



SYMPOSIUM ABSTRACT BOOK

Role of Medical Nutrition in Wellbeing in Older People with Losses in Intrinsic Capacity

Satellite Symposium

18th International Congress of the European Union
Geriatric Medicine Society (EUGMS)

29 SEP.
2022

FOR HEALTHCARE PROFESSIONALS ONLY

NNI Nestlé
Nutrition
Institute

AGENDA

Introduction CHAIRPERSON

Prof Dr Leocadio Rodríguez Mañas. Head of the Department of Geriatrics at Hospital Universitario de Getafe, Madrid. Scientific Director of CIBER of Frailty and Healthy Aging (CIBERFES), Madrid, Spain.



Nutritional facts and functional decline in older people: what we know, what we ignore

Prof Dr Leocadio Rodríguez Mañas.



Measuring and monitoring intrinsic capacity: The implementation of ICOPE WHO programme into clinical practice

Prof Dr María Eugenia Soto-Martin. Head of Aging and Disability Prevention Team of Gérontopôle, Toulouse University Hospital, France.



Do we need more EFFORT to improve nutritional status in the elderly patients

Prof Dr Philipp Schütz. Head of Internal Medicine & Emergency Medicine, Kantonsspital Aarau, Switzerland.



Ketogenic intervention and brain performance in mild cognitive impairment

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



Invitation for audience conversation & Closing session





Prof. Dr. Leocadio Rodríguez Mañas.

Head of the Department of Geriatrics at Hospital Universitario de Getafe, Madrid. Scientific Director of CIBER of Frailty and Healthy Aging (CIBERFES), Madrid, Spain.

Introduction

Speaker biography

Prof Leocadio Rodríguez Mañas is Head of the Geriatrics Service of the Getafe University Hospital (Madrid), Scientific Director of the Spanish Center for Biomedical Research on Frailty and Healthy Aging (CIBERFES) (Ministries of Health and of Economy and Competitiveness), and Co-Director of the Toledo Study on Healthy Aging, carried out in 2,895 elderly people followed over 9 years.

He is Director of the Global Aging Research Network of the International Association of Gerontology and Geriatrics (GARN-IAGG) since July 2017. He has led more than 40 publicly-funded research projects, many of them focused on frailty and functional decline in older people, including the Joint Action on Frailty (ADVANTAGE) funded by DGSANTE-European Union.

He has published more than 350 originals in indexed journals peer-reviewed articles and written books and book chapters on various aspects of aging, frailty and diabetes in older people. He has participated in the preparation of technical reports on these topics for national organizations (Ministry of Health, Scientific Societies, Research Organizations and Agencies) and international organizations (WHO, PAHO, DG-SANTE, DG-Research, IAGG, Governments of Mexico, Costa Rica and Chile, etc) and is an international advisor to WHO and PAHO.



Abstract

Intrinsic capacity has emerged in the last decade as one of the most promising concepts in defining how functional decline takes place along time, the risk factors for this decline and the mechanisms involved. Embracing domains related to several aspects linked to functioning and reflecting the interaction between genetics, life styles and diseases, intrinsic capacity offers an opportunity for a new paradigm of healthy aging, based on function, and a good explanation of disability as the net effect of the balance between what the person is able to do and the challenges of the environment.

Nutrition plays a relevant role in determining intrinsic capacity, but also in its recovery when it is lost.

In this Symposium we will briefly review the state of the art of the relationships between nutritional facts and function in older people, including our lacks of knowledge. Afterwards, we will know the last novelties in the implementation of ICOPE, the program that WHO is trying to develop with the purpose of early detection and intervention on functional decline. The third topic will be focused in the program EFFORT, which has shown to improve several outcomes through a complex intervention, including Oral Nutritional Supplements, in older people admitted to hospital and followed-up after discharge. Finally, the role of ketogenic diets will be revisited, in this case focused on people with Mild Cognitive Impairment, where data from recent clinical trials suggest its usefulness in this condition which up-to-date do not have many validated treatments.

References

1. Bernabei R et al. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project). *BMJ*. 2022 May 11;377:e068788. doi: 10.1136/bmj-2021-068788.
2. Tavassoli N et al. Implementation of the WHO integrated care for older people (ICOPE) programme in clinical practice: a prospective study. *Lancet Healthy Longev* 2022; 3: e394-404.
3. Schuetz P, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet* 2019; 393(10188):2312-2321.
4. Fortier M et al. A ketogenic drink improves cognition in mild cognitive impairment: Results of a 6-month RCT. *Alzheimers Dement*. 2021 Mar;17(3):543-552.





Prof. Dr. Rodríguez Mañas

Head of the Department of Geriatrics at Hospital Universitario de Getafe, Madrid. Scientific Director of CIBER of Frailty and Healthy Aging (CIBERFES), Madrid, Spain.

