

Clinical Trials Corner

Dear Readers,

Welcome to the Clinical Trials Corner of *Nutrition and Healthy Aging*. The aim of this section is to inform readers of upcoming clinical trials and highlight new findings. If you would like to draw attention to a specific topic or trial, please email: leonie.heilbronn@adelaide.edu.au

Ketone bodies are produced by the liver in response to very low carbohydrate diets, prolonged fasting, and exercise (1). Ketones have traditionally been considered solely as an alternative energy source, but are also key signalling molecules with putative therapeutic benefit (1,2). The development of ketone ester supplements that induce physiological ketosis, without the need for restrictive dieting, has sparked interest in their role in exercise performance, as anti-diabetic agents or as therapeutics to support cognitive health.

A recent study by investigators at the University of British Columbia showed that oral supplementation with exogenous ketones improved glucose tolerance in healthy lean individuals (3). These investigators are now conducting a randomised cross-over trial to studying the effects of 14 days of exogenous oral ketone monoester supplementation prior to each meal in 15 individuals with obesity and pre-diabetes, aged 30-65 years old. The primary outcome is glucose tolerance as assessed by glucose area under the curve in response to an oral glucose tolerance test. Importantly, all meals will be provided and standardised throughout the trial to examine effects, independently of changes in nutrition.

Interest also surrounds the putative neuroprotective effects of ketone supplementation. The *Ketocognition* trial was completed in February of this year to examine the effects of an acute exogenous ketone infusion versus saline infusion on cognitive performance in 18 patients with type 2 diabetes. Finally, the Benefic trial, slated for completion in December 2019, is examining the effects of a ketogenic supplement in 50 participants aged over 55 with mild cognitive impairment. Participants will be randomised for 6 months to one arm to examine the effect of elevations in blood ketones on brain energy metabolism and cognitive function. However, investigators have selected to utilise 30 grams of a medium chain triglyceride versus sunflower oil consumed during the morning and evening meals to mildly elevate blood ketones.

We await publication of these acute trials as to the efficacy of ketone supplementation on parameters of healthy aging, as well as on safety, tolerability and side-effects.

Sincerely,
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References

- [1] Evans M. et al. Metabolism of ketone bodies during exercise and training: physiological basis for exogenous supplementation. *J Physiol* 2017; 595:2857-71
- [2] Kovacs et al. Therapeutic potential of exogenous ketone supplementation induced ketosis in the treatment of psychiatric disorders: Review of the current literature. *Frontiers in Psychiatry*; 2019; 10:363. doi:0.3389/fpsy.2019.00363
- [3] Myette-Cote *et al.* Prior ingestion of exogenous ketone monoester attenuates the glycaemic response to an oral glucose tolerance test in healthy young individuals. *J Physiol* 2018: 1385-95

<https://www.clinicaltrials.gov/>

A). Study Title: The effect of exogenous ketone monoester supplement on glycemic response to an oral glucose tolerance test.

Clinicaltrials.gov identifier: NCT03461068

Sponsor: University of British Columbia

Primary Outcome: Change in glucose area under the curve [Time Frame: 2-hour]

Secondary Outcomes: Change in insulin, C-peptide, free fatty acid, GLP-1, glucagon area under the curve [Time Frame: 2-hour], Change in caspase-1 activation, inflammatory cytokines. [Time Frame: 15 minutes]

B). Study Title: Effects of Ketone Bodies on Cognition in Type 2 Diabetes (KETOCOGNITION)

Clinicaltrials.gov identifier: NCT03657537;

Sponsor: Bispebjerg Hospital.

Collaborator: Psychiatric Centre Righospitalet

Primary Outcome: Cognitive composite score (global score) [Time Frame: When glucose levels have been stabilized for 40 minutes]

Secondary Outcomes: Symbol Digit Modalities Test (SDMT) [Time Frame: When glucose levels have been stabilized for 40 minutes]

C). Study Title: Proof of Mechanism of a New Ketogenic Supplement using Dual Tracer PET (BENEFIC).

Clinicaltrials.gov identifier: NCT02551419

Sponsor: Universite de Sherbrooke

Collaborator: Alzheimer's Association

Primary Outcomes: Change in global ketone (11C-AcAc) uptake in grey matter [Time Frame: Baseline and 6 months of intervention]

Secondary Outcomes: Changes in global brain FDG uptake in grey matter (CMR-G), Change in regional brain ketone uptake CMR-A, Change in regional glucose uptake CMR-G in the temporal and parietal cortex, changes in brain blood flow by ASL, brain activation by rs-fMRI, integrity of brain white matter tracts by dMRI, and regional brain volumes by vMRI, Change in cognitive status assessed by the verbal fluency test (D-KEFS), Boston Naming Test, Trail Making test (D-KEFS), Stroop Color and Word Test (D-KEFS), Digit Span (WAIS III), Digit Symbol (WAIS III), Brief Visuospatial Memory Test-revised, 16-item free/cued word learning (Buschke and Grober test) [Time Frame: Baseline and 6 months of intervention]