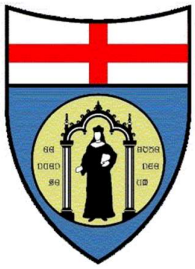
UNIVERSITÀ DEGLI STUDI DI GENOVA

SCUOLA DI SCIENZE MEDICHE E FARMACEUTICHE



DOTTORATO DI RICERCA IN EMATO ONCOLOGIA E MEDICINA INTERNA CLINICO-TRASLAZIONALE

Curriculum di GERONTOLOGIA, FISIOPATOLOGIA DELLA MALATTIE GERIATRICHE E MEDICINA ANTI-AGING (XXXIV CICLO)

# PRELIMINARY RESULTS OF A PHASE I / II STUDY WITH PERIODIC CYCLES OF A LOW-PROTEIN AND ONLY MODERATELY LOW-CALORIE DIET IN PATIENTS WITH COGNITIVE IMPAIRMENT

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## 2. INTRODUCTION

### 2.1 MILD COGNITIVE IMPAIRMENT AND ALZHEIMER DISEASE: EPIDEMIOLOGY, DIAGNOSIS AND CURRENT TREATMENTS

XXI century is characterized by an increase in life's length and life expectancy (*lifespan*) coupled with a continued decline of fertility rates, with the consequent result of a progressive ageing of the world's populations. In 2020, there are an estimated 727 million persons aged 65 years or over worldwide. This number is projected to more than double by 2050, reaching over 1.5 billion persons (1).

In Italy, the oldest country in Europe, the aging of the population is even more evident. As of 1 January 2019, people resident in the country aged 65 and over amounted to 13.8 million (22.8% of the total population) a proportion that has been steadily increasing since the 1960s. This demographic change brings with it several issues we need to face, in particular in the prevention of age-related chronic diseases, in the creation of age-friendly environments and in facilitating the access to age-friendly primary health care

Among age-related diseases, in addition to the most common cardiovascular diseases and various types of cancer, neurodegenerative diseases are frequent, highly disabling (both for patients and their families) and difficult to treat, as there are currently no effective prevention strategies and drugs.

Alzheimer disease (AD) is the main cause of dementia (50-80% of cases) and the 7th leading cause of mortality globally, so it represents actually one of the most lethal, expensive and burdening diseases of this century. In 2018, Alzheimer Disease International (ADI) estimated a dementia prevalence of about 50 million people worldwide, projected to triple in 2050 (2).

Until 2011, the diagnosis of AD was based on the NINCDS-ADRDA Alzheimer's Criteria proposed in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (3). These criteria defined AD as having a single stage, dementia, and based diagnosis solely on clinical symptoms confirmed by neuropsychological testing, so indicating an impairment of several cognitive domains (such as memory, language, attention, etc..) or neurobehavioral symptoms of

enough severity to determine evident functional impact on daily life and loss of independence. These characteristics are the key features that distinguish AD from Mild Cognitive Impairment (MCI).

In 2011, clinical diagnostic criteria for Alzheimer's disease dementia were revised by the National Institutes of Health and the Alzheimer's Association (4). The updated diagnostic guidelines describe three stages of Alzheimer's disease:

- *Preclinical*—Brain changes, including amyloid buildup and other initial neuronal damages, but in absence of significant clinical symptoms.
- *Mild cognitive impairment (MCI) due to AD*—A stage marked by an impairment of one or more cognitive functions, like memory and problem solving, that is greater than expected for the person's age and education, but that do not interfere with his or her independence. People with MCI may or may not progress to Alzheimer's dementia and amnestic MCI (aMCI) is the most common form that evolves to AD. Studies suggest that these individuals tend to progress to probable Alzheimer's disease at a rate of approximately 10% to 15% per year (5).
- *Alzheimer's dementia*—The final stage of the disease with severe clinical symptoms that led to a progressive loss of functional abilities and independence.

Cognitive assessment is most often conducted with well-established tests in use for many years and familiar to clinicians. Noteworthy are the Mini Mental State Examination (MMSE) that evaluates the cognitive state in general (6) and other tests that evaluate several cognitive domains (short-term memory, attention, language, etc...).

The biological diagnosis of AD is made with the use of ATN framework, defined by Jack and colleagues (7), where "A" represents amyloid, "T" is phosphorylated tau, and "N" is neurodegeneration. The three best validated neuroimaging biomarkers for AD are medial temporal lobe atrophy on magnetic resonance imaging (MRI) and posterior cingulate and temporoparietal hypometabolism on 18-fluorodeoxyglucose (18FDG)-PET as measures of neurodegeneration, and cortical amyloid β deposition on amyloid-PET imaging. Amyloid β, phosphorylated tau, and neurodegeneration can also be observed in body fluid biomarkers, in particular in cerebrospinal fluid (amyloid β1–42, amyloid β1–40, phosphorylated tau 181, and total tau) (8) and blood (neurofilament light, a major axonal cytoskeleton protein marker of neurodegeneration) (9).

As seen before, dementia due to AD is only the end result of a long-time presence the end result of a long-time presence of AD pathology characterized by progressive alterations in neurons, microglia, and astroglia, together with neuroinflammation, alteration in vessels and in the glymphatic system (10). AD is continuum, stretching over a period of 15–25 years, in which AD pathology can be present without any symptoms via a stage of mild cognitive impairment leading up to overt dementia, even if not every patient will necessarily follow this path by definition.

The strongest risk factors for AD are advanced age, having a first-degree relative with a history of AD and carrying at least one Apolipoprotein E (APOE) ε4 allele (11). In addition, female sex (especially after the age of 80 years), cardiovascular risk factors such as hypertension and an unhealthy lifestyle have been associated with an increased risk of dementia (10).
It is estimated that 12 modifiable risk factors together account for roughly 40% of the worldwide risk of any type of dementia, and this is of great relevance when thinking about strategies to prevent the development of cognitive decline and dementia.

To date there are two types of medications approved to treat AD: those that can temporarily ease some symptoms, and those that can slow the progression of the disease. Medications tend to be most effective for people with mild to moderate Alzheimer's, even if they don't work for everyone, and they may lose effectiveness over time. The Food and Drug Administration (FDA) has approved Cholinesterase inhibitors and Memantine specifically to treat symptoms of AD, but are not approved for MCI. The efficacy of drugs thus far approved for AD treatment is limited (12,13) and AD still has no cure. More recently, studies on anti-amyloid therapies and antibody-based intervention have been conducted but the results are poor or the rate of side effects is high, thus limiting their use at the highest and most effective doses, therefore there is a huge need for new treatments from which patients can benefit.

## 2.2 NUTRITIONAL STATUS AND LIFESTYLE RECOMMENDATIONS IN DEMENTIA

Aging is characterized by progressive alterations of various organs and systems which can contribute to increasing the risk of anorexia, insufficient oral intake of macro and micronutrients, weight loss and malnutrition. All these aspects are more common in patients suffering from cognitive decline or overt dementia. The mechanisms underlying weight loss and the worsening of nutritional status are complex, multifactorial and not completely understood. In ageing, age-related gradual decrease in smell and taste perception, hormonal changes in gut mediators (for example, cholecystokinin [CCK], glucagon-like peptide 1 [GLP-1]), and altered secretion pattern of ghrelin after nutrient intake, affect satiation and dietary behaviors. Pathological modifications in olfactory system can occur several years before the onset of cognitive decline in AD (primarily in APOEe4 carriers) and some studies suggest that olfactory impairment is a pre-clinical marker for dementia (14,15). Moreover, in AD patients the brain atrophy of specific regions may alter appetite regulation and eating behaviors. Another contributor to anorexia and weight loss is the low-grade inflammation detected in older people (called “inflammaging”) (16) and the neuroinflammation typical of neurodegenerative diseases that causes high levels of circulating proinflammatory cytokines in cerebrospinal fluid and plasma of AD patients also in preclinical stages (17). The association of age-related nutritional deficits with several adverse outcomes has led to the so called "anorexia of aging” (18), a specific geriatric syndrome that can lead to malnutrition if not appropriately diagnosed and treated and a well-known independent predictor of morbidity and mortality both in the community and across clinical settings.

In more advanced stages of AD, other nutritional problems can affect nutritional status: attention deficits during meals; executive function deficits with consequent problems in shopping, storing and preparing food; modifications in dietary habits with reduced variety of diet and unbalanced nutrient intake; behavioral problems (agitation and hyperactivity) that increase energy expenditure; loss of eating skills (dyspraxia); oropharyngeal dysphagia and risk of aspiration (19).

For all these reasons listed above, continuous monitoring of people diagnosed with cognitive decline and overt AD is essential. In clinical practice, geriatric nutritional assessment (when properly done) usually includes nutritional screening with Mini Nutritional Assessment (MNA) or other screening tools, a simple anthropometric assessment (height, weight, BMI, waist circumference), measurement of various biochemical parameters (serum albumin, total proteins, vitamins and trace elements, hemoglobin) and sometimes (not always) body

composition analysis. The inadequate caloric and / or protein intake, the reduction in the intake of specific micronutrients (e.g., vitamin B12 and other B vitamins, iron, selenium) and concomitant digestion / nutrient absorption alterations can all contribute to weigh loss and negative changes in the body composition of patients.
Numerous studies have documented that patients with dementia have reduced body cell mass and muscle mass compared to healthy controls (20,21).

