levels are $\approx 50$ $\mu$mol/L) have all been suggested to explicate this finding.\(^4\) We are unaware of human studies suggesting that the insulin-resistant state is associated with muscle carnitine deficiency. Thus, the empirical evidence supporting the stated scientific rationale is rather weak. Considering the short half-life ($\approx 10$ to 45 hours) of L-carnitine and the lack of any appreciable effect of oral carnitine therapy on skeletal muscle carnitine pool, the biochemical and physiological mechanisms mediating the sustained and substantial effects of acetyl-L-carnitine on insulin sensitivity and blood pressure observed in this study are unclear and speculative at this time. In addition to the mentioned study limitations, the lack of a robust scientific rationale, placebo group, randomization, and adequate blinding, as well as the potential for allocation, assessment, and performance biases in this study, warrants further well-designed randomized, controlled trials to confirm the reported beneficial effects of carnitine. Future study designs must include measurements that shed light on the plausible mechanisms that underlie the beneficial effects of carnitine, in particular, the pharmacokinetics of carnitine, plasma and tissue acylcarnitine profiles, proteomic/genomic changes in the skeletal muscle, and relevant circulating biomarkers.

Disclosures

None.

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