SYMPOSIUM ABSTRACT BOOK

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SYMPOSIUM

Live Satellite Symposium
at the ESPEN Virtual Congress

Functional and cognitive decline in older adults:
The role of clinical nutrition in maintaining autonomy

42nd Virtual Congress of the European Society for Clinical Nutrition and Metabolism (ESPEN)

19th September 2020

SATELLITE SYMPOSIUM PROGRAMME:

12:15 - 12:25

INTRODUCTION

Chairperson: Prof Tommy Cederholm, MD. PhD

Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden

Theme Ageing, Karolinska University Hospital, Stockholm, Sweden

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12:25 - 12:45

FUNCTIONAL AND COGNITIVE IMPAIRMENTS AS A MAIN RISK FACTORS FOR LOSS OF INDEPENDENCE IN AGEING POPULATION

Prof. Cornel Sieber, MD, PhD

Director Department of Internal Medicine, Kantonsspital Winterthur, Switzerland

Chair Internal Medicine- Geriatrics, University Erlangen-Nürnberg

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12:45 - 13:05

KEY NUTRIENTS FOR MAINTAINING AND POTENTIALLY IMPROVING MUSCLE FUNCTIONALITY IN MALNOURISHED PATIENTS

Prof. Alberto Mijan, MD, PhD

Chief of Section of Clinical Nutrition Unit, Department of Internal Medicine, Hospital Universitario de Burgos, Burgos, Spain

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13:05 - 13:25

WHEN AN ORAL NUTRITIONAL SUPPLEMENT IMPROVES COGNITIVE OUTCOMES IN MILD COGNITIVE IMPAIRMENT

Prof. Stephen Cunnane, PhD

Research Center on Aging and Department of Medicine. Université de Sherbrooke. Sherbrooke, Québec, Canada

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13:25 - 13:45

Q&A INTERACTIVE

Chairperson: Prof Tommy Cederholm, MD. PhD

INTRODUCTION

Prof. Tommy Cederholm
MD, PhD

CHAIRMAN BIOGRAPHY

Dr. Tommy Cederholm is Professor of Clinical Nutrition, and Professor Emeritus at Uppsala University, Sweden.

Currently he is Senior consultant, Head of R&D, at Theme Ageing, Karolinska University Hospital, Stockholm. Board certified in Geriatric Medicine and Internal Medicine.

His research focus is on nutrition and catabolism in old and chronically ill subjects. He has been principal investigator of several nutrition intervention studies, including the OmegAD Trial on omega-3 fatty acid supplementation to patients with Alzheimer's disease.

He has co-authored >275 peer-reviewed articles. During 2012 to 2016 he served as Executive Committee member of ESPEN.

Prof Cederholm is member of the European Working Group on Sarcopenia in Older people. Professor Cederholm has recently contributed to the launch of the GLIM criteria for malnutrition.

FUNCTIONAL AND COGNITIVE IMPAIRMENTS AS A MAIN RISK FACTORS FOR LOSS OF INDEPENDENCE IN AGEING POPULATION

Prof. Cornel Sieber
MD, PhD

SPEAKER BIOGRAPHY

Prof. Cornel Sieber is a physician, specialist in Internal Medicine, Gastroenterology and Hepatology and Geriatric Medicine (University Basle and Hammersmith Hospital London).

At the present time, he is Chair of the Internal Medicine and Geriatric Medicine at the Friedrich-Alexander-Universität Erlangen-Nuremberg, Director Institute for Biomedicine of Aging Nuremberg in Germany. He is Director of the Department of Internal Medicine Kantonsspital Winterthur in Switzerland.

He is President elect at the European Union Geriatric Medicine Society (EuGMS), Vice President Interdisciplinary Center for Gerontology at FAU, and World Health Organization (WHO) member of the "Clinical Consortium on Healthy Ageing" (CCHA).

He was President of the German Society of Internal Medicine (DGIM) (2017-2018), President of the European Academy for Medicine of Ageing (EAMA) (2007-2015), President of the German Society of Nutritional Medicine (DGEM) (2010-2012),and President of the German Society of Geriatrics (DGG) (2005-2008).

He serves on the editorial Boards of different local and international journals. In addition, he is a regular referee to different German and international governmental and private foundations for different fields of Geriatric Medicine.

ABSTRACT

Functional decline is a main challenge for older adults, even when not combined with multimorbidity. This geriatric syndrome may be part of frailty (physical, psychological and/or social) or being part of intrinsic capacity (WHO). Whereas physical frailty with functional decline has gained lot of attendance in the past, the interplay with cognitive impairments has not yet been explored in such depth. This summary therefore focuses more on psychological impairment and here at early stages, namely mild cognitive impairment (MCI).

