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BROADCAST Congress

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EFFECT OF NUTRITION AND KETOGENIC INTERVENTION ON BRAIN PERFORMANCE IN MILD COGNITIVE IMPAIRMENT

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Prof. Antonio Cherubini, MD, PhD

Director of Geriatria, Accettazione geriatrica e Centro di ricerca per l' invecchiamento, IRCCS INRCA, Ancona, Italy.

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Dr. Bernard Cuenoud, PhD

Aging and Energy Metabolism, Translation Research, Nestlé Health Science, Lausanne, Switzerland. Adjunct Professor, Faculty of Medicine and Health Sciences, Sherbrooke University, Canada.

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Introduction
Chairperson

Prof Antonio Cherubini, MD, PhD
Director of Geriatria, Accettazione geriatrica e Centro di ricerca per l' invecchiamento, IRCCS INRCA, Ancona, Italy.

CHAIRPERSON BIOGRAPHY

Antonio Cherubini, MD, PhD, is a geriatrician. He performed research activities at the Geriatric Research Education Clinical Center (GRECC), VA hospital, Gainesville, Fl.; at the Massachusetts General Hospital, Harvard Medical School, Boston, Ma; at the Human Nutrition research Center on Aging, Tufts university, Boston, Ma; at the Longitudinal branch Section, National Institute of Aging, Baltimore, Md.

He is currently Director of Geriatria, Accettazione geriatrica e Centro di ricerca per l'invecchiamento at IRCCS INRCA, Ancona, Italy. He is also Associate Professor of Gerontology and Geriatrics at the University of Perugia Medical School.

He is member of the Geriatric Expert Group at the European Medicine Agency and of the Academic Board of the EuGMS. He is vice Chairman of the Ethics committee at IRCCS INRCA.

Author of more than 400 papers in peer reviewed journals. He is Associate Editor of European Geriatric Medicine and Editor of the geriatric section of Panminerva medica.

His main research interests are: comprehensive geriatric assessment; geriatric pharmacotherapy, including inappropriate prescription, adverse drug reactions and exclusion of older subjects from clinical research; delirium; frailty and sarcopenia. H index (Scopus 69).

ABSTRACT:

Cognitive impairment is considered one of the greatest challenge for health and social care in the XXIst century. Due to reduction of premature death and increasing life expectancy, the prevalence of cognitive impairment is expected to increase both in high income and medium-low income countries. The most severe form of cognitive impairment is dementia. Although some epidemiological studies found a reduction in dementia incidence, particularly in high income countries, the increase of the number of older subjects suffering from this condition will continue in the near future. Therefore, it is extremely important to try and prevent or slow down the onset of dementia. Several risk factors have been identified whose reduction during the life course might contribute to achieve this purpose. While age, sex and genetic predisposition cannot be modified, other risk factors should be properly addressed. Among

them less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact, excessive alcohol consumption, traumatic brain injury, and air pollution (Figure 1)

However, it should be pointed out that the majority of subjects do not develop dementia acutely but rather they experience a decline in cognitive functions before the onset of overt dementia.