Nutritional facts and functional decline in older people: what we know, what we ignore

Speaker biography

Prof Leocadio Rodríguez Mañas is Head of the Geriatrics Service of the Getafe University Hospital (Madrid), Scientific Director of the Spanish Center for Biomedical Research on Frailty and Healthy Aging (CIBERFES) (Ministries of Health and of Economy and Competitiveness), and Co-Director of the Toledo Study on Healthy Aging, carried out in 2,895 elderly people followed over 9 years.

He is the Director of the Global Aging Research Network of the International Association of Gerontology and Geriatrics (GARN-IAGG) since July 2017. He has led more than 40 publicly-funded research projects, many of them focused on frailty and functional decline in older people, including the Joint Action on Frailty (ADVANTAGE) funded by DG-SANTE-European Union.

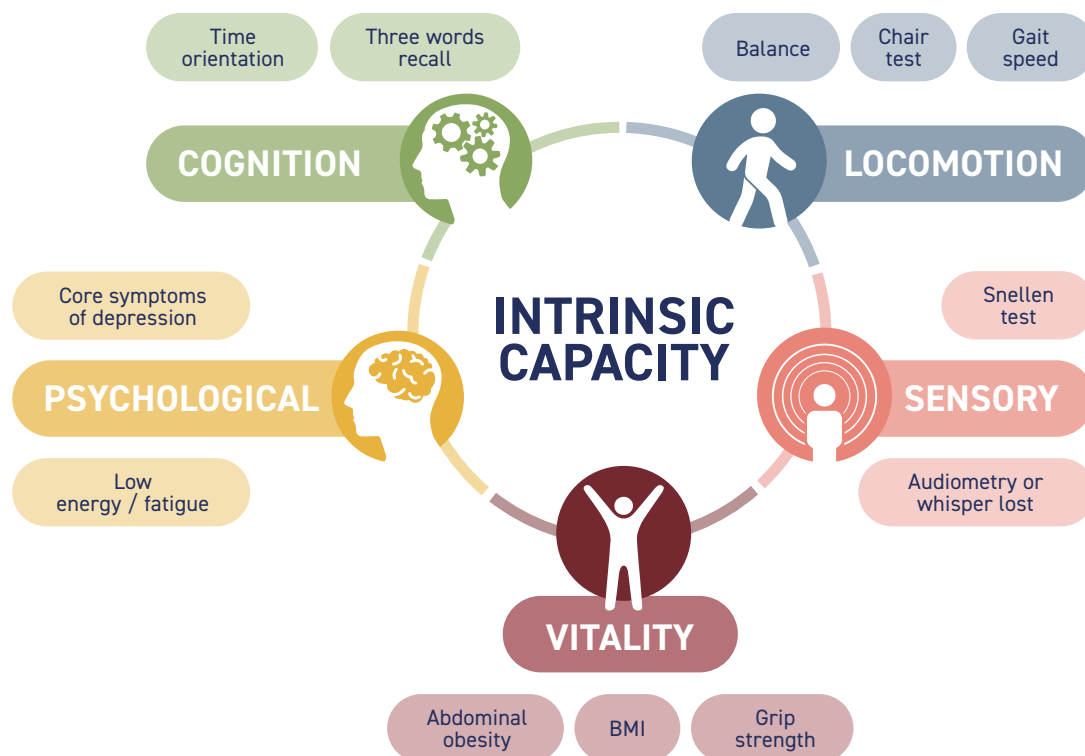
He has published more than 350 originals in indexed journals peer-reviewed articles and written books and book chapters on various aspects of aging, frailty, and diabetes in older people. He has participated in the preparation of technical reports on these topics for national organizations (Ministry of Health, Scientific Societies, Research Organizations, and Agencies) and international organizations (WHO, PAHO, DG-SANTE, DG-Research, IAGG, Governments of Mexico, Costa Rica and Chile, etc) and is an international advisor to WHO and PAHO.



Abstract

As we age, the determinants of our health change, as it does its main components. These changes embrace the manifestation of the diseases, the aim of care, the prognostic significance of several factors, the progressive importance of functional status, and the comparative relevance of disease and life-styles in determining that functional status.

Accordingly, a change in the paradigm of healthy aging has come, promoted not only by international associations (WHO, EU) but also by groups of researchers¹. According to this paradigm, healthy aging is a concept linked to functioning more tightly than to the absence or control of diseases, and the aim of promotion, prevention, and treatment is oriented to maintain functional independence as much and as long as possible. So, according to World Health Organization (WHO), healthy ageing is "the process of developing and maintaining the functional ability that enables well-being in older age" (WHO, 2021). Intrinsic capacity (IC) has recently been proposed by the WHO as a multidimensional indicator of health. IC framework comprises five domains: Cognitive, Psychological, Sensory (vision and hearing), Locomotor, Vitality/nutrition. All of them are crucial to: meet basic needs; learn, grow and make decisions; be mobile; build and maintain relationships; and contribute to society.



Inside this conceptual framework, factors associated to the maintenance of functional status or its recovery when it has been lost are of the utmost relevance. Three main factors must be taken into account²: primary aging, with a strong genetic influence, comorbidities, with a moderate role in determining functional status, and lifestyles, with a high predominance of physical activity and nutrition. The interaction among these three factors will lead the changes in function, and at the same time, the diseases will be increasingly manifested by functional changes³.