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Mild cognitive impairment (MCI) refers to the transitional stage between normal aging and dementia. MCI is defined by a decline in cognitive functioning that has exceeded the expected level given the patient's age and education. This decline may include a variety of cognitive domains, including complex attention, executive functions, language, learning and memory, perceptual-motor domain, and social cognition. MCI is also defined by the Alzheimer's Association as a noticeable cognitive decline that does not impair activities of daily living (ADL). The ICD-9 code for MCI is 331.83 (ICD List, 2020) and F06.7 in ICD-10 (World Health Organization, 2016). In ICD-10, MCI is categorized under "mild cognitive disorder".

As MCI is part of the dementia continuum, recommendations for the diagnosis of MCI have been integrated into clinical practice guidelines.
Screening tools are used to assess the extent of cognitive impairment as this is a criterion for the diagnosis of MCI; however, types of tools have neither been specified nor standardized. Commonly used screening tools for MCI are presented in the Figure 1.

Figure 1: Cognitive assessment tools for MCI screening

ICD

International Classification of Diseases

- An international diagnostic classification standard for identifying global health trends and reporting diseases and health conditions.
- ICD-9 for 1979-1998.
- ICD-10 for 1999-present.
- ICD-11 to be launched in 2022.

MoCA
10 mins

Montreal cognitive assessment

- A cognitive screening assessment that has specifically been designed for MCI.
- MCI cut-off = 25/26.
- MCI cut-off for people aged 60 years or above = 24/25.

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General Practitioner Assessment of Cognition

- Patient examination (4 mins) + informant interview (2 mins).
- Cognitive impairment = Patient score 0-4 or informant score 0-3.
- Similar effectiveness as MMSE in detecting suspected cases of dementia.
- Suitable for people with different culture and linguistic background.

Alzheimer's Disease Assessment Scale-cognitive subscale

- Designed to assess global cognition outcome of dementia interventions.
- Validated assessment tools for AD but is widely used for MCI.
- Consists of 11 tasks assessing multiple cognitive domains including attention, language, memory and praxis.
- Suitable for people with different culture and linguistic background.

Mini-Mental State Examination

- A scored form for assessing cognitive mental status.
- Age and education level dependent.
- Cut-off scores for MCI varied from 21 to 27 out of 30.

Dementia Detection

- A cognitive screening test designed for detecting the whole dementia spectrum.
- Final scores are adjusted to be independent of age and education level.
- MCI scoring = 9-12 out of 18.

6-item Cognitive Impairment Test

- Recommended for detecting dementia in primary setting.
- Superior to MMSE for the detection of MCI and mild dementia.
- Suitable for people with visual impairment.

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The Mini-Cog©

- Recommended for detecting cognitive impairment in older adults.
- For healthcare and community settings.
- It consists a 3-item recall test for memory and a simply scored clock drawing test.

Among US Older Adults with probable dementia, 58.7% were either undiagnosed (39.5%) or unaware of the diagnosis (19.2%) . In primary care, dementia is probably under-diagnosed and under-treated with an estimated 50% of patients >65 are not diagnose by their primary care physicians.

The problem of underdiagnosis of MCI has been reported. Recognition of cognitive impairment by hospital staff is also a key factor in underdiagnosis. Moreover, underestimation of cognitive impairment has been hypothesized to occur since patients in a primary care setting are generally recruited to participate in research due to their own subjective memory complaint or through the complaint of a friend or family member; therefore, a group of individuals likely exist that are not screened/diagnosed because cognitive impairment has not been identified.

People with MCI may progress to dementia, revert to normal cognition, or remain at MCI. As the most prevalent form of dementia, AD accounts for 60% to 80% of all dementia cases worldwide. People diagnosed with aMCI are more likely to progress to AD and naMCI to non-AD dementia (e.g. Vascular dementia, VaD). Approximately 35% of people with MCI progress to AD or dementia, 20% revert to normal cognition, and 45% remain at MCI . Figure 2.