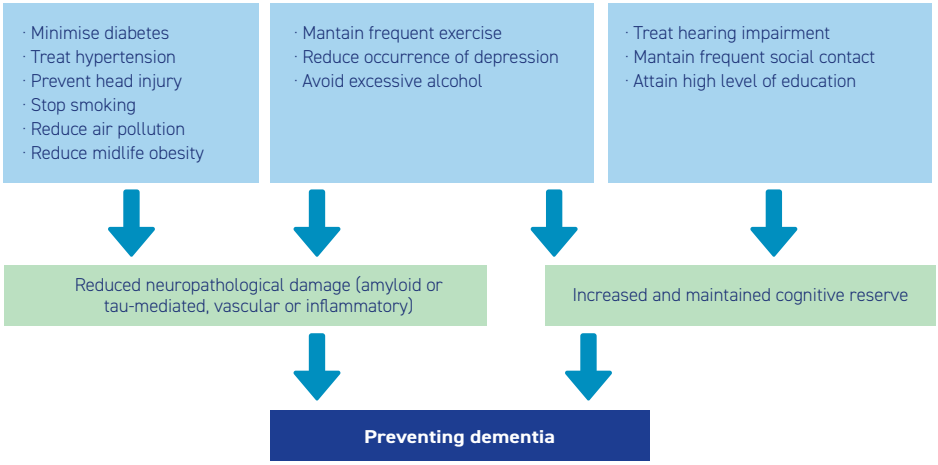

Figure 1. Dementia prevention

Mild cognitive impairment (MCI) is a clinical syndrome, which is characterized by an objective decline of cognitive functions, documented on neuropsychological tests, which is greater than expected considering the subject's age and education level, but does not impair the ability to perform activities of daily living. Most importantly, MCI is associated with a higher risk of experiencing cognitive and functional decline, although not all subjects with MCI will progress to dementia.

The epidemiology of MCI is not well known, since different studies provided variable figures, in view of the heterogeneity of populations, diagnostic tools and criteria. It is however well established that the probability to develop MCI increases with age. Therefore, MCI is mainly affecting older subjects. The prevalence increases from 6.7% at the age 60 to 64 years up to 25.2% in the age group 80 to 84 years. (Figure 2). Moreover, it is very likely that MCI is underdiagnosed, since in many instances older age is considered the cause for cognitive deficits by older subjects, their family members and even their physicians.

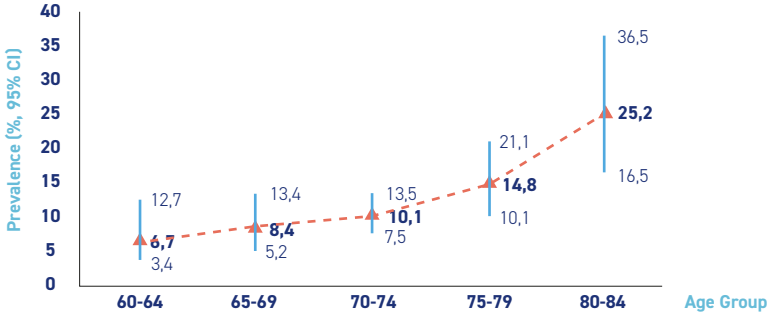

Fig 2. Prevalence of MCI by age group (random effects model)

Although several studies investigated potential therapeutic interventions in subjects with MCI, there is currently no authorized pharmacological intervention to improve cognitive functions or prevent the progression of MCI to dementia. Analogously, there is no dietary agent that has demonstrated efficacy in the treatment of MCI. Nevertheless, in view of the fact that nutrition has a paramount role in healthy and cognitive aging, nutritional interventions have attracted considerable interests and their potential benefits have been evaluated in MCI patients. Until now, there is insufficient evidence that whole diets or specific dietary compounds improve cognitive outcomes in patients with MCI.

The current symposium will present the latest studies concerning a promising dietary treatment, i.e. the use of a ketogenic intervention to improve cognitive performance in subjects with MCI. The rationale underlying this approach as well as the results of a clinical trial will be presented and discussed today by renowned experts in the field.

The first speaker will be Prof Robin Williams, working at the Centre for Biomedical Sciences, School of Biological Sciences, Royal Holloway University of London, The United Kingdom, who will elucidate the mechanisms underlying the beneficial effects on cognition of ketogenic medium chain triglycerides.

The second speaker will be prof. Bernard Cuenoud, PhD, working at the Aging and Energy Metabolism, Translation Research, Nestlé Health Science, Lausanne, Switzerland and, as adjunct Professor, at the Faculty of Medicine and Health Sciences, Sherbrooke University, Canada, who will present a clinical trial evaluating the effects of a ketogenic supplement on cognitive functions in patients with MCI.

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Understanding how Ketogenic-Medium Chain Triglycerides (kMCTs) provide cognitive improvements

Prof. Robin S B Williams, PhD
Centre for Biomedical Sciences,
School of Biological Sciences,
Royal Holloway University of
London, The United Kingdom.

SPEAKER BIOGRAPHY

Prof Williams is a basic-translational researcher in the field of epilepsy and drug discovery, with special interest in ketogenic diets and the development of new treatments.