What do we know about the role of nutrition in determining maintenance or impairment in functional status?. Nutrition has been a classical factor considered when this topic has been addressed. However, the major part of the research has been focused on people with clinical malnutrition/undernutrition) and in specific settings where the prevalence of malnutrition is high but does not represent the usual setting where older people are (own homes, or with family members /community). Thus, data about nutritional factors associated with functional status in older people living in the community are very scarce. Moreover, until very recently, the majority of the studies were cross-sectional, not allowing to discriminate relationships of causality among the different factors shown to be associated.

A good example of this assertion is a systematic review published in 2017⁴, where they only found 19 studies assessing the relationship between nutrition and frailty, being only 5 among them longitudinal ones. Two topics are worthy to be considered when analysing this relationship.

The first one is the role of the global nutritional status (malnourished/at risk/well-nourished) and incident of frailty, disability, and death, and the second is the association between some aspects of the diet, ranging from type of diet to the analysis of several micronutrients.

I will review the available data in older people living in the community focused in these two aspects. The role of overweight and obesity will not be mentioned.

Concerning the role of nutritional status as a risk factor for incident of frailty our study (n=1660 older adults; 98% community-dwelling) and a systematic review conducted by Lorenzo-Lopez et al, showed a significantly and positively association between malnutrition and the probability of being frail^{4,5}. Regarding disability, the results are quite controversial. Moreover depending upon the criteria used to assess nutritional status (BMI, abdominal perimeter, waist-to-hip ratio), there is a tendency to find a positive association between undernutrition and incident disability. Data on the effect of being at-risk are more scarce indeed.

Finally in regard to mortality, the Toledo Study showed that Malnutrition was associated with a higher mortality using the Global Leadership Initiative on Malnutrition (GLIM) criteria⁵. These findings highlight the importance of assessing the nutritional status of community-dwelling older adults.



It is noteworthy that in contrast with the few studies analyzing the role of nutritional status in the community, there are many studies analyzing the role of different types of diets, components of the diets, and micronutrients on incident frailty. In summary, different types of a healthy diet (including Mediterranean and Atlantic diet, DASH and some others), virgin olive oil, resveratrol, wine (if taken according to the so-called Mediterranean pattern), and vegetables have shown to protect from frailty.

The role of proteins is controversial. Several studies have shown a short-term benefit while a long-term study found that proteins were associated to the risk of frailty. Three recent studies have thrown some light to this controversy showing a protective role, in combination with physical exercise, of a higher protein intake (Newcastle 85+ study), but conferring this benefit to the consume of protein of vegetal origin, while protein intake coming from red meat increases the risk (Nurses Health Study)⁶.

It is time to integrated care to help older adults maximize their Intrinsic Capacity and Functional Ability in the community. The ICOPE guidance for person-centred assessment helps community health and care workers put the recommendations outlined in the ICOPE Guidelines into practice. THERE IS NO TIME TO LOSE to regain autonomy in the malnourished older adults.

References

1. WHO. World report on aging and health. WHO, 2015
2. Seals DR, Justice JN, LaRocca TJ. Physiological geroscience: targeting function to increase healthspan and achieve optimal longevity. *J Physiol.* 2016; 594: 2001-24
3. Angulo J et al. Physical activity and exercise: Strategies to manage frailty. *Redox Biol.* 2020; 35: 101513.
4. Lorenzo-Lopez L et al. Nutritional determinants of frailty in older adults: A systematic review. *BMC Geriatrics* 2017
5. Rodriguez-Mañas et al. Impact of nutritional status according to GLIM criteria on the risk of incident frailty and mortality in community-dwelling older adults. *Clin Nutr.* 2021;40:1192-1198.
6. Struijk EA, et al. Protein intake and risk of frailty among older women in the Nurses' Health Study. *J Cachexia Sarcopenia Muscle.* 2022 Jun; 13: 1752-1761.





Prof Dr María Eugenia Soto-Martin.

Head of Aging and Disability Prevention Team of
Gérontopôle, Toulouse University Hospital, France.

Measuring and monitoring intrinsic capacity: The implementation of ICOPE WHO programme into clinical practice

Speaker biography

Prof. Maria Eugenia Soto Martin, MD, PhD, is geriatrician and head of the Alzheimer's clinical and research center in the Department of Geriatric Medicine at the Toulouse University Hospital in France. She is also head of the Aging and Disability Prevention Team of the Gerontopole, a WHO-collaborating centre for Frailty, Clinical Research and Geriatric Training. Currently, she leads with Prof Bruno Vellas the implementation of ICOPE WHO program in the region of Occitanie in France.

