Therapeutic efficiency of lowering branched-chain amino acid levels in patients with type 2 diabetes using sodium-phenylbutyrate: *a randomized placebo-controlled clinical intervention study*

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Background: Branched-chain amino acid (BCAA) levels are elevated in patients with type 2 diabetes (T2DM) and associate with insulin resistance. An impaired BCAA catabolism may possibly lead to increased BCAA levels and affect metabolic health. Sodium-phenylbutyrate (NaPB), a drug known to boost BCAA oxidation, may therefore lower BCAA levels and improve metabolic health in T2DM. This was investigated in the present study.

Methods: Sixteen men and women (3f/13m) with T2DM underwent a 2-week NaPB (4.8 mg/kg/day) treatment in a randomized, placebo-controlled, double-blind cross-over design with a wash-out of 6-8 weeks. The primary outcome was whole-body insulin sensitivity, measured with 2-step hyperinsulinemic-euglycemic clamps expressed as insulin-stimulated glucose disposal rate minus baseline (ΔRd). Secondary outcomes were *ex-vivo* mitochondrial oxidative capacity measured with high-resolution respirometry expressed as O_2-flux and metabolic flexibility using indirect calorimetry expressed as the insulin-stimulated respiratory exchange ratio minus baseline (ΔRER).

Results: End-of-treatment fasting BCAA levels significantly decreased after NaPB vs. placebo (479 ± 12 vs. 501 ± 16 µmol/l, p=0.05) and tended to decrease for glucose levels (7.8 ± 0.4 vs. 8.2 ± 0.5 mmol/L, p=0.06). Furthermore, whole-body insulin sensitivity was 27% higher (ΔRd: 13.2 ± 1.84 vs. 9.7 ± 1.8 µmol/kg/min, p=0.02) and *ex-vivo* mitochondrial oxidative capacity on glycolytic substrate was 10% higher after NaPB compared to placebo (O_2-flux: 74.0 ± 4.1 vs. 67.1 ± 4.3 pmol/(s*mg), p=0.05). In addition, metabolic flexibility tended to be higher after NaPB treatment compared to placebo (ΔRER: 0.09 ± 0.01 vs. 0.08 ± 0.01, p=0.09).

Conclusion: NaPB-reduced BCAA plasma levels in patients with T2DM seem to improve glucose metabolism. This data strengthens future research to investigate the metabolic effects of long-term NaPB administration in T2DM.

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