Given the strong connection between the lifestyle, the relationship between the individual and the surrounding environment, the cognitive functions and cognitive reserve (brain's ability to cope with damage and still function adequately) and the risk of cognitive decline and dementia, great attention is paid to maintaining correct eating habits and adequate levels of physical activity, as well as social interactions. In 2019, the World Health Organization (WHO) released the first guidelines for reduction of the risk of cognitive decline and dementia, in which some recommendations were provided: being physically active, not smoking, avoiding harmful use of alcohol, controlling their weight, eating a healthy diet, and maintaining healthy blood pressure, cholesterol and blood sugar levels (22).
Several studies showed that physical activity is able to counteract psychological stress, vascular and metabolic risk factors (like hypertension and high blood glucose); moreover, it is involved in the modulation of amyloid β turnover, inflammation, synthesis and release of neurotrophins, and improvements in cerebral blood flow (23). High levels of physical activity are associated with larger brain volumes and higher levels of brain derived neurotrophic factor (BDNF), one of the most important neurotrophic factors involved in neurogenesis neuronal activity and synaptic communications (24). Thanks to all these positive effects, physical activity can help to maintain functional abilities and cognitive reserve (25).
Similarly, preventive strategies and nutritional interventions seem to be promising approaches to delay neurocognitive decline and reduce the risk of AD and other non-psychiatric co-morbidities. Preclinical and clinical studies have demonstrated that some nutrients can help to reduce oxidative stress and inflammation, maintain vascular health and neuronal membrane integrity (the latter in the case of polyunsaturated fatty acids), upregulate the secretion of neurotrophic factors, participate to neurotransmitter synthesis, and modulate epigenetics mechanisms (26,27). By virtue of the role of cardiovascular risk factors in the onset of AD (28), nutritional approaches targeting insulin resistance, lipid metabolism and oxidative stress have been found to ameliorate the related clinical conditions, such as diabetes, metabolic syndrome, and dyslipidemia and ultimately reduce the risk of AD and vascular dementia (29).

Several nutrients ("neuro-nutrients") play a role in the modulation of those mechanisms that have been identified as pathogenetic in AD, in some cases with a synergistic effect, like omega-3 fatty acids, vitamins and bioactive compounds with antioxidant properties. However, none of these compounds are effective on their own and clinical trials focused on on the supplementation of single nutrients in healthy old people or in patients with initial cognitive decline failed to demonstrate a significant effect in terms of preventing or slowing AD (30-32). Conversely, preventive strategies that focus on dietary patterns rather than on an approach based on individual foods or nutrients seem to provide better results thanks to the synergistic action of several compounds.

To counter the pathophysiological processes underlying the development of AD and at the same time to minimize the negative effects that this neurodegenerative disease potentially has on the nutritional status and therefore on the prognosis of patients, different dietary regimens have been proposed which in their variety and complexity of composition in macro- and micro -nutrients can satisfy all nutritional needs, prevent any nutritional deficiencies and help counteract inflammation, oxidative stress and anabolic resistance typical of aging and AD pathophysiology. The most studied are the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet (33). All of these regimens have in common some characteristics, like the high consumption of fruits and vegetables (in particular in the MIND diet leafy green vegetables and berries), whole grains, legumes, olive oil (the milestone of the Mediterranean diet), nuts, seeds, moderate consumption of fish, low to moderate consumption of dairy products, and low intake of red and processed meats and other sources of saturated fats (34).

As to the above mentioned "dietary pattern approach" with a protective combination of multiple nutrients within a dietary regimen, in recent years scientists researching strategies to prevent cognitive decline and dementia have used a multidomain lifestyle-based intervention to reduce in individuals at risk for dementia. The most relevant study was the Finnish FINGER trial, the first largescale, long-term, randomized controlled trial showing that the combination of a healthy balanced nutrition, physical exercise, cognitive training and social activities, and vascular and metabolic risk management can lead to benefits on cognition, even in people with genetic susceptibility to Alzheimer's disease (35,36).

In the wake of these results, in 2020 more than 25 countries joined the World Wide FINGERS network, which aims to adapt, test, and optimize the FINGER multidomain model in different geographical, cultural, and economic settings, in patients with prodromal Alzheimer's disease.

This type of trial is useful to identify the prevention potential of a multimodal intervention that can be combined with drugs.

## 2.3 NEW EXPERIMENTAL STRATEGIES AGAINST BRAIN AGEING AND NEUROCOGNITIVE DECLINE

As already discussed in the first paragraph, given the aging of the population and the consequent increase in the incidence and prevalence of AD expected in the coming decades, the scientific community looks with great interest at innovative therapies for the prevention and treatment of this condition, including lifestyle interventions and in particular dietary interventions. Alongside the ongoing pharmacological research, in recent years several study groups have been trying to broaden therapeutic horizons in an attempt to identify effective alternative strategies in the treatment of AD. Increasing evidence suggests that different forms of dietary interventions may have protective effects against the ageing process, the oxidative stress and neurodegeneration, all factors involved in brain ageing and in AD pathogenesis, as summarized in Figure 1 (37).

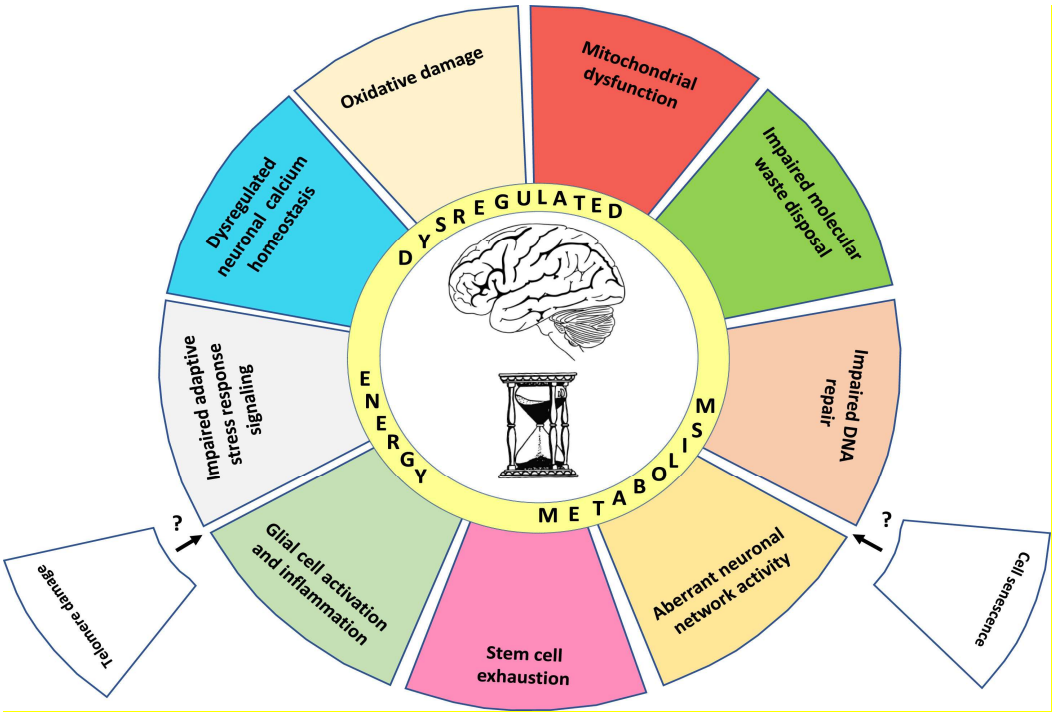


*Figure 1: the nine hallmarks of brain ageing that contribute to determine a dysregulation of the cellular energy metabolism and consequently a reduced cellular stress resistance, repair, and growth. Adapted from Mattson MP et al Cell Metab. 2018.*

Caloric restriction (CR) usually refers to a 20% - 40% reduction of the normal daily calorie intake without malnutrition, while dietary restriction (DR) refers to a dietary regiment which accounts

restriction of one or more macronutrients (proteins, carbs or fats) and with normal or restricted calorie intake (38).

Intermittent fasting (IF) includes daily fasting periods of 12 or more hours, twice weekly fasting (5:2) and alternate day fasting (ADF), along with no restriction on water intake (39).

Given that different fasting regimens have been shown to slow down and partially reverse cellular aging in rodent models (40), a number of studies have investigated their potential application to the prevention and treatment of age-related diseases.

Studies in animal models of AD demonstrated that both CR and ADF led to a reduction in the accumulation of Aβ plaques and decreased Aβ plaque-associated astrocyte activation (41) and slowed the progression of Aβ deposition in the hippocampus and in cerebral cortex (42,43). However, chronic dietary restrictions are associated with both safety and compliance concerns, because are often difficult to maintain over time and are frequently associated with progressive weight loss, body composition modifications and other side effects; this is particularly dangerous in the elderly population and especially in AD subjects that are at high risk of malnutrition and loss of body cell mass and lean body mass with correlated sarcopenia and loss of strength (44,45).

For that purpose, in recent years alternative strategies were developed, and in contrast to the short and very frequent fasting periods of IF, prolonged fasting (PF) and fasting-mimicking diets (FMDs) can be used more easily also in humans, because they last in most cases between 4 and 7 days and are followed by a high-nourishment refeeding period of at least 1 week, so they are well tolerated. Thanks to an intermittent periodic essential amino acid/protein restriction and reduction of simple sugars PF and FMDs are as effective as CR/DR to modulate the most studied nutrient-sensing signaling pathways that regulate ageing (see figure 2) and can be more feasible in humans and for long periods of time (46).

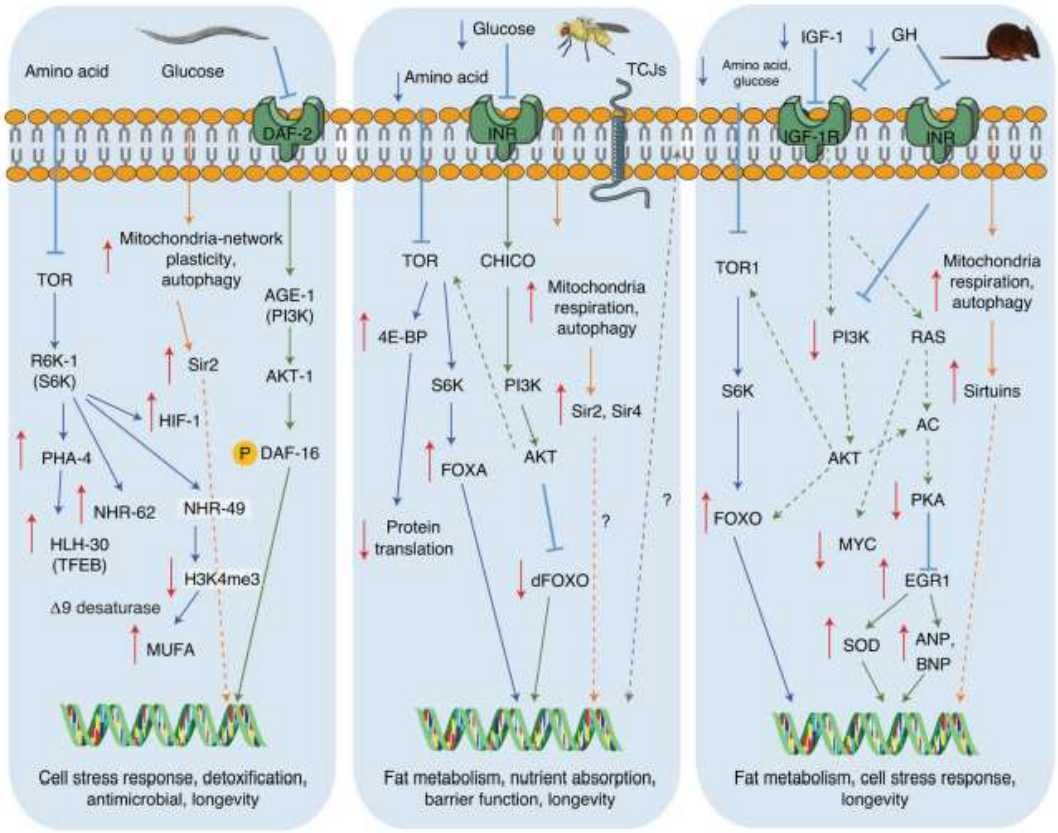


*Figure 2: The nutrient-sensing pathways that regulate longevity and stress-response mechanisms in different model organisms.*

FMDs were developed to reach the same effects of fasting while standardizing dietary composition, providing nourishment and minimizing the burden and side effects associated with water-only fasting (47). The FMD composition, which includes low protein, low sugar and high unsaturated fat, achieves a reduction in IGF-1 and glucose, and an increase in ketone bodies, and IGFBP-1, similar to that caused by water-only fasting, by acting on GH–IGF-1 axis and mTOR–PI3K–AKT-1 and PKA signaling (two of the most studied nutrient-sensing pathways).

In triple transgenic mice a 4-month protein restriction improved behavior performance and reduced phosphorylated tau as compared to ad libitum fed animals and these improvements were accompanied by reduced IGF-1 signaling during the restricted period (48). Moreover, FMD cycles administered to “old” mice (months 16-30) showed a relevant effect in promoting hippocampal neurogenesis which was correlated with a significant improvement in motor coordination and cognitive performance) (49).

Recently another study showed that FMD cycles in E4FAD and 3xTg AD mouse models can reduce hippocampal Aβ load and hyperphosphorylated tau, enhance neurogenesis, reduce microglia cell activation and expression of neuroinflammatory genes, including superoxide-generating NADPH oxidase (Nox2), all markers of AD pathology (50).

FMDs followed by refeeding cycles were applied also in humans to identify effective and safe interventions against aging and age-related diseases, with minimal side effects and risk of malnutrition. In a clinical trial with 100 healthy subjects, 3 monthly cycles of FMD for 5 days decrease insulin-like growth factor 1 (IGF-1), weight and fat mass, and several markers/risk factors of ageing (blood pressure, lipid profile, fasting glucose and C -reactive protein), either caused no loss or an increase in lean body mass and function (51). Recently, two pilot studies conducted by our research group were conducted in oncologic patients, one in female with breast cancer treated with hormone therapy (52) and the other in oncologic patients undergoing active antineoplastic treatment (chemotherapy and/or radiotherapy) (53).

Concerns have been raised regarding a possible detrimental effect on the nutritional status of fasting/modified fasting in cancer patients due to the known increased risk of malnutrition and an impaired immune system in predisposed subjects (54). In our studies, thanks to a careful evaluation and selection of patients upon enrollment, a close follow-up (every 3-4 weeks) with monitoring of anthropometric parameters and body composition accompanied by nutritional counseling performed by expert staff, the FMD was associated with favorable changes in bioimpedance phase angle and in body composition.

Because of the documented effects of FMDs on metabolism (in particular on the insulin and GH/IGF-1 axis), inflammation, and regeneration in the nervous system, we proposed to evaluate the role of a similar dietary regimen with a periodical restriction in the protein intake in ameliorating the clinical trajectory of MCI and AD, starting from a feasibility and safety study to establish whether it is well-tolerated and safe for older individuals.

# 3. MATERIALS AND METHODS

## 3.1 DESIGN, SETTING AND PARTICIPANTS

This was a pilot, double arm, single blind randomized and prospective clinical trial (NCT05480358) assessing feasibility and safety of a 5-day low protein fasting-mimicking diet for 12 months vs a placebo diet in 60 patients affected by MCI or early AD. The design of the study is summarized in Figure 3.

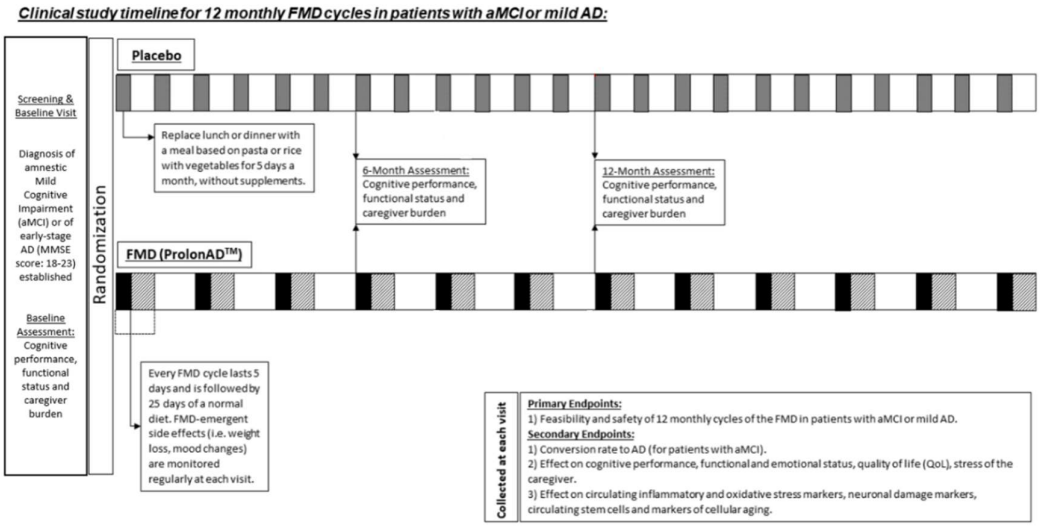


*Figure 3: design of the study.*

The study started in October 2019 in accordance with the Declaration of Helsinki (October 2013) at the IRCCS Ospedale Policlinico San Martino (Genoa, Italy) and at the Ospedale Santa Maria della Misericordia (Perugia, Italy), after protocol approval by the Ethics Committee of the Regione Liguria. The trial was financed by the Italian Ministry of Health in 2018. A subsequent request to change the research plan, accepted by the Ministry of Health in 2021, made it possible to extend the enrollment period and reduce the number of patients enrolled to 40 subjects due to the difficulties related to the COVID-19 pandemic.

All patients enrolled needed to have a diagnosis of MCI or mild AD (even already in therapy with acetylcholinesterase inhibitors) according to the international diagnostic criteria (4, 5 55). Other inclusion criteria were: age 55-80 years, normal organ function (liver and kidney); adequate nutritional status, adherence to informed consent. Exclusion criteria were: age > 80 years, a diagnosis of diabetes mellitus, any organ impairment (liver, kidney), food allergies to the components of the diet, patients on therapy with vitamin K antagonist anticoagulants;

patients at risk of malnutrition or malnourished (Mini-Nutritional Assessment < 24 points), patients who lived alone or were not adequately supported by the family context, other experimental therapies in progress.

The primary study outcome were the feasibility and safety of this type of dietary regimen in old subjects with aMCI or early AD. The feasibility of FMD, which was monitored through interviews (even by telephone when necessary) or through the analysis of patients' 24-hour dietary recall, was define as the assumption of at least one cycle of FMD every two months with the possibility of admitting the consumption of only 50% of the prescribed diet and/or a maximum consumption of 10 Kcal/kg of unplanned food in only one of days 1-5 of each cycle. The safety of the ProlonAD$^{TM}$ was evaluated on the basis of the adverse effects experienced (according to the Common Terminology Criteria for Adverse Events version 5.0) and the consequences on the nutritional status and body composition (specifically in terms of impact on the lean body mass and body cell mass). Adverse events were recorded at each visit and were monitored throughout the duration of the study.

Secondary pre-specified outcomes were:

- The percentage pf conversion rate to AD (in patients with aMCI)
- The episodic memory evaluated with the Free and Cued Selective Reminding Test (FCRST)
- The general cognitive status with Addenbrooke's Cognitive Examination-Revised (ACE-R)
- The functional state assessed with Barthel Index (BI)
- The emotional state assessed with the Center for Epidemiologic Studies Depression Scale Revised (CESD-R)
- The caregiver stress assessed through Caregiver Burden Inventory (CBI)
- The quality of life of patients assessed with Quality of Life AD (QLQ-AD)
- The prevention of Frailty with 40-item Rockwood frailty index (FI)
- The nutritional status assessed with anthropometric measures and body composition analyzed with electric bioimpedance
- The inflammatory markers, oxidative stress markers, neuronal damage markers (Neurofilament Light, NfL), quantification of circulating stem cells, cell aging markers (e.g., evaluation of the telomerase activity of lymphocytes)

3.2 ARMS AND INTERVENTIONS

Subjects enrolled in the intervention arm were subjected to monthly cycles of a medically-designed 5-day dietary regimen called ProlonAD™ diet (provided for free by L-Nutra Inc., Los Angeles, CA, USA), that was a diet low in calories (30% restricted) and proteins (50% restricted), but that provided all the vitamins and minerals needed daily and was also supplemented with both non-essential and essential amino acids and other bioactive compounds identified in animal studies to have neuroprotective, anti-inflammatory and antioxidant properties.

The ProlonAD™ diet consisted of two kits:

- the kit "A" was the same of the Prolon™ diet already in commerce and it supplied approximately 4600 kj (1099 kcal) on Day 1 (11% protein, 46% fat and 43% carbohydrates), approximately 3000 kj (717 kcal) (9% protein, 44% fat and 47% carbohydrates) on Days 2–5 and it consisted of plant-based ingredients all generally recognized as safe (GRAS) according to the FDA and selected for their fasting-mimicking properties. They included vegetable soups (tomato, spinach, mushrooms, pumpkin, etc.), energy bars, snacks (chips of black cabbage, dried / baked vegetable chips, olives, etc.), energy drinks, tea, softgels with algae oil (rich of omega-3 essential fatty acids), dietary supplement pills [Vitamin A (as beta carotene), vitamin C (ascorbic acid), vitamin D (as cholecalciferol), vitamin E (as DL-alpha-tocopherol acetate), vitamin K (as phytonadione), thiamine (as thiamine mononitrate), riboflavin, niacin (as niacinamide), vitamin B6 (as pyridoxine HCl), folic acid, vitamin B12 (as cyanocobalamin), biotin, acid pantothenic (as calcium-D-pantothenate), calcium (as calcium carbonate and calcium phosphate tribasic), iron (as ferrous fumarate), phosphorus (as tribasic calcium phosphate), iodide potassium, magnesium (as magnesium oxide), zinc (zinc oxide), selenium (as selenate sodium), copper (as cupric sulfate), manganese sulfate, chromium (as picolinate chromium), molybdenum (as sodium molybdate)]. It also includes a patented mix consisting of beetroot powder, spinach leaf powder, tomato powder, carrot root powder, cabbage powder (Brassica oleracea), kale leaf powder.
- The kit "S" contained all the supplements (caffeine, nuts, coconut oil, olive oil, algal oil and cocoa) specific to this trial in patients with cognitive decline and provided a substantial increase in daily calories (about 300-500 kcal/day) compared to Prolon™. Patients in the intervention group continued to assume the supplements even in the period between FMD cycles according to the indications provided by the investigators. Patients were advised not to take more than one coffee a day for the entire duration

of the experiment so as not to add the effects to the caffeine contained in the supplement kit. The ingredients that cause or potentially cause side effects (like insomnia and tachycardia) were eliminated and when possible, replaced by other ingredients listed above in order to provide the same number of kcal.

A more detailed composition of the diet and the distribution of meals and supplements during the days of the FMD cycle is described in the Supplementary Material (Appendix A and B).

Between FMD cycles, patients were encouraged to follow a healthy balanced and isocaloric diet as recommended by dietary guidelines in elderly people with dementia (19) (25–30 kcal/kg weight/day and protein intake 1.2 g protein/kg weight/day, mainly derived from fish, legumes, eggs and dairy products), and they were also invited to carry out (if possible) a mild-to-moderate daily physical activity with the aim to minimize the loss of weight and of muscle mass especially in the intervention group.

The placebo diet (the kit "B") assigned to patients in the control arm consisted of replacing lunch or dinner with a meal (of about 600-800 Kcal) based on pasta or rice with vegetables and olive oil for 5 days a month, without supplements.

### 3.4 EVALUATION OF NUTRITIONAL STATUS

The evaluation of nutritional status was carried out by an expert clinical nutritionist at the enrollment and at least every two months. At each visit the following data were collected: anthropometric measures [weight (kg), height (m), body mass index (BMI) in kg/$m^2$], vital signs [blood pressure (mmHg), heart rate (bpm)], and body composition [fat mass (FM), fat-free mass (FFM), body cell mass (BCM), phase angle (PhA), total body water (TBW), extracellular body water (ECW), intracellular body water (ICW)] analyzed with a Single Frequency Bioimpedance Analyzer (BIA 101®, Akern, Florence, Italy) after at least 3 hours of fasting. Bioelectrical impedance measurements were subsequently processed with the Bodygram Plus® software (Akern, Florence, Italy).

In the period following the diet cycle, if there was a worsening of the nutritional status (reduction of body weight> 5% of the basal weight or reduction of the PhA to bioimpedance analysis> 10% of the initial value), the corresponding kit of the diet was not administered, and the patient was re-evaluated after 3 or 4 weeks and eventually supplemented orally with essential amino acids (Aminotrofic®: 5.5 g b.i.d.). Patients who, despite dietary and physical activity recommendations and the aminoacidic supplementation for the periods between

cycles show a progressive or persistent worsening of the nutritional status were excluded from the study.

### 3.5 STATISTICAL ANALYSIS

Data on general patient characteristics are expressed as mean and standard deviation (SD) or frequency as needed. The above data were analyzed with the use of the Wilcoxon-Mann-Whitney test for numerical variables and the Chi-square test for data expressed as frequencies, in order to evaluate whether there were statistically significant differences between the group of treatment and placebo.

To evaluate the variations of the bioimpedance measurements as a function of time, a linear mixed effects model was applied with a random covariate represented by the ID of the subject (package lme4 of R). The bioimpedance measures taken into consideration were FM (Kg and% of body weight), FFM (Kg and% of body weight), BCM (Kg), body weight (Kg), PhA (degrees), TBW (liters) and ICW (liters).

# 4. RESULTS

## 4.1 PATIENT CHARACTERISTICS

From October 2019 to August 2022, 40 patients were enrolled and randomized to the intervention group or the placebo group. The enrollment period was extended by one year due to the COVID-19 pandemic and the obvious difficulties associated with conducting an experimental study in a frail elderly population with a high infectious risk such as the one in our study.

The patients of the two groups, 23 females (57.5%) and 17 males (42.5%), were homogeneous in demographic and clinical characteristics, with a majority percentage of patients affected by aMCI in both groups. Indeed, the neuro-geriatric diagnosis was aMCI in 32 patients (80%) and early AD in 8 patients (20%). At baseline, the average patient age was 72.4 ± 6.2 years, the average BMI at enrollment was 25.8 ± 4.3 kg/m2 (range 18.1–36.9 kg/m2), and median PhA was 4.6 ± 0.8° (range 3.1°−7.9°). All the patients' characteristics are summarized in Table 1.

| | **ProlonAD™ (N=20)** | **Placebo diet (N=20)** | ***p* value** |
|---|---|---|---|
| Age (years) | 72.3 (SD 7.0) | 72.3 (SD 5.6) | 0.94 |
| Male, N (%) | 7 (35%) | 10 (50%) | 0.34 |
| Female, N (%) | 13 (65%) | 10 (50%) | 0.34 |
| aMCI, N (%) | 15 (75%) | 17 (85%) | 0.43 |
| AD, N (%) | 5 (25%) | 3 (15%) | 0.43 |
| BMI ($Kg/m^2$) | 24.8 (SD 4.0) | 26.6 (SD 4.6) | 0.17 |

*Table 1: Patients' characteristics at baseline*

## 4.2 FEASIBILITY

To date, a total of 38 patients (95%) completed at least 1 diet cycle, whereas 2 patients were lost to follow-up in the period between the enrollment and the first re-evaluation ("early drop-out") both in the placebo arm and were so excluded from the statistical analysis. To date, patients in the intervention group completed on average 6.6 ± 4.7 FMD cycles, while in the placebo group 8.2 ± 4.4 cycles.

A total 18 patients (45%) completed the study with the 12 cycles established in the study protocol, of whom 8 patients in the FMD group and 10 patients in the placebo group.

All the patients who underwent at least one FMD cycle (n = 38) fulfilled our feasibility criteria. The low palatability of some of the components of the kits (in particular some soups and snacks) and the feeling of hunger and/or of weakness that was communicated by the patients were the main reported reasons for reducing the percentage of the assumed foods or the consumption of unplanned food, even if always below the criteria set by the protocol for the definition of feasibility. Moreover, diet compliance has been satisfactory also during the periods between diet cycles in FMD group, when patients had to take several supplements during the day.

Figure 4 summarized all the reasons for the drop-out in the two study groups in their respective pie charts.

Seven cases of drop-out were recorded in the FMD arm (17.5 %) after an average of 2.9 (SD 1.2) FMD cycles. These were due to poor acceptance of the FMD components and more generally to the proposed dietary regimen (n=2), personal reasons (n=2), worsening of the nutritional status (n=2) and worsening of the disease-related behavioral disorder (n=1).

On the other hand, in the placebo diet arm, eight cases of drop-out (20 %) after an average of 3.3 (SD 2.8) were also recorded, as a result of worsening of the nutritional status (n=2), poor acceptance of the prescribed diet (n=4) or personal reasons (n=2).

The study is still ongoing with 7 patients (17.5 %) who completed a range of 1-10 cycles, 5 subjects (25%) in the FMD group and 2 subjects (10 %) in the placebo group.

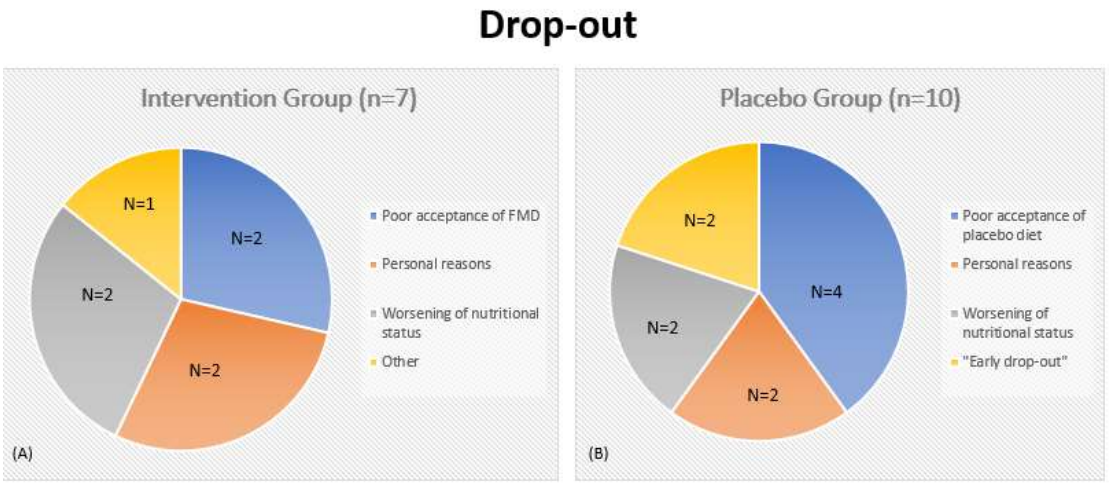


*Figure 4: chart (A) shows the 7 cases of drop-out in the intervention group, while chart (B) shows the 10 cases of drop-out, included the two patients who were lost to follow-up before the first visit after the enrollment (indicated as "early drop-out").*

## 4.3 SAFETY

Overall, patients reported mild and transient adverse events (graded according to Common Terminology Criteria for Adverse Events version 5.0, grading 1-5), and no severe adverse events (grade 3-5) were reported throughout the study. They include:

- In the FMD group: headache [G1-2; n=4 (10%)]; fatigue [G1; n=6 (15%)]; depression [G1; n=3 (7.5%)]; autoimmune reaction [G2; n=1 (2,5%); transient worsening of a pre-existing pemphigus]; vomiting [G1; n=1 (2.5%)], abdominal pain [G1; n=2 (5%)], insomnia [G1; n=1 (2.5%)] hypotension [G2; n=1(2.5%)], irritability [G2; n=1 (2.5%)], tingling [G1; n=1 (2.5%)].
- In the placebo group: fatigue [G1; n=1 (2.5%)]; depression [G1; n=1 (2.5%)];

## 4.4 NUTRITIONAL STATUS AND BODY COMPOSITION

The patients' nutritional status and body composition were evaluated at least every two months, even if the monitoring was closer (once a month) especially for the first two or three cycles, in order to detect as early as possible any worsening of nutritional status or the occurrence of adverse events related to the proposed dietary regimen.

Patients in the treatment group reported an average weight loss of 0.5-2 kg between before and after each FMD cycle, which was normally re-gained during the in between period with the normal diet and the caloric support of the supplementations.

Two patients (5%) in the FMD group and two patients (5%) in the placebo group showed a significant reduction in body weight (on average 3-4 kg) compared to the basal body weight, associated to negative modifications of the body composition (decrease of PhA, BCM, FFM). In all of these cases an intercurrent disease could be identified as the cause of a period of bed rest, weight reduction and the worsening of general clinical conditions. In the FMD arm, patient #21 was hospitalized for a pneumonia, while patient #33 had a viral gastroenteritis. In the placebo arm, patient #2 was hospitalized for a minor ischemic stroke, and patient #3 underwent orthopedic surgery for a hip fracture.

Data regarding weight and body composition (evaluated with serial bioimpedance analysis) in patients re-evaluated at least one time after the first diet cycle (n=38, 95%) were collected and their trend over time (first 6 months of the study) is summarized in figures 5 and 6.

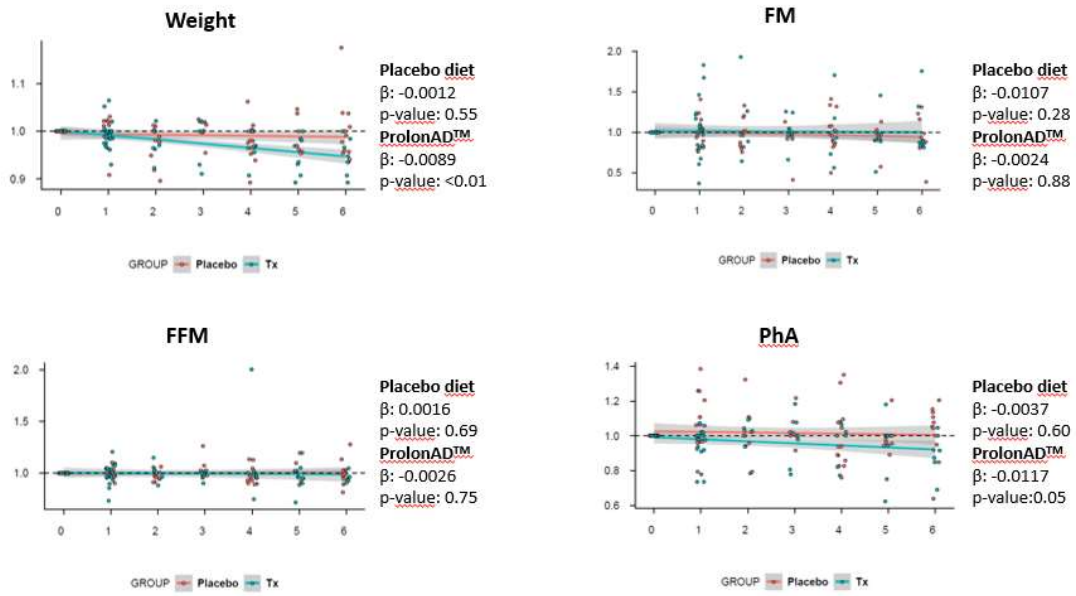


*Figure 5: Body weight, phase angle, fat-free mass, fat mass variations during the first 6 months of the study (data normalized at baseline).*

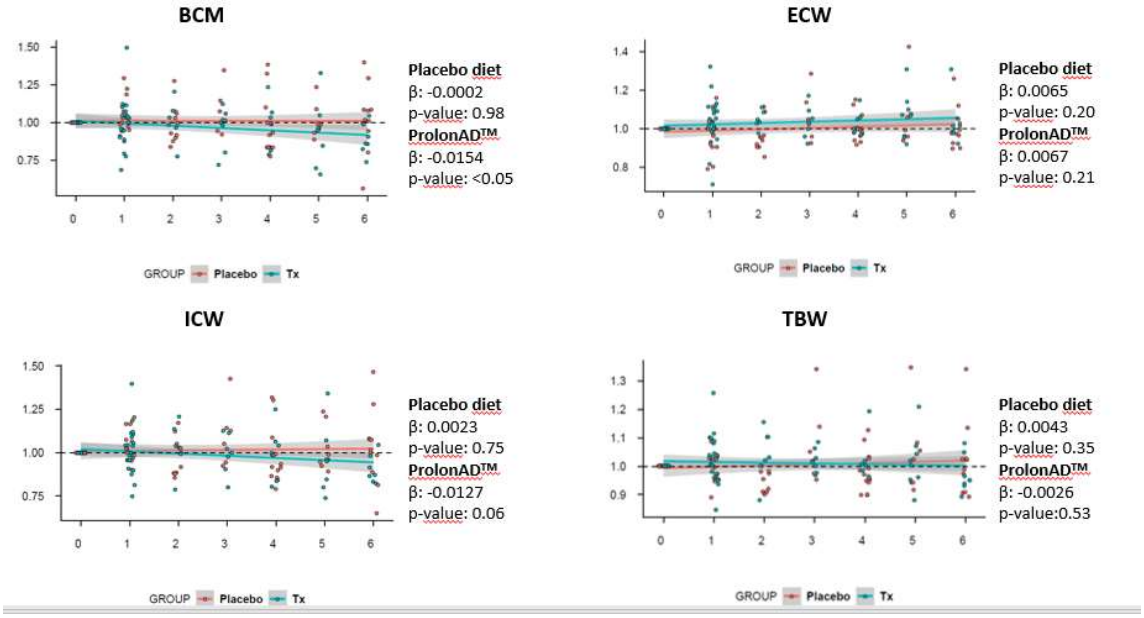


*Figure 6: Body cell mass (BCM), total body water (TBW), extra-cellular water (ECW) and Intra-cellular water (ICW) variations during the first 6 months of the study (data normalized at baseline).*

As shown by the graphs of Figures 5 and 6, there are no statistically significant differences between the treatment group and placebo group with regard to the trend of all the parameters of the body composition with the exception of the body cell mass (BCM), which is reduced in

the treatment group. The other aspect that sees statistical significance is represented by the weight always in the treatment group, with a reduction over time of the latter from baseline (β: -0.0089, p-value: <0.01), compared to the control group.

However, by carrying out an analysis of all the variables in the two groups adjusted for sex (male) and number of visits and calculating the odds ratio (OR), none of the variables analyzed, including body weight, showed a statistically significant difference in relation to the group (treatment or placebo). See Table 2 for the summary of the results of the aforementioned analysis.

| **Variable** | **VISIT (OR)** | **VISIT (p-value)** | **GROUP (OR)** | **GROUP (p-value)** | **SEX (OR)** | **SEX (p-value)** |
|---|---|---|---|---|---|---|
| ICW | 0,86 | <0,05 | 1,08 | 0,92 | 2,26E-03 | <0,01 |
| BCM | 0,78 | <0,05 | 1,38 | 0,77 | 7,46E-04 | <0,01 |
| TBW | 0,91 | 0,26 | 0,84 | 0,88 | 5,87E-06 | <0,01 |
| ECW | 1,06 | 0,32 | 0,65 | 0,58 | 2,20E-03 | <0,01 |
| FM | 0,86 | 0,13 | 2,62 | 0,70 | ND | <0,01 |
| FFM | 0,83 | 0,23 | 0,21 | 0,30 | 1,43E-07 | <0,01 |
| Weight | 0,76 | <0,01 | 2,15 | 0,35 | 3,36E-02 | 0.30 |
| PhA | 0,96 | <0,05 | 1,07 | 0,74 | 7,73E-01 | 0.23 |

*Table 2: OR analysis based on number of visits, group (treatment) and sex (male).*

## 5. DISCUSSION

In this phase I/II trial we showed that periodic cycles of a FMD low in proteins and sugars but only partially reduced in calories is feasible and safe in patients aged 55 to 80 with cognitive impairment (aMCI or early AD) and a good nutritional status at baseline.

The trial is still ongoing with 5 patients in the treatment group (25 % of patients in this group) and 2 patients in the placebo group, so these data are only partial, especially regarding the tolerability of the FMD diet and its effects on the nutritional status over a year of treatment.

Overall, the adherence to the proposed diet was good despite the delay of visits every two months and not every month as initially planned, this to reduce the risk of Sars-Cov-2 infection and to simplify access to the hospital especially during the most complicated period of the pandemic. The nutritionist dedicated to the study, who carried out nutritional counseling at each visit and periodic telephone interviews between one visit and another to evaluate the effective progress of the planned diet cycles and identify any critical issues, was a valuable tool for maximizing the adherence to treatment and early detection of adverse events.

To date, the number of drop-outs is quite high (17 patients, 42.5%) but it can be overlapped in the two groups both in terms of absolute numbers (7 patients in the treatment group and 8 patients in the placebo group) and for the underlying reasons. The rate of drop-out is in line with other clinical trials based on a nutritional intervention applied in the context of cognitive problems, where the number of dropouts is frequently high (56), but it was higher than the rate of drop-out in clinical trials with a FMDs applied to healthy adults (51) or in other clinical conditions (52,53).

One of the main causes of drop-out was the poor tolerance to the proposed diet, even if the number of drop-out was higher in the placebo group, where only one replacement meal was offered for 5 days a month. Patients in the Intervention Group complained of poor palatability of some of the foods provided with the kit or of some supplements. Note that average age of patients enrolled in the study was high (on average 72 years), so it must be taken into account that the reduction in appetite, alterations in taste, difficulties in chewing or simply the difficulty of modifying their own eating behaviors and habits may have contributed to the choice to leave the study. In planning future studies on a similar population, it will be useful to take advantage of this experience and develop a diet consisting of products with better palatability and consistency. Moreover, the underlying pathology of the patients enrolled must be taken into consideration, with the consequent behavioral problems associated with it that make

adherence to a prolonged experimental treatment more difficult. In this context, the role of the caregiver and of family and social support is fundamental to guarantee the continuity of the proposed treatments. Finally, it should be noted that several patients were enrolled just before the COVID-19 pandemic. This has consequently led to several problems in the management of the clinical trial and is partly responsible for the dropouts of the first patients enrolled.

Patients did not experience serious adverse events (grade 3 to 5), confirming the general safety of this nutritional approach in this population. The more frequent side effects were asthenia, headache, thymic tone deflection and gastro-intestinal symptoms, as already shown in other FMD studies (52,53). The rates of headache (10% of patients in the FMD group) and asthenia (15% of patients in the FMD group) seemed to be lower than in previous studies, and this difference could be explained by the fact that the diet in the trials with cancer patients was similar to ProlonAD$^{TM}$ but more restricted in calories (1100 Kcal on the first day and 800 Kcal from Day 2 to Day 5 of the cycle in the absence of supplements). For the same reason, patients in the treatment group reported a smaller weight reduction (0.5-2 kg vs 2-2.5 kg) at the end of each FMD cycle, weight that was recovered during the refeeding period in which the supplements (about 300-350 Kcal) required by the study were added to the normal diet.

When taking into account all the adverse events documented during the study, the percentage of patients who developed adverse events was slightly higher (60%). This is probably due to the older age of the patients enrolled in this clinical study. In fact, we know that among the various factors that correlate with the risk of developing adverse events there is also age, which is one of the most relevant (57). Anyway, this aspect does not affect the safety of this nutritional approach in these patients, given that only mild adverse events have occurred, mainly during the first treatment cycles, with a tendency to reduce in frequency throughout the study.

In relation to the nutritional data, the serial assessment of nutritional parameters showed that there are no statistically significant differences over time in all the individual variables considered with the exception of the body weight and BCM. However, by analyzing the ORs attributable to the number of visits (consequently to the follow-up time) and to sex (with male sex as a reference), belonging to the intervention group or to the placebo group loses significance. This is probably attributable to a possible sex-related effect in time of the patients who dropped out of the study in the two groups.

## 6. CONCLUSIONS

ProlonAD$^{TM}$ has a good safety profile in patients with aMCI or mild AD, with a number of patients who deteriorate from a nutritional point of view and drop out of the study substantially comparable to the group subjected to the placebo diet.

Patients undergoing ProlonAD$^{TM}$ develop adverse events, albeit relatively frequent, that were mild and transient.

The study, although designed on the basis of previous experiences in patients with other clinical conditions, is presented as an absolute novelty as it applies a dietary protocol with reduced protein content and only moderately hypocaloric that mimics the effects of fasting in the neuro-geriatric patient.

In the near future it will be interesting to analyze both neuropsychological and bio-humoral data to evaluate the effects of ProlonAD$^{TM}$ on cognitive functions, energy metabolism, oxidative stress and markers of neurodegeneration.

These data will have to be confirmed at the end of the study and with further randomized and controlled phase III clinical trials.

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8.SUPPLEMENTARY MATERIAL

Appendix A

*FMD cycle with ProlonAD$^{TM}$: (a) daily distribution of the components Kit "A" from Day 1 to Day 5 of the FMD cycle and (b) nutritional tables of the various foods contained in the kit. (c) supplements provided with kit "S" and (d) their distribution during the weeks (supplements need to be consumed both during the FMD cycle and in the refeeding period)*

*(a)*

| | GIORNO 1 | GIORNO 2 | GIORNO 3 | GIORNO 4 | GIORNO 5 |
|---|---|---|---|---|---|
| COLAZIONE | L-Bar con noci<br>Tisana<br>Olio di alga (2) | L-Bar con noci<br>Tisana | L-Bar con noci<br>Tisana | L-Bar con noci<br>Tisana | L-Bar con noci<br>Tisana<br>Olio di alga (1) |
| PRANZO | Zuppa di Zucca violina<br>NR-3 (2)<br>Cracker<br>Olive | Zuppa di fagioli bianchi e spinaci<br>NR-3 (1)<br>Cracker | Zuppa di Zucca violina<br>NR-3 (1)<br>Cracker | Zuppa di Pomodoro<br>NR-3 (1)<br>Olive | Zuppa di fagioli bianchi e spinaci<br>NR-3 (1)<br>Cracker |
| POMERIGGIO | Tisana<br>L-Bar con noci | Tisana<br>Olive | Tisana | Tisana<br>Olive | Tisana |
| CENA | Zuppa di fagioli neri<br>L-Bar Barretta al cioccolato | Zuppa di Zucca violina e Quinoa<br>L-Bar Barretta al cioccolato | Minestrone Zuppa | Zuppa di fagioli neri<br>L-Bar Barretta al cioccolato | Zuppa di Zucca violina e Quinoa |
| | | L-Drink | L-Drink | L-Drink | L-Drink |

*Day 1 provides 1100 Kcal while Days 2-5 provide about 800 Kcal, to which add about 300-360 kcal provided by the supplements.*

## ZUPPA DI POMODORO

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 33 g | %CR* porzione 33 g |
| ENERGIA | 1378 KJ 328 Kcal | 455 KJ 108 Kcal | 5 % |
| GRASSI di cui: saturi | 6,0 g 0,9 g | 2,0 g 0,3 g | 3 % 1 % |
| CARBOIDRATI di cui: zuccheri | 50 g 11 g | 17 g 3,7 g | 7 % 4 % |
| FIBRE | 20 g | 4,0 g | |
| PROTEINE | 7,8 g | 2,6 g | 5 % |
| SALE | 5,7 g | 1,9 g | 31 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** FARINA DI RISO, POMODORI*, INULINA, CIPOLLA*, SALE MARINO, OLIO D'OLIVA* (OLIO D'OLIVA, FECOLA DI PATATE, ESTRATTO DI ROSMARINO), RISO INTEGRALE, ESTRATTO DI LIEVITO, BASILICO*, PREZZEMOLO*.

*ESSICCATI

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 33g e

## ZUPPA DI VERDURE

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 33 g | %CR* porzione 33 g |
| ENERGIA | 1398 KJ 332 Kcal | 461 KJ 110 Kcal | 5% |
| GRASSI di cui: saturi | 4,9 g 0,8 g | 1,6 g 0,3 g | 2% 1% |
| CARBOIDRATI di cui: zuccheri | 56 g 8,7 g | 18 g 2,9 g | 7% 3% |
| FIBRE | 17 g | 5,5 g | |
| PROTEINE | 7,9 g | 2,6 g | 5% |
| SALE | 4,6 g | 1,5 g | 25% |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** FARINA DI RISO, INULINA, CIPOLLA*, POMODORO*, CAROTE*, RISO INTEGRALE, SALE MARINO, OLIO D'OLIVA (OLIO D'OLIVA, FECOLA DI PATATE, ESTRATTO DI ROSMARINO), PEPERONE ROSSO*, PORRO*, ESTRATTO DI LIEVITO, SPINACI*, BASILICO*, PREZZEMOLO*.

*ESSICCATI

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 33g e

## ZUPPA DI FUNGHI CHAMPIGNON

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 33 g | %CR* porzione 33 g |
| ENERGIA | 1440 KJ 342 Kcal | 475 KJ 113 Kcal | 6 % |
| GRASSI di cui: saturi | 3,1 g 0,8 g | 1,7 g 0,3 g | 2 % 1 % |
| CARBOIDRATI di cui: zuccheri | 59 g 5,3 g | 20 g 1,7 g | 8 % 2 % |
| FIBRE | 11 g | 2,1 g | |
| PROTEINE | 9,0 g | 3 g | 6 % |
| SALE | 6,3 g | 2,1 g | 35 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** FARINA DI RISO, RISO INTEGRALE, FUNGHI CHAMPIGNON IN PEZZI E POLVERE (AGARICUS BISPORUS), CAROTE*, CIPOLLA*, INULINA, SALE MARINO, OLIO D'OLIVA (OLIO D'OLIVA, FECOLA DI PATATE, ESTRATTO DI ROSMARINO), ESTRATTO DI LIEVITO, PREZZEMOLO*.

*ESSICCATI

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 33g e

**ISTRUZIONI PER LA PREPARAZIONE DI ZUPPA DI POMODORO, ZUPPA DI VERDURE, ZUPPA DI FUNGHI CHAMPIGNON:**
Aprire la confezione e aggiungere 250 ml di acqua fredda al contenuto (33 gr). Mescolare e aggiustare il volume di acqua a piacimento. **Fornello:** scaldare a fuoco medio in un pentolino/tegame, mescolando di tanto intanto. Portare a ebollizione per 2 minuti e poi rimuovere dal calore. **Microonde:** a potenza massima per circa 2 minuti. Lasciate riposare per un minuto. Mescolare bene e rimettere nel forno a microonde per un altro minuto. Mescolare di nuovo prima di servire.

## CRACKERS AL CAVOLO RICCIO

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 33 g | %CR* porzione 33 g |
| ENERGIA | 2249 KJ 542 Kcal | 742 KJ 179 Kcal | 9 % |
| GRASSI di cui: saturi | 39 g 4,0 g | 13 g 1,3 g | 19 % 7 % |
| CARBOIDRATI di cui: zuccheri | 26 g 3,6 g | 8,5 g 1,2 g | 3 % 1 % |
| FIBRE | 11 g | 3,8 g | |
| PROTEINE | 16 g | 5,2 g | 10 % |
| SALE | 1,4 g | 0,5 g | 8 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI: MANDORLE,** SEMI DI **SESAMO,** FARINA DI TAPIOCA, SEMI DI CHIA, SEMI DI LINO, OLIO DI SEMI DI GIRASOLE, CAVOLO RICCIO, SALE MARINO, ZUCCHERO DI COCCO, ACETO DI COCCO, CIPOLLA IN POLVERE, PEPERONCINO, SEMI DI CUMINO, PEPE NERO, ANTIOSSIDANTE: ESTRATTO RICCO DI TOCOFEROLO, AGLIO, ORIGANO, ACIDIFICANTE: ACIDO CITRICO.

**CONSIGLI SULL'ALLERGIA:** Per gli allergeni, vedi gli ingredienti in **grassetto.**

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 33g e

## L-BAR
BARRETTA AL CIOCCOLATO

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 23 g | %CR* porzione 23 g |
| ENERGIA | 1693 KJ 407 Kcal | 389 KJ 94 Kcal | 5 % |
| GRASSI di cui: saturi | 20 g 3,2 g | 4,6 g 0,7 g | 7 % 4 % |
| CARBOIDRATI di cui: zuccheri | 35 g 14 g | 8,1 g 3,2 g | 3 % 4 % |
| FIBRE | 23 g | 5,2 g | |
| PROTEINE | 9,7 g | 2,2 g | 4 % |
| SALE | 0,24 g | 0,06 g | 1 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** INULINA, BURRO DI **MANDORLE,** RISO INTEGRALE, POLVERE DI CACAO NATURALE, **MANDORLE** TRITATE, GOCCE DI CIOCCOLATO (ZUCCHERO DI CANNA, MASSA DI CACAO, BURRO DI CACAO), FIOCCHI D'**AVENA,** SCIROPPO DI RISO INTEGRALE, OLIO DI SEMI DI LINO, DESTRINA DI RISO, SUCCO D'UVA, SALE

**CONSIGLI SULL'ALLERGIA:** Per gli allergeni, vedi gli ingredienti in **grassetto.**

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO USA

Peso Netto 23g e

## L-BAR
BARRETTA ALLE NOCI

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 46 g | %CR* porzione 46 g |
| ENERGIA | 2377 KJ 575 Kcal | 1094 KJ 264 Kcal | 13 % |
| GRASSI di cui: saturi | 48 g 9,1 g | 22 g 4,2 g | 32 % 21 % |
| CARBOIDRATI di cui: zuccheri | 19 g 19 g | 8,9 g 8,9 g | 3 % 10 % |
| FIBRE | 11 g | 5,3 g | |
| PROTEINE | 10 g | 4,8 g | 10 % |
| SALE | 0,38 g | 0,18 g | 3 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI: NOCI DI MACADAMIA,** MIELE, **NOCI DI PECAN, MANDORLE** TRITATE, BURRO DI **MANDORLE,** NOCE DI COCCO ESSICCATA, INULINA, SEMI DI LINO, OLIO DI COCCO, FARINA DI COCCO, SALE MARINO, AROMA NATURALE, ANTIOSSIDANTE: ESTRATTO RICCO DI TOCOFEROLO, ACIDIFICANTE: ACIDO CITRICO, ANTIOSSIDANTE: ACIDO ASCORBICO.

**CONSIGLI SULL'ALLERGIA:** Per gli allergeni, vedi gli ingredienti in **grassetto.**

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO USA

Peso Netto 46g e

## MINESTRONE

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 35 g | %CR* porzione 35 g |
| ENERGIA | 1433 KJ 341 Kcal | 501 KJ 119 Kcal | 6 % |
| GRASSI di cui: saturi | 5,9 g 0,9 g | 2,1 g 0,3 g | 3 % 1 % |
| CARBOIDRATI di cui: zuccheri | 54 g 9 g | 19 g 3 g | 7 % 3 % |
| FIBRE | 14 g | 5 g | |
| PROTEINE | 11 g | 3,7 g | 7 % |
| SALE | 5,2 g | 1,8 g | 30 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** FIOCCHI DI PATATE, FARINA DI RISO, FAGIOLI BIANCHI, PISELLI*, CAROTE*, INULINA, SALE MARINO, CIPOLLA*, PORRI*, CAVOLO*, OLIO DI OLIVA* (OLIO DI OLIVA, FECOLA DI PATATE, ESTRATTO DI ROSMARINO), POMODORO*, **SEDANO***, ESTRATTO DI LIEVITO, SPINACI*, PREZZEMOLO*, CURCUMA.

*ESSICCATI

**CONSIGLI SULL'ALLERGIA:** Per gli allergeni, vedi gli ingredienti in **grassetto.**

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 35g e

## MINESTRONE DI QUINOA

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 33 g | %CR* porzione 33 g |
| ENERGIA | 1393 KJ 330 Kcal | 488 KJ 116 Kcal | 6 % |
| GRASSI di cui: saturi | 3,5 g 0,5 g | 1,2 g 0,2 g | 2 % 1 % |
| CARBOIDRATI di cui: zuccheri | 56 g 12 g | 19,4 g 4,1 g | 7 % 5 % |
| FIBRE | 13 g | 4,7 g | |
| PROTEINE | 12 g | 4,4 g | 9 % |
| SALE | 3,0 g | 1,1 g | 18 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** QUINOA, FARINA DI RISO, FIOCCHI DI PATATE, PISELLI, VERZA*, CAROTE*, CIPOLLA* ZUCCHINE*, POMODORO*, INULINA, **SEDANO***, SALE MARINO, AGLIO*, BASILICO*, PORRI*, OLIO D'OLIVA (OLIO D'OLIVA, FECOLA DI PATATE, ESTRATTO DI ROSMARINO), ESTRATTO DI LIEVITO, BROCCOLI*, SPINACI*, SEMI DI **SEDANO***, CURCUMA.

*ESSICCATI

**CONSIGLI SULL'ALLERGIA:** Per gli allergeni, vedi gli ingredienti in **grassetto.**

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 33g e

**ISTRUZIONI PER LA PREPARAZIONE DI MINESTRONE, MINESTRONE DI QUINOA:**
**FORNELLO:** aprire la confezione e versare il contenuto in una padella. Aggiungere 300 ml di acqua fredda, mescolare e portare a bollore a fuoco moderato. Ridurre il calore a fuoco basso e lasciar bollire per 15 minuti. Lasciar riposare lontano dal fornello per 1 minuto prima di servire. **NON USARE IL FORNO A MICROONDE.**

## L-DRINK
GUSTO ARANCIA

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 ml | porzione: per 17 ml | %CR* porzione 17 ml |
| ENERGIA | 500 KJ 118 Kcal | 85 KJ 20 Kcal | 1 % |
| GRASSI | 0 g | 0 g | 0 % |
| CARBOIDRATI | 29 g | 5 g | 2 % |
| FIBRE | 0 g | 0 g | 0 % |
| PROTEINE | 0 g | 0 g | 0 % |
| SALE | 0 g | 0 g | 0 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** ACQUA, GLICERINA VEGETALE, AROMA. CONSERVANTE: SORBATO DI POTASSIO.

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 120ml e

## L-DRINK
GUSTO LIMONE

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 ml | porzione: per 17 ml | %CR* porzione 17 ml |
| ENERGIA | 500 KJ 118 Kcal | 85 KJ 20 Kcal | 1 % |
| GRASSI | 0 g | 0 g | 0 % |
| CARBOIDRATI | 29 g | 5 g | 2 % |
| FIBRE | 0 g | 0 g | 0 % |
| PROTEINE | 0 g | 0 g | 0 % |
| SALE | 0 g | 0 g | 0 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** ACQUA, GLICERINA VEGETALE, AROMA. CONSERVANTE: SORBATO DI POTASSIO.

CONSERVAZIONE: Conservare in luogo fresco e asciutto.
PRODOTTO ITALIANO

Peso Netto 120ml e

**ISTRUZIONI PER LA PREPARAZIONE DI L-DRINK:**
1) Usando come riferimento la scala graduata sul lato etichetta, versare il contenuto dell'L-Drink nella bottiglia da 950ml in dotazione finchè il livello del liquido restante non corrisponda al proprio peso. Gettare via il liquido restante.
2) Aggiungere 950ml di acqua alla bottiglia in dotazione e mescolare delicatamente.
3) Consumare la bevanda da 950ml durante il corso della giornata.

## OLIVE
VERDI AL SALE

| INFORMAZIONI NUTRIZIONALI | | | |
|---|---|---|---|
| VALORI TIPICI | 100 g | porzione: per 20 g | %CR* porzione 20 g |
| ENERGIA | 703 KJ 170 Kcal | 140 KJ 34 Kcal | 2 % |
| GRASSI di cui: saturi | 17 g 3,2 g | 3,3 g 0,6 g | 5 % 3 % |
| CARBOIDRATI di cui: zuccheri | 1,8 g 0,2 g | 0,4 g 0 g | 0 % 0 % |
| FIBRE | 2,7 g | 0,5 g | |
| PROTEINE | 2,1 g | 0,4 g | 1 % |
| SALE | 2,0 g | 0,4 g | 6 % |

*Consumi di riferimento di un adulto medio (8.400 kJ / 2.000 kcal).

**INGREDIENTI:** OLIVE, OLIO D'OLIVA, SALE MARINO, REGOLATORE DI ACIDITÁ: ACIDO LATTICO.

Può contenere noccioli o frammenti di noccioli

CONSERVAZIONE: Conservare in luogo fresco e asciutto. Dopo l'apertura conservare in frigo.

PRODOTTO ITALIANO

Peso Netto 20g e

(b)

# NR-3

## INTEGRATORE ALIMENTARE MULTIVITAMINICO E MINERALI

**INFORMAZIONI NUTRIZIONALI**

PORZIONE: 2 CAPSULE

| | per 2 capsule | % VNR* |
|---|---|---|
| L-Cistina | 159,6 mg | ** |
| L-Metionina | 38,6 mg | ** |
| Vitamina C | 38 mg | 48 % |
| Niacina | 12 mg | 75 % |
| MSM (metilsulfonilmetano) | 12 mg | ** |
| Zinco | 11 mg | 110 % |
| Vitamina E | 6,6 mg | 55 % |
| Acido pantotenico | 4 mg | 67 % |
| Vitamina B6 | 1,4 mg | 100 % |
| Vitamina B2 | 1 mg | 71 % |
| Rame | 1 mg | 100 % |
| Vitamina B1 | 0,92 mg | 84 % |
| Vitamina A | 400 µg RE | 50 % |
| Biotina | 100 µg | 200 % |
| Acido folico | 67 µg | 34 % |
| Selenio | 56 µg | 102 % |
| Vitamina B12 | 1,2 µg | 48 % |

*VALORI NUTRITIVI DI RIFERIMENTO
**VNR NON DETERMINATI.

**INGREDIENTI:** ANTIAGGLOMERANTI: AMIDO PREGELATINIZZATO, CALCIO CARBONATO, SILICE PRECIPITATA IDRATA, MAGNESIO STEARATO. INVOLUCRO: IDROSSIPROPIL METILCELLULOSA, GOMMA GELLANO. L-CISTINA, L-METIONINA, ACIDO ASCORBICO, NIACINA, MSM (METILSULFONILMETANO), ZINCO GLUCONATO, DL-ALFA-TOCOFEROLO, ACIDO PANTOTENICO, PIRIDOSSINA CLORIDRATO, RIBOFLAVINA, RAME GLUCONATO, TIAMINA CLORIDRATO, BETA-CAROTENE, BIOTINA, ACIDO FOLICO, SELENIO-METIONINA, CIANOCOBALAMINA.

**ISTRUZIONI:** assumere due capsule al giorno durante i pasti.

**CONSERVAZIONE:** Conservare in luogo fresco e asciutto a temperatura inferiore di 25°C, al riparo dalla luce diretta del sole

PRODOTTO IN ITALIA

2 CAPSULE da 500 mg

**AVVERTENZE:** Non superare la dose quotidiana raccomandata. Gli integratori non vanno intesi come sostituti di una dieta variata. Tenere fuori dalla portata dei bambini.

# OLIO DI ALGAE

## INTEGRATORE ALIMENTARE DHA 200mg

**INFORMAZIONI NUTRIZIONALI**

PORZIONE: 1 CAPSULA GEL

| | per capsula gel |
|---|---|
| Olio di Algae fonte di DHA (acido Docosaesaenoico) | 500 mg 200 mg |

**INGREDIENTI:** OLIO DI SCHIZOCHITRIUM ALGAE, GELATINA BOVINA, OLIO DI SEMI DI GIRASOLE, GLICERINA, ACQUA PURIFICATA, MENO DEL 2% DI: TOCOFEROLI (ANTIOSSIDANTE), ESTRATTO DI ROSMARINO (ANTIOSSIDANTE), LECITINA DI **SOIA** (EMULSIONANTE), PALMITATO DI ASCORBILE (ANTIOSSIDANTE).

**CONSIGLI SULL'ALLERGIA:** Per gli allergeni, vedi gli ingredienti in **grassetto**.

**ISTRUZIONI PER L'USO:** Assumere una capsula gel per porzione, insieme al cibo.

**CONSERVAZIONE:** Conservare in luogo fresco e asciutto a temperatura inferiore di 25°C, al riparo dalla luce diretta del sole

PRODOTTO NEGLI USA

1 CAPSULA GEL da 949 mg

**AVVERTENZE:** Non superare la dose quotidiana raccomandata. Gli integratori non vanno intesi come sostituti di una dieta variata. Tenere fuori dalla portata dei bambini.

# TISANA ALLA MENTA

**INGREDIENTI:** FOGLIE DI MENTA BIOLOGICA *(non EU)*.

**PREPARAZIONE:** Mettere 1 bustina di tè in una tazza. Aggiungere acqua bollente e lasciare in infusione per 5-7 minuti.

**COME GUSTARE L-DRINK:** Seguire le istruzioni per preparare L-DRINK. Aggiungere la bustina di tè al mix nella bottiglia. Lasciare il tè in infusione per tutto il tempo che si desidera.

**CONSERVAZIONE:** Conservare in luogo fresco e asciutto.

PRODOTTO IN USA CON INGREDIENTI PROVENIENTI DALL'EGITTO.

Peso Netto 1,4g e

# TISANA ALL'IBISCO

**INGREDIENTI:** FIORI DI IBISCO BIOLOGICO *(non EU)*.

**PREPARAZIONE:** Mettere 1 bustina di tè in una tazza. Aggiungere acqua bollente e lasciare in infusione per 5-7 minuti.

**COME GUSTARE L-DRINK:** Seguire le istruzioni per preparare L-DRINK. Aggiungere la bustina di tè al mix nella bottiglia. Lasciare il tè in infusione per tutto il tempo che si desidera.

**CONSERVAZIONE:** Conservare in luogo fresco e asciutto.

PRODOTTO IN USA CON INGREDIENTI PROVENIENTI DALL'EGITTO.

Peso Netto 1,4g e

# TISANA MENTA LIMONE

**INGREDIENTI:** FOGLIE DI MENTA BIOLOGICA *(non EU)*, SCORZA DI LIMONE BIOLOGICO, CITRONELLA BIOLOGICA.

**PREPARAZIONE:** Mettere 1 bustina di tè in una tazza. Aggiungere acqua bollente e lasciare in infusione per 5-7 minuti.

**COME GUSTARE L-DRINK:** Seguire le istruzioni per preparare L-DRINK. Aggiungere la bustina di tè al mix nella bottiglia. Lasciare il tè in infusione per tutto il tempo che si desidera.

**CONSERVAZIONE:** Conservare in luogo fresco e asciutto.

PRODOTTO IN USA CON INGREDIENTI PROVENIENTI DALL'EGITTO E DALL'AUSTRALIA.

Peso Netto 1,4g e

(c)

*CAFFEINE FOOD SUPPLEMENT*

INGREDIENTS: Caffeine (25 mg); OTHER INGREDIENTS: Excipient for capsules Nolat. Directions: Three after breakfast and two after lunch, preferably within 2 pm. 110 X 0,26 g CAPSULES NET WT 29 g

*RAW DARK CHOCOLATE 85%*

INGREDIENTS: raw cacao mass*, coconut sugar* (15%), raw cacao butter*. *OrganicMay contain traces of tree nuts, peanuts and sesame seeds. NET WT 30 g

Nutrition Information:

| TYPICAL VALUES | 100 g | Serving size:30g | %RI°<br>serving size 30 g |
|---|---|---|---|
| ENERGY | 687 kcal | 206 kcal | |
| TOTAL FAT<br>of which: saturates | 54,9 g<br>35 g | 16,5 g<br>10,5 g | 25%<br>53% |
| CARBOHYDRATE<br>of which: sugars | 32,6 g<br>12,5g | 9,8 g<br>3,7 g | 3% |
| FIBER | 15,1 g | 4,5 g | 18% |
| PROTEIN | 8,1 g | 2,4 g | 5% |
| SODIUM | 36,9 mg | 11,1 mg | 0,5% |

°Reference Intake of an average adult (8400 kJ/2000 kcal)

***ALMOND AND CACAO SPREAD***

INGREDIENTS: coconut oil*, almond flour*, coconut sugar*, cacao powder*, puffed quinoa*,psyllium husk*. Organic*

Allergy advice: for allergens, see ingredients in bold.NET WT 40 g

Nutrition Information:

| TYPICAL VALUES | 100 g | Serving size:40 g | %RI°<br>serving size 40 g |
|---|---|---|---|
| ENERGY | 651 kcal | 260 kcal | |