After graduating from the Seville University College of Physicians (Spain), obtaining his medical degree in 2000, she completed his clinical training and internship as resident in the Department of Geriatrics at the Getafe University Hospital of Madrid (Spain) where she obtained her specialization degree in Geriatrics in 2005. In the same year, she moved to the Department of Geriatric Medicine at the Toulouse University Hospital in France. She is member of the Research Aging Team MAINTAIN (CERPOP UMR 1295). In 2009 she obtained a Master M2 degree in statistics and epidemiology from the Paul Sabatier University of Toulouse. Pr. Soto has a PhD in Alzheimer's disease and cognitive progression from the same University.



Abstract

In 2017 the World Health Organization (WHO) published "Integrated care for older people (ICOPE)" guidelines which outlined evidence-based interventions to clinical care for older people. Rather than a focusing on the diseases, this approach emphasizes the optimization of intrinsic capacity (the composite of all the physical and mental capacities of an individual) as the key to "healthy" aging and thus to reducing the number of care dependent older people.

The ICOPE care pathways is based on the assessment and monitoring at regular intervals of six core domains of intrinsic capacity (mobility, vitality/nutrition, vision, hearing, cognition, psychology) and aims at improving, maintaining or slowing declines in intrinsic capacity (IC).

While consistent with similar approaches to preventing frailty, the IC construct differs by being framed as a dynamic continuum and its trajectory can potentially be monitored across the life course to shed interesting light on the effectiveness of clinical actions, as well as in public health, on the needs of populations.

Since January 2020, the G rontop le of the Toulouse University Hospital (France), a WHO collaborating Center on Frailty, Clinical Research, Geroscience and Training in Gerontology, has been implementing ICOPE in routine clinical practice in a large territory (Occitania region). This deployment, called the ICOPE CARE program, uses digital tools for screening allowing the routine collection and monitoring of data on IC by healthcare professionals over time. This program has been implementing in primary care. The ICOPE approach proposes a pathway composed of 5 steps: screening of participants for potential declines in one or more of the 6 domains of IC (Step1), in-depth assessment of participants in domains of interest identified by screening as having deficits (Step2) and development of a "personalized care plan" considering declines in IC, associated diseases, socio-environmental needs and most importantly goals and preferences of older person (Step3). Step4 recommends the monitoring of IC every 6 months and of the implementation of the personalized care plan proposed. Step5 concerns the involvement of communities and support for caregivers.

Between January 1, 2020 and November 18, 2021, 10,903 older persons (participants) and 2,714 professionals joined the ICOPE CARE program via the digital tools. The mean age of participants was 76.0 ± 21.1 and 60.8% were female. 1,536 participants (14.1%) completed their first self-assessment Step1 and 9,367 (85.9%) were assessed by a professional. In total, 18,301 step 1 were completed including 10,903 initial screenings and 7,398 follow-up. 94.3% of participants ($n = 10,285$) had potential declines in at least one IC domain at the first screening, suggesting potential declines in vision (68.1%), cognition (59.5%), hearing (50.6%), psychology (38%), mobility (34.6%) and vitality/nutrition (18.7%). A 6-month follow-up screening was performed for 70.4% of participants who had an initial screening test.

In total, 1,232 Step2 in-depth assessment were recorded in the database for all the potentially abnormal Step1. Most of the Step2 assessments (95%) were performed within two days of an abnormal Step1. Of 958 participants who received an initial Step2, 90.3% ($n = 865$) had at least one impaired capacity confirmed by the Step2. The mean age was 80.4 ± 7.6



years and 68.6% (n = 657) were female. According to Fried's criteria, 15.8% were robust, 42.9% pre-frail and 27.4% frail. 117 (12.2%) had an abnormal Amsler grid.

Concerning cognition, the mean MMSE score was 24.8 ± 4.6 and 268 (28%) participants presented memory complaints reported by family.

Concerning the nutritional status, median MBI was 25.9 ± 4.9 , according to the MNA scale, 275 (28.7%) were at risk of malnutrition and 65 (6.8%) had a probable malnutrition. At the end of the Step2, the majority of the recommendations proposed within the framework of the Step3 concerned the domain of mobility for 86.4% of the Step2 (n = 674) followed by vitality/nutrition (n = 740, 77.2%) and cognition (n = 623, 65.0%). Recommendations for nutrition domain were as follows: nutritional counselling (67.0%), weight monitoring (31.1%), fortified diet and oral nutritional (20.5%) and referral to the dentist (8.5%).

Recommendations for cognition domain were nutritional and physical activity counselling (27.4%), referral to a memory consultation (17.2%), cognitive stimulation exercises (16.6%), and proposal of participating in multi-domain workshops (8.4%).

In this presentation data from ICOPE CARE program implementation and data from IC nutritional and cognitive domains from these participants will be discussed. Special attention will be given to how ICOPE approach seems to detect early deficits in IC nutrition domain (by step1 and 2) allowing an early intervention (by step3) to prevent malnutrition and all its devastating health-related negative outcomes. On the other hand, ICOPE represents an opportunity to detect mild cognitive impairment (MCI) allowing early intervention in order to prevent further cognitive decline. Data will also show the feasibility of the ICOPE CARE program implementation in primary care clinical practice using digital tools, setting up a new care pathway integrated with prevention of care dependence. In fact, this program allows early detection of declines in intrinsic capacity, including nutritional and cognitive status, and allows to implement fast and personalized interventions to prevent loss of autonomy in elderly 60 and over years old.