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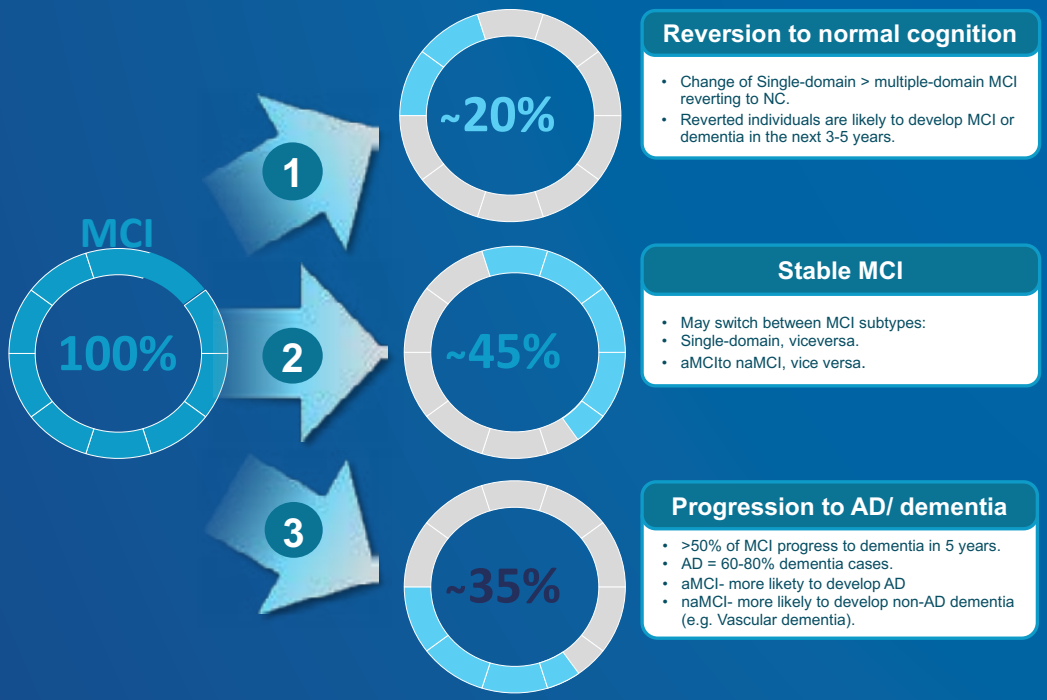
Figure 2: Progression pathway of MCI



Source: Hu, C., et al. 2017; Canevelli, M., G., et al . 2016; Malek-Ahmadi, M. 2016 ;Manly, J. J., et al. 2008 ; Roberts, R., et al. 2014 ; Arevalo-Rodriguez, I., N., et al. 2015; Han, J. W., et al. 2012.
AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; naMCI, non-amnestic MCI; NC, normal cognition.

The WHO's Global Action Plan on the Public Health Response to Dementia 2017-2025 identified risk reduction as one of the seven key action areas to address the impact and burden of dementia worldwide (World Health Organization, 2017). Providing an effective diagnosis and management option for MCI will benefit in addressing the global burden of dementia. This holds true as MCI as an early stage of the dementia continuum may be especially prone to preventive and therapeutic strategies including both physical activity and nutritional interventions, successful options also for different aspects of frailty. In times, when no pharmacological treatments for MCI have proven effective, such non-pharmacological interventions appear even more promising.

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Prof. Alberto Mijan
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SPEAKER BIOGRAPHY

Alberto Miján-de-la-Torre studied Medicine at the Universidad Complutense in Madrid and obtained a further PhD in Medicine from the University of Valladolid. He is an internal medicine specialist (M.I.R, Burgos) and pursued a Fellowship in Nutrition (University of Toronto) and a MSc in Clinical Nutrition (Universidad Autonoma, Madrid). He also carried out a postgraduate diploma in Design and Statistics in Health Sciences (Universidad Autonoma, Barcelona) and has been certified as a Nutrition Support Clinician CNSC (2010-2020) by the NBSC, USA. As a teacher, he has been Assistant Professor of Nutrition in the Faculty of Medicine of the University of Valladolid and Visiting Professor in a number of Latin American Universities. He is also Faculty Member of the European Society of Clinical Nutrition and Metabolism (ESPEN).

At present he is Chief of Section and runs the Unit of Clinical Nutrition at the Department of Internal Medicine in Burgos University Hospital. He also chairs the Nutrition and Dietetics Committee in the same Centre.

His work includes 4 books as editor and 134 publications. Among his research areas are the assessment of body composition and the impact of malnutrition and sarcopenia in chronic diseases.