He graduated with a PhD in molecular cell biology at the University of Melbourne (Australia) in 1994, and pursed subsequent postdoctoral positions at St Andrews University and University College London (UCL) in the UK, followed by an independent Wellcome Trust Career Development fellowship at UCL. He moved to Royal Holloway University of London in 2006, where he is now Professor of Molecular Cell Biology in the Centre for Biomedical Sciences.

His expertise relates to molecular cell biology, neuroscience, pharmacology, drug development, and pharmacogenetics, where he often initiates his studies in a tractable non-animal model system, with breakthroughs translated to well-accepted pre-clinical models.

His recent studies have provide a range of key new insights to the molecular mechanism of the MCT ketogenic diet, where this information has helped to develop a novel MCT recently demonstrated in clinical trials to be highly effective in the treatment of adults and children with drug-resistant epilepsy without severe dietary restrictions.

He is also a founding member of the International Neurological Ketogenic Society (INKS).

ABSTRACT:

It is clear brain energy glucose metabolism is about 10% below normal in Mild Cognitive Impairment (MCI) and deteriorates further in Alzheimer disease and an alternative energy source for brain cells (neurons and astrocytes) is needed.

Medium chain triglycerides (MCTs) consumption, without stringent dietary restrictions, has recently been shown to give rise to mild ketosis, in addition to elevating levels of specific medium chain fatty acids, 60% octanoic and 40% decanoic fatty acid (kMCT) because of their rapid absorption and oxidation, and produce ketones and lactate which brain cells are able to use as an energy source. Figure 1

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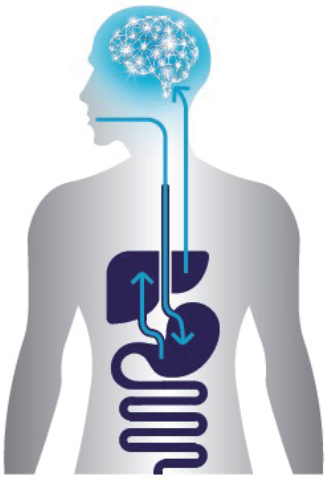
1. The kMCTs move through the GI and is broke down in the gastrointestinal tract.

2. Medium-chain fatty acids are absorbed directly through the gut wall and transferred to the liver where are rapidly metabolized through β-oxidation

3. Metabolism of these fatty acids mainly results in the generation of three major ketones, β-hydroxybutyrate, acetoacetate, and acetone



4. These ketones and fats thet escape metabolism are distributed through the blood in the circulatory system, cross the blood-brain barrier, reaching brain concentration and providing an alternative energy source for brain cells (neurons & astrocytes).

Fig 1. Metabolism of ketogenic medium-chain triglycerides

In the treatment of MCI, a range of mechanisms have been proposed for these kMCTs. These mechanisms include the well-accepted process of energy provision to neurons, restoring that lost through reduced glucose metabolism. In addition both ketones and decanoic acid function to elevate the number of mitochondria in cells, again providing improved energy supply to the brain cells.

Furthermore, a range of other therapeutic mechanisms have been recently identified, including adenosine-dependent effects, the reduction of reactive oxygen species (ROS) production, the prevention of cell death (neuroprotection), signaling effects such as the inhibition of mTORC1, and the reduction of over-activated synapses through the inhibition of AMPA receptor activity. All of these processes may contribute to the treatment of patients with mild cognitive impairment.

This presentation will briefly outline these mechanisms, to provide an overview of potential effects of kMCTs in the treatment of mild cognitive impairment.

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Brain Energy Rescue: Effects of a Ketogenic Oral Nutritional Supplement in patients with Mild Cognitive Impairment

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Aging and Energy Metabolism, Translation Research, Nestlé Health Science, Lausanne, Switzerland. Adjunct Professor, Faculty of Medicine and Health Sciences, Sherbrooke University, Canada.

SPEAKER BIOGRAPHY

Dr Bernard Cuenoud was a researcher in the pharma industry for 17 years, spearheading the discovery, development and launch of many innovative drugs for indications such as Parkinson's disease, multiple sclerosis and respiratory diseases.

He joined Nestlé Health Science in 2012 and initiated a clinical research program focusing on ketone metabolism and its effects on brain pathophysiology, resulting in a new product launch and several publications and patents in this field.