References

1. World Health Organization. (2019). Integrated care for older people (ICOPE): guidance for person-centred assessment and pathways in primary care. World Health Organization.
2. Implementation of the WHO integrated care for older people (ICOPE) programme in clinical practice: a prospective study. Tavassoli N et al. Lancet Healthy Longev 2022; 3: e394–404





Prof Dr Philipp Schütz.

Head of Internal Medicine & Emergency Medicine,
Kantonsspital Aarau, Switzerland.

Do we need more EFFORT to improve nutritional status in the elderly patients

Speaker biography

Prof. Philipp Schuetz was born in Switzerland and studied Medicine at the University of Basel, Switzerland, and the University Kremlin Bicetre in Paris, France. He is a board-certified internist, endocrinologist and specialist for clinical nutrition. He is head of internal medicine and emergency medicine at the Kantonsspital Aarau and Professor of Medicine and Endocrinology/Nutrition at the University in Basel, in Switzerland. He is also president of the Federal Commission for Nutrition in Switzerland. He has published > 300 studies and research articles in high-impact journals including the Lancet, JAMA, Annals of internal medicine among others. Prof. Schuetz obtained a research professorship of the Swiss National Science Foundation (SNF) and was principal investigator of the EFFORT trial, the largest-yet randomized-controlled trial looking at clinical effects of clinical nutrition in medical ward patients.



Abstract

Malnutrition is a common condition among medically complex elderly inpatients. Emerging evidence demonstrates that malnutrition directly increases the risk for adverse clinical outcomes including mortality, morbidity and functional impairments, as well as increasing hospital length-of-stay and the risk for hospital readmission. The field of nutrition for elderly inpatients has advanced significantly in recent years with several recent trials looking at the role of nutritional support in the hospital having changed our understanding of nutrition.

Among these trials, the Swiss multicenter Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients Trial (EFFORT) included >2000 patients and found strong reductions in the risk for morbidity and mortality for patients receiving individualized nutritional support.

EFFORT is a pragmatic, investigator-initiated, open-label, non-commercial, multicenter, randomized-controlled trial, that tested the hypothesis that individualized nutritional support to reach protein and energy goals reduces the risk of adverse clinical outcomes in medical inpatients at nutritional risk.

This effectiveness trial was conducted in eight Swiss hospitals and randomized 2028 medical inpatients at nutritional risk, defined by a Nutritional Risk Screening [NRS 2002] score ≥ 3 points, to receive protocol-guided individualized nutritional support to reach protein and energy goals (intervention group) or standard hospital food (control group).

The composite primary endpoint was adverse clinical outcomes defined as all-cause mortality, intensive care admission, non-elective hospital readmission, major complications and decline in functional status at 30 days, with mortality being the principal secondary endpoint of interest. In the trial, nutritional support was provided according to a previously established nutritional protocol², which is in line with the ESPEN guidelines for polymorbid medical inpatients³. For each patient, individualized nutritional energy and protein goals were defined and set upon hospital admission. The protocol also proposed nutritional interventions to reach these goals by the establishment of an individual nutritional plan by a trained registered dietician.

The EFFORT trial found that nutritional goals could be reached, mostly by using oral nutrition including oral nutritional supplements (ONS), in a majority of intervention group patients. Importantly, regarding the primary endpoint, the trial found that upon 30 days 232 of 1015 patients (22.9%) in the intervention group experienced an adverse clinical outcome compared to 272 of 1013 (26.9%) of the control group patients corresponding to a number needed to treat of 25 to prevent one severe complication. There were also significant lower rates of death in the intervention group compared to the control group (7.2% vs. 9.9%) and notable improvements in functional outcomes and in quality of life measures.

These results provided strong evidence for the concept of systematically screening medical inpatients on hospital admission in terms of nutritional risk, independent of the medical condition, followed by a nutritional assessment and initiation of nutritional support in at-risk patients.



Patients who struggle with their daily intake of ONS benefit from products designed to optimise compliance. There is a need for an ONS that optimises key compliance-enhancing features, but also offers highly energy-protein concentrated nutrition, including high-quality protein, to improve the nutritional status and net protein balance of malnourished individuals.

Nutrition risk screening (NRS 2002) within 48 h of hospital admission in all patients

If increased risk for malnutrition > individual assessment of the patient > if risk for malnutrition is present and nutritional therapy is not contraindicated > establish strategy to achieve individual nutritional target

Individual nutrition targets

Caloric requirements

Harris-Benedict equation with adjusted bodyweight or indirect calorimetry

Protein requirements

1-2-1-5 g/kg bodyweight per day (0-8 g/kg of bodyweight per day in patients with renal failure with no dialysis)

Micronutrient requirements

Multivitamin use; other micronutrients according to specific laboratory results

Specific targets

Disease-specific adaptations (eg. medium-chain triglycerides, low potassium in patients with renal failure)

Strategy to reach the nutrition targets

Level 1: oral nutrition (meal adapted to preferences, food fortification or enrichment, and snacks between meal and oral nutritional supplements)

+

Multivitamins and multiminerals according to 100% of recommended dietary allowance

↑ Yes

Reassessment every 24-48 h: $\geq 75\%$ of caloric and protein target met?