ABSTRACT

The ageing process, where a gradual reduction in physical activity takes place, is associated with a progressive and physiological loss of skeletal muscle mass and function called **sarcopenia**, now considered a muscle disease and included in ICD -10-MC Diagnosis Code. A sarcopenia prevalence of 10% is estimated in people over 60, while in nursing homes it can rise to 51% in men and 31% in women. Consequences of sarcopenia comprise adverse outcomes such as physical disability, an augmented risk of falls, worse quality of life, higher health care costs, and greater mortality. Moreover, considering the demographic changes, it is expected an increased number of people with sarcopenia around the world. Likewise, in order for the **diagnosis of sarcopenia to be externally valid, it is necessary to delimit precise cut-off points** accepted by the scientific community for low muscle strength, low muscle quantity or quality and low physical performance.

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Frailty presents major similarities with sarcopenia, however, they are different entities. Sarcopenia is an important element for frailty but the latter is a geriatric syndrome that also involves social dimensions. There is also an interconnection between bone and muscle defined as a musculoskeletal unit. Among the elderly population the two main diseases of muscle and bone are sarcopenia and osteoporosis/osteopenia that, when together, define an entity called **osteosarcopenia** which may have a clinical approach similar to that of sarcopenia.

The **net content of muscle protein** results from the balance between protein **synthesis (anabolism) and its breakdown (catabolism).** Under basal conditions, the balance is similar between young and senior adults. On the opposition, it seems that one of the causes of loss of muscle mass in the elderly is a **weakened response to normal anabolic stimuli**, which has been tagged as **anabolic resistance**. Important anabolic stimuli include diet and exercise. It also seems to exist an age-related resistance of muscle protein synthesis to physiological levels of insulin, probably related to the failure of insulin to increase muscle blood flow, thus **insulin acting with a role more as permissive than modulating.**

Regarding **sarcopenia management**, it is now generally accepted that a **combination of nutritional intervention and exercise is the most efficient approach** to its treatment. Food intake declines by about 25% from 40–70 years of age, and even more when comorbidities are associated. Therefore, in the first place, we **must provide enough energy** through the diet to feed the elderly, preventing protein intake from being derived in the mitochondria to produce ATP or glucose.

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The protein content of the diet, in particular amino acids levels in plasma, is essential for muscle protein synthesis. Some data indicate that the threshold necessary for amino acids to stimulate skeletal muscle protein synthesis increases with ageing, therefore **older adults have greater protein needs to compensate for anabolic resistance.** According to **ESPEN recommendations** regarding optimal dietary protein intake for older adults above 65 years, a diet that includes at least 1.0-1.2 g or 1.2-1.5 g protein/kg body weight/day for healthy older adults or those who have acute or chronic illnesses respectively, are recommended. **PROT-AGE study group** recommendations increase the amount of protein up to 2.0 g protein/kg body weight/day for people with severe illness or with marked malnutrition.

Aside from total protein intake, protein source (EAA, BCAA, etc.), digestion, absorption kinetics and transport are important in terms of muscle synthesis. Terms as **true digestibility, protein digestibility-corrected amino acid score (PDCAAS) or Net Protein Utilization (NPU) are of crucial interest to weight the bioavailability of protein supply** to build muscle protein synthesis. It is also important to **distribute a sufficient amount of protein with each meal.** It seems, despite there have been subsequent conflicting results, that a 20-30 g of high-quality protein per meal provides better results than an isolated meal with almost the entire daily amount of protein in the diet. Finally, protein needs to reach the muscle system through **adequate blood flow** and, for that, exercise is a splendid allied.

There is growing evidence that **vitamin D plays a role** on several tissues including skeletal muscle and bone metabolism. Low vitamin D levels have been proposed to decrease skeletal muscle mass, leading to sarcopenia. It seems that the deterioration in muscle mass and function linked with increasing age in parallel with decline in skeletal muscle vitamin D receptor expression.

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Systematic research of randomized controlled trials conducted by Beaudart et al. found that vitamin D supplementation had a small positive impact on muscle strength, being significantly more important with people who presented a 25-OH vitamin D level <30 nmol/L; supplementation seemed also more effective on people aged 65 years or older compared to younger subjects. A very fresh study has demonstrated that the effect of vitamin D on muscle strength and physical performance depends on the level of physical activity in older adults. Moreover, it has been shown that vitamin D status may also influence **fatty degeneration in muscle**.