Recently he was nominated Adjunct Professor at the Faculty of Medicine and Health Sciences , Sherbrooke University. He received his PhD from Yale University and completed his post-doctoral training at Harvard Medical School.

ABSTRACT:

1 out of 6 people aged 65 and above experiences a decline in memory and thinking ability that exceeds the level expected due to aging: a condition which is referred to as MILD COGNITIVE IMPAIRMENT (MCI). Over 50% of MCI patients progress to Alzheimer Diseases over 5 years, and there is no drug approved to treat MCI.

New science paradigm suggests that the decline in brain glucose metabolism is causal to dementia progression, and that ketones, the brain's main alternative fuel, can rescue the brain energy deficit. Importantly, early intervention in dementia might slow the disease progression.

Supporting this view, it has been demonstrated that the decrease in brain glucose metabolism is strongly associated with a decrease in cognitive decline. This correlation is much stronger than the one observed between the increase in brain amyloid protein deposits and the decline in cognition in MCI and Alzheimer's (AD) patients. This suggest that brain glucose metabolism is a superior indicator of cognitive performance compared to amyloid protein aggregation in Alzheimer's Disease and Mild Cognitive Impairment.

Here we report that an oral nutritional supplement containing a ketogenic medium chain triglyceride (kMCT), BrainXpert Energy Complex, improved cognitive performance over 6 months in MCI patients. The Brain Energy, Functional Imaging, and Cognition (BENEFIC) randomized controlled trial

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demonstrated that the BrainXpert Energy Complex increased blood and brain ketones, and improved cognition in MCI participants. Improvement in cognition was associated with blood ketone level. While the improvement in performance on the free recall test is predictive of AD diagnosis, the impact on transition from MCI to AD or on the delay of onset remains to be established.

New analysis of the white matter fibers (neuron) revealed that the ketone cerebral metabolic rate was increased by about 2 fold by kMCT and correlated with an improvement in processing speed abilities, suggesting that ketones may have a role in myelin integrity in MCI.

A secondary data analysis to investigate changes in cardiometabolic markers and peripheral inflammation during the 6-month intervention revealed that kMCT have a minimal effect on an extensive profile of circulating metabolic, fatty acid and inflammatory markers as compared to a placebo calorie-matched drink, supporting the safety of kMCT supplementation in elderly with MCI.

These results provide robust support for the concept that brain energy rescue with ketones such as kMCT can improve cognitive outcomes in elderly MCI. Longer clinical studies will determine if a keto-therapeutic intervention can slow disease progression toward AD during the MCI phase.

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Clinical Evidence behind BRAINXPERT

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Clinical Evidence behind BRAINXPERT

References:
Fortier M, et al. A ketogenic drink improves cognition in mild cognitive impairment: Results of a 6-month RCT. Alzheimers' Dement 2021;17(3):543-552. doi: 10.1002/alz.12206.. https://doi.org/10.1002/alz.12206

INTRODUCTION

It is known that **brain glucose uptake decreases with age and is about 10% below normal in Mild Cognitive Impairment (MCI)** and **deteriorates further in Alzheimer's disease** (AD). On the other hand, uptake of the **brain's alternative fuel : ketones** (acetoacetate and beta-hydroxybutyrate) **remains normal in both MCI and mild-moderate AD.** Furthermore, evidence is growing that an endogenous or exogenous source of ketones can at least partially compensate 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 can positively impact cognitive performance in MCI or AD.**

PRIMARY OBJECTIVE

To assess whether counteracting the brain glucose deficit with an **Oral Nutritional Supplement containing ketogenic medium chain triglycerides** (kMCT-ONS), BRAINXPERT ENERGY COMPLEX, could **improve cognitive performance** and **episodic memory** over 6 months in MCI.