↓ No

After 5 days escalate to level 2

Level 2: enteral nutrition

+

Oral nutrition, no additional vitamins and mineral supplements needed if enteral nutrition provides ≥ 1500 kcal per day

↑ Yes

Reassessment every 24-48 h: $\geq 75\%$ of caloric and protein target met?

↓ No

After 5 days escalate to level 3

Level 3: parenteral nutrition

+

Enteral and oral nutrition

Use concomitant oral or enteral nutrition (to avoid villous atrophy)



References

1. Schuetz P, Fehr R, Baechli V, Geiser M, Deiss M, Gomes F, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet*. 2019.
2. Bounoure L, Gomes F, Stanga Z, Keller U, Meier R, Ballmer P, et al. Detection and treatment of medical inpatients with or at-risk of malnutrition: Suggested procedures based on validated guidelines. *Nutrition*. 2016;32(7-8):790-8.
3. Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, et al. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. *Clin Nutr* 2018;37(1):336-53.





Prof Stephen Cunnane.

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

Ketogenic intervention and brain performance in mild cognitive impairment

Speaker biography

Stephen Cunnane is a professor in the Department of Medicine, University of Sherbrooke, and researcher at the Research Center on Aging. His team is assessing the links between deteriorating brain energy metabolism and risk of cognitive decline during aging. They were the first to show that ketones can at least partially correct the brain energy deficit in older people at risk of Alzheimer's disease. This observation that led to the concept of 'brain energy rescue' by ketones to treat neurodegenerative disorders. In the recent 6-month BENEFIC trial in MCI, his ketogenic medium chain triglyceride drink improved outcomes in all five cognitive domains. It was commercialized as BrainXpert by Nestlé in 2020 and is the first treatment available for MCI. Dr. Cunnane has published over 350 research papers and five books, two of which highlight the key role of ketones in brain expansion during human evolution. He was elected to the French National Academy of Medicine in 2009. In 2016, he was inducted as a 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.



Abstract

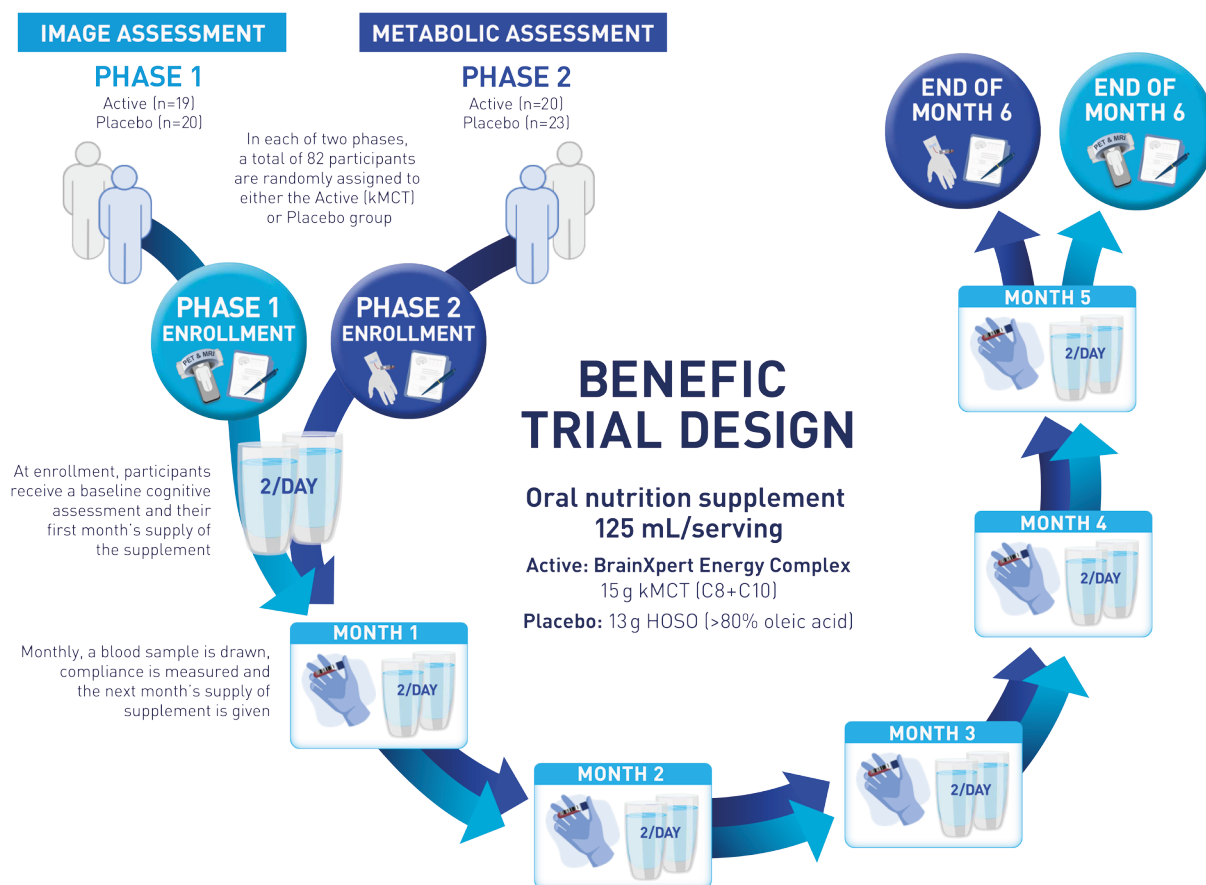
The relative risk of mild cognitive impairment (MCI) patients converting to AD within five years is about 3.0¹, although it varies according to the criteria used to define MCI. The brain has a high energy requirement relative to its weight, i.e. 20%-23% of whole body energy requirements². Uptake of the brain's main fuel - glucose - starts to decline in older people. In MCI, lower brain glucose uptake is present specifically in the posterior cingulate cortex and is also commonly reported in medial temporal lobe regions, including the hippocampus and entorhinal cortex³⁻⁵. White matter glucose deterioration is also evident in MCI and specific to limbic fascicles (or tracts)⁶⁻⁷. Lower brain glucose uptake in these brain regions clearly seems to be linked to the earlier onset of AD, particularly impaired episodic memory.

Brain energy rescue with ketones: An emerging strategy to delay the onset of Alzheimer disease is to use ketones to overcome the brain energy gap in older people caused by declining brain glucose uptake. The uptake of ketones, the brain's main alternative fuel to glucose, is now known to be unaffected in both mild cognitive impairment (MCI) and AD⁸. One recent example of successful application of brain energy rescue in MCI was with a ketogenic medium chain triglyceride (kMCT) supplement (BrainXpert Energy Complex) in the randomized, placebo-controlled Benefic Trial (NCT02551419) as reported recently^{9,10}.

Design of the Benefic Trial: In the Benefic Trial, the MCI population was heterogeneous but 80% had an amnesic deficit. Cognitive outcomes pre- and post-intervention were obtained for both the active arm which was 6 months of 15 g kMCT twice/day in a lactose-free skim milk emulsion (n=39 completers) and the placebo arm which was non-ketogenic vegetable oil of equivalent energy value and formulation as for the kMCT (n=44 completers). Brain ketone and glucose metabolism were assessed by positron emission tomography (PET) as were other neuroimaging outcomes. Safety, tolerability and metabolic assessments were also done^{9,10}. Figure 1.



Figure 1. **BENEFIC** trial design



Cognitive improvement: Several cognitive domains improved in the kMCT group: trial 1 of the Free and Cued Recall Test showed a +1 word improvement on kMCT (+0.5 Δ Z-score), correct answers on the Verbal Fluency Test increased by 2 words on kMCT (+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 on kMCT only, time taken on the Stroop Colour Naming Test decreased by 1 sec on the kMCT ($p=0.09$), and errors on the Trail Making Test decreased by 0.9 on kMCT but increased by 0.8 on placebo ($p=0.02$). Processing speed increased directly as a function of ketone uptake in several white matter tracts measured using a combination of brain ketone PET and diffusion imaging¹¹. Improved attention was associated with increased ketone uptake and connectivity only in the dorsal attention network as measured by functional MRI and brain ketone PET¹². Presence of apolipoprotein E4 did not significantly influence cognitive performance but this trial was underpowered for this outcome.

Safety, tolerability and metabolic effect: There was no clinically significant difference between groups in a range of cardiometabolic or inflammatory markers but interleukin-8 was increased in the kMCT group¹³. Both the active and placebo interventions were well tolerated with a mean retention of 68% and a mean compliance of 89%¹⁰. The kMCT drink was as ketogenic after 6 months as at baseline¹⁰. In a separate study, the kMCT drink was equally ketogenic in older (65 y) as in younger adults (28 y) or when taken with a high or low carbohydrate breakfast¹⁴.



Interpretation: The effect size of this kMCT intervention indicated a clinically meaningful benefit on several cognitive outcomes directly related to risk of progression of MCI toward AD, changes that arose directly as a result of improved brain energy supply by ketones. The improved result with kMCT on Free and Cued Recall test would be predicted to delay the onset of AD by about a year (Fortier et al 2021). Other studies with kMCT have reported similar results (reviewed in Cunnane et al. 2020). The ketogenic effect of this kMCT drink is robust to a wide age range and carbohydrate intake making it a flexible yet efficient supplement for brain energy rescue.

Implications and future studies: Recent evidence shows that interventions such as exercise, in particular aerobic exercise (AE), kMCT and supplementation with vitamins B12, B6 and folic acid may positively impact cognitive performance in MCI and AD. Although further studies might be necessary to understand the exact pathways through which this occurs, there are good reasons to suspect that, in combination, these interventions could have a synergetic effect.

The BrainXpert Energy Complex assessed in the Benefic Trial has been launched and commercialized for the dietary management of Mild Cognitive Impairment (www.brainxpert.com).

References

1. Petersen RC, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:126–35.
2. Holliday MA. Metabolic rate and organ size during growth from infancy to maturity and during late gestation and early infancy. *Pediatrics* 1971;47:Suppl 2:169+.
3. Nestor PJ, et al. Limbic hypometabolism in Alzheimer's disease and mild cognitive impairment. *Ann Neurol* 2003;54:343–51.
4. Croteau E, et al. A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. *Exp Gerontol* 2018;107:18–26.
5. Villain N, F et al. Sequential relationships between grey matter and white matter atrophy and brain metabolic abnormalities in early Alzheimer's disease. *Brain* 2010;133:3301–14.
6. Roy M, et al. Fascicle- and Glucose-Specific Deterioration in White Matter Energy Supply in Alzheimer's Disease. *J Alzheimers Dis* 2020;76:863–81.
7. Roy M, et al. A ketogenic supplement improves white matter energy supply and processing speed in mild cognitive impairment. *Radiology and Imaging* 2021.
8. Cunnane, SC. et al. Brain energy rescue: an emerging therapeutic concept for neurodegenerative disorders of ageing. *Nat Rev Drug Discov* 2020 Sep;19(9):609-633.
9. Fortier M et al. A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment- BENEFIC. *Alzheimer's Dement* 2019;15(5):625-634



10. Fortier M et al. A ketogenic drink improves cognition in MCI: Benefic Trial Results of a 6-month RCT. *Alzheimer's Dement* 2021;17(3):543-552
11. Roy M et al. A ketogenic supplement improves white matter energy supply and processing speed in mild cognitive impairment. *Alzheimer's Dement (N Y)* 2021; 17 (1):e12217
12. Roy M et al. A ketogenic intervention improves dorsal attention network functional and structural connectivity in mild cognitive impairment. *Neurobiol Aging* 2022 Jul;115:77-87.
13. Myette-Cote E. et al. The effect of a 6-month ketogenic medium-chain triglyceride supplement on plasma cardiometabolic and inflammatory markers in mild cognitive impairment. . *Prostaglandins Leukot Essent Fatty Acids* 2021;169:102236.
14. Vandenberghe C. et al. Medium Chain Triglycerides Modulate the Ketogenic Effect of a Metabolic Switch *Front Nutr* 2020; 31:7:3.



Educational resources for healthcare professionals:



NUTRITIONAL STRATEGIES FOR COUNTERING MILD COGNITIVE IMPAIRMENT IN AGING

Educational material focuses on the latest news on MCI description/definition, diagnostic criteria, and clinically relevant evidence-based intervention.

<https://www.medscape.org/viewarticle/962844>

GOAL STATEMENT

The goal of this activity is to highlight that the use of nutritional interventions (including neuroketotherapeutics) as part of a multidomain intervention strategy could be an important way to counter MCI in aging.

LEARNING OBJECTIVES

Upon completion of this activity, participants will:

- Have increased knowledge regarding the
- Link between brain glucose metabolism and MCI during aging
- Therapeutic strategies for countering MCI in aging patients

ACCREDITATION STATEMENT

The Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians of the United Kingdom (FPM) has reviewed and approved the content of this educational activity and allocated it 0.25 continuing professional development credits (CPD).



Mild Cognitive Impairment. FROM ASSESSMENT TO INNOVATIVE INTERVENTIONS.



CHIEF EDITOR

Prof Luis F. Agüera-Ortiz, MD, PhD. Instituto de Investigación Sanitaria (imas12). Servicio de Psiquiatría. Hospital Universitario 12 de Octubre. Madrid. Spain. Centro de Investigación Biomédica en Red de Salud Mental. CIBERSAM

TABLE OF CONTENTS

1. The historical evolution of Mild Cognitive Impairment
Dr. Javier Olazarán, MD, PhD. Spain
2. Mild Cognitive Impairment relevance and role in the prevention of dementia
Dr. Javier Olazarán, MD, PhD. Spain
3. Clinical assessment of Mild Cognitive Impairment
Prof. Andreas U. Monsch, PhD. Switzerland
4. Mild Behavioral Impairment. A new concept
Dr. Luis F. Agüera Ortiz MD, PhD.
5. Non-pharmacological interventions for Mild Cognitive Impairment
Dr. Philippe Robert, MD, PhD. France
6. Pharmacological interventions in Mild Cognitive Impairment
Dr. Krista Lanctot, PhD. - Dr. Krushnaa Sankhe, MSc, PhD. Canada
7. Neuroketotherapeutic strategies for countering Mild Cognitive Impairment
Dr. Maggie Roy, PhD. - Prof. Stephen Cunnane, PhD. Canada





**Role of Medical Nutrition
in Wellbeing in Older People with
Losses in Intrinsic Capacity**

NNI **Nestlé**
Nutrition
Institute