Fatty acids (omega-3 polyunsaturated fatty acids) have reached consideration as nutrients that may debilitate the development of sarcopenia. **Omega-3 EPA and DHA** are precursors for the synthesis of mediators of inflammation and have been shown to influence anabolic signalling associated with protein turnover, supposedly by modifying the phospholipid membrane content. Some evidence proposes that omega-3 fatty acids are able to reduce muscle wasting by increasing the functional capacity in the elderly by growing the intracellular metabolic signal. It has been shown that supplementation with EPA plus DHA for 6 months lessen the normal decline in muscle mass and function in healthy older adults in comparison with the corn-oil supplemented placebo group. According to Rondanelli et al, fish contains biologically active compounds, such as omega-3 polyunsaturated fatty acids, proteins, vitamin D, magnesium, and carnitine, which are able to intervene positively on muscle metabolism. In an epidemiological study conducted among older adults (The Hertfordshire cohort study), Robinson et al found that fatty fish consumption was the most significant dietary component positively affecting grip strength, concluding that **fatty fish consumption can have an important influence on muscle function** in older men and women.

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Exercise is a major component for the enhancing of muscle decline in older adults. A number of publications point out that muscle function in older adults can be balanced and even augmented by physical exercise. Different types of exercise have been proposed: Resistance Training, Aerobic Exercise, High-Intensity Interval Training (HIIT), Multimodal Exercise including a mix of strength training, cycling, aerobic training, equilibrium training, and Whole-Body Vibration Therapy in case of active inability to exercise. It appears that an adequate exercise program accompanied by nutritional intervention should be of key importance for a better evolution of **sarcopenic, sarcopenic-malnourished and geriatric patients**. A systematic review of Yoshimura et al. indicated some positive effects of exercise and nutritional interventions for treating sarcopenia in older people. It has been revealed that the **intake of protein, after a period of resistance exercise** produces a higher rate of muscle protein synthesis and a net protein anabolic situation within the muscle. Another meta-analysis completed by Cermak NM et al. suggested that protein supplementation during resistance exercise training is related to greater increases in muscle strength and lean mass in both young and older adults.

In summary, we conclude that tailored nutritional support accompanied by an appropriate exercise program should be of major importance for a better outcome of muscle functionality among older adults, even more, if malnourished

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Prof. Stephen Cunanne
PhD

SPEAKER BIOGRAPHY

Stephen Cunnane was a professor in the Department of Nutritional Sciences at the University of Toronto for 17 years prior to moving to Sherbrooke, Québec, Canada, in 2003 as a full professor and senior Canada Research Chair at the Research Center on Aging, Université de Sherbrooke. Dr. Cunnane studies whether ketone-based interventions can bypass deteriorating brain glucose metabolism during aging to slow down aging-associated cognitive decline and Alzheimer's disease.

His team was the first to conduct dual tracer PET imaging studies of brain ketone and glucose uptake, and the first to show that the energy status of the Alzheimer brain can improved by ketones. This work led to them showing that a ketogenic supplement can improve cognitive outcomes in the pre-Alzheimer stage - mild cognitive impairment - in direct relation to the increase in brain ketones. Dr. Cunnane has published over 300 research papers and five books. Two of his books highlight the key role of ketones in human brain evolution. His concept of 'brain energy rescue' by ketones to treat neurodegenerative disorders is the subject of his very recent review in Nature Reviews Drug Discovery (to be published in July 2020, Impact Factor of 58).

He was elected to the French National Academy of Medicine in 2009. In 2016, he was honored as a founding Fellow of the International Society for the Study of Fatty Acids and Lipids (ISSFAL). He received the Chevreul Medal from the French Society for the Study of Lipids in 2017 for his research on fats, nutrition and health. In 2018, his team won the Université de Sherbrooke's top research prize for clinical sciences, and he was the Lurie Lecturer at the University of Cincinnati.

Dr. Cunnane consults on the topic of keto-therapeutics and is the founder of Senotec, a start-up company with IP for novel ketogenic molecules.

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ABSTRACT

Brain glucose uptake is about 10% below normal in Mild Cognitive Impairment (MCI) **and deteriorates further in Alzheimer disease** (AD). It is now clear that in contrast to glucose, uptake of **the brain's main alternative fuel – ketones** (acetoacetate and beta-hydroxybutyrate) – **remains normal in both MCI and mild-moderate AD**. Furthermore, evidence is accumulating that an endogenous or exogenous source of ketones can at least partially bypass brain glucose hypometabolism and improve brain energy metabolism in both MCI and mild-moderate AD. The key question now is **whether improved brain energy metabolism also improves cognitive performance in MCI or AD**.