SECONDARY OBJECTIVE

To assess whether BrainXpert Energy Complex:

- Changes **brain energy metabolism**
- Changes **cognitive performance**
- Changes **blood metabolites**
- Gastrointestinal **tolerance**
- **Compliance**

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STUDY DESIGN

Study Type : Randomized Controlled trial

Study population : Following screening with a comprehensive cognitive battery, **people suffering from MCI** were recruited (amnestic and non-amnestic MCI combined). An overall sample size of **n=82** for both arms 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 before and after **6 months intervention.**

Intervention : During 6 months, the participants **were requested to consume the kMCT-ONS** which was a lactose-free **containing 15g kMCT twice a day** (active arm; n=39 completers) or an **energy equivalent placebo providing 12g non-ketogenic vegetable oil twice a day** (placebo arm; n=43 completers). The formulation and organoleptic properties of both interventions were identical for both active and placebo arms.

INCLUSION CRITERIA

- Aged 55 and over
- MCI (Peterson criteria, 2004):
- Presence of a subjective memory complaint
- Objective cognitive deficit in at least one cognitive domain
- MoCA score 18 to 26; MMSE score 24 to 27 and/or diagnosis of a physician
- 2 scores <1.5 standard deviations on standard cognitive tests
- Normal autonomy of daily living
- Absence of depression

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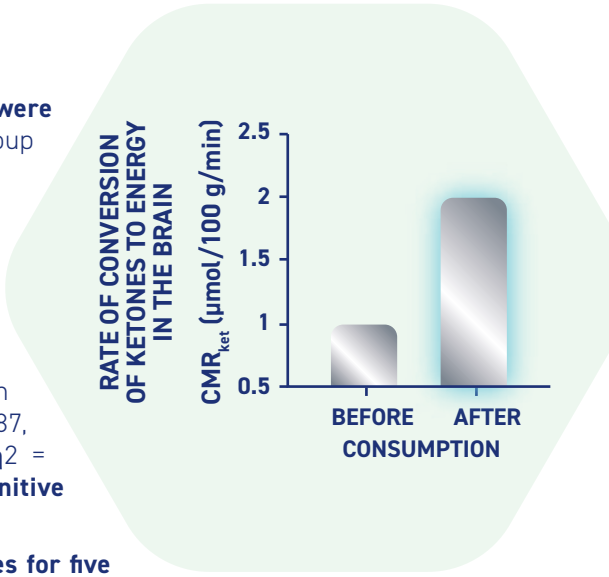
Clinical Evidence behind BRAINXPERT

RESULTS:



- Post-intervention, **total plasma ketones were increased significantly** in the kMCT group compared to placebo (P<.0001).
- **Whole brain CMR Ketones increased by +230% at the end of the active treatment (P<.001) with no change in the placebo group**
- **Global brain ketone uptake doubled on the kMCT-ONS** arm directly correlated with **the increase in plasma ketones** (r = +0.87, p<0.01). **Moderate effect sizes** (partial η2 = 0.06 - 0.14) were seen for **several cognitive outcomes on the kMCT-ONS only.**
- **Raw scores as well as normalized Z-scores for five cognitive tests in three different cognitive domains shown statiscally improved results post-intervention on the kMCT-ONS arm only (p≤0.01).**
- **Free and cued recall, Trail-making, and Boston Naming test scores all correlated significantly and directly with increase in plasma and 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 dose of 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.**

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Clinical Evidence behind BRAINXPERT

Conclusions - BRAINXPERT ENERGY COMPLEX:

- **Improved cognitive outcomes in patients with Mild Cognitive Impairment** as the increased availability of ketones **significantly improved brain energy supply.** This includes clinical proof of **improving memory, word recall, thinking speed and multitasking when taken twice per day for six months.**

- Proved it is **safe and feasible** for an **MCI population** to comply with an intervention of **15g of ketogenic-Medium Oral Nutritional Supplement twice daily for 6 months.**

These results demonstrate efficacy, safety, acceptability, and feasibility of long-term use of BRAINXPERT ENERGY COMPLEX twice daily in improving cognitive performance in MCI

BRAINXPERT IS A BREAKTHROUGH INNOVATION WITH A KETOGENIC ENERGY COMPLEX THAT HELPS SUPPORT YOUR PATIENTS' BRAIN ENERGY

Financial support for this Trial was provided by the Alzheimer Association USA, FRQS, Université de Sherbrooke and Nestlé Health Science Societé des Produits Nestlé S.A., Vevey, Switzerland

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