The objective of the randomized, placebo-controlled Benefic trial (NCT02551419) was **to assess whether counteracting the brain glucose deficit with an Oral Nutritional Supplement containing a ketogenic medium chain triglyceride** (kMCT-ONS), **BrainXpert Energy complex**, could **improve cognitive performance** over **6 months** in Mild Cognitive Impairment. Following screening with a comprehensive cognitive battery, n=122 MCI were recruited (amnestic and non-amnestic MCI combined). An overall sample size of n=82 for both arms combined was required to have the necessary power to detect at least a moderate effect size on cognitive outcomes of episodic memory and executive function. **Outcomes in all five main cognitive domains were assessed** immediately before and at the end of the intervention.

The **ONS was lactose-free skim milk emulsion containing 15 g kMCT twice/day** (active arm; n=39 completers) or an **energy equivalent placebo providing 12 g non-ketogenic vegetable oil twice/day** (n=44 completers). The formulation and organoleptic properties of the ONS were identical for both active and placebo arms. **Brain ketone** and **glucose PET** were done **before and at the end** of the 6-month intervention on sub-groups of **both arms** (n=19/arm pre- and post-intervention). The **plasma ketone** response was assessed before and after the intervention in a different sub-group (n=10/arm pre- and post-intervention). **Plasma cardiometabolic and inflammatory marker profiles** were also assessed.

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Data were analyzed by ANCOVA using pre-intervention cognitive score plus age, sex, education and apolipoprotein E4 status combined as covariates.

Raw scores as well as normalized Z-scores for five tests in three cognitive domains improved post-intervention on the kMCT arm only ($p \leq 0.01$). Specifically, on the kMCT-ONS, trial 1 of the:

- Free and Cued Recall Test showed a +1 word improvement (+0.5 Δ Z-score),
- Correct answers on the Verbal Fluency Test increased by 2 words (+0.3 Δ Z-score) but decreased by 1 word on placebo (-0.1 Δ Z-score),
- Correct answers on the Boston Naming Test increased by 1.1,
- Time taken on the Stroop Colour Naming Test decreased by 1 sec ($p=0.09$),
- Errors on the Trail Making Test decreased by 0.9 on the kmct-ONS but increased by 0.8 on placebo ($p=0.02$).

Global brain ketone uptake doubled on the kMCT-ONS only and directly **as the increase in plasma ketones** ($r = +0.87$, $p<0.01$). **Moderate effect sizes** (partial $n2 = 0.06 - 0.14$) were seen for **several cognitive outcomes on the kMCT-ONS only. Free and cued recall, Trail-making, and Boston Naming test scores all correlated significantly** and directly as the **increase in plasma or global brain ketone uptake on kMCT-ONS** ($r = +0.23 - +0.33$, $p = 0.013 – 0.042$). **Increased uptake of ketones in multiple brain white matter fascicles** was **significantly positively correlated** with **faster processing speed on the kMCT-ONS** ($r = +0.47 – +0.61$, $p = 0.014 – 0.047$; $n=16$). **Plasma ketone response to a single 15-gram dose of the kMCT-ONS did not change significantly** at the end vs. before the 6-month intervention; ketones did not increase at all on the placebo arm. Changes in anthropometry (weight, BMI) and plasma markers of cardiometabolic health (insulin, glucose, cholesterol) were not clinically significant post-intervention on either arm. Amongst the **plasma inflammatory markers**, only interleukin 8 increased on the kMCT-ONS (+3 pg/ml; interaction $p = 0.002$ vs. post-placebo; $n=17$). Average drop-out rate on both arms was 31%. In completers, protocol **adherence was 89% over six months.**

Nestlé HealthScience

WHEN AN ORAL NUTRITIONAL SUPPLEMENT IMPROVES COGNITIVE OUTCOMES IN MILD COGNITIVE IMPAIRMENT

Prof. Stephen Cunanne
PhD

CONCLUSIONS

The **Benefic Trial** was **powered to assess outcomes of memory and executive function in Mild Cognitive Impairment** and demonstrated that this **Oral Nutritional Supplement containing a ketogenic medium chain triglyceride** (kMCT-ONS), **BrainXpert Energy complex, improved several cognitive outcomes that were positively correlated with the improved brain energy status achieved by the enhanced supply of ketones.**

Hence, there was a direct mechanistic link between raising brain ketones with the kMCT-ONS and improving cognitive performance in MCI. The consistent plasma ketone response suggests there was no metabolic adaptation or loss of response to an oral dose of kMCT-ONS after daily consumption over six months.

These results demonstrate efficacy, safety, acceptability, and feasibility of long-term use of BrainXpert Energy complex twice daily dose to improve cognitive performance in MCI.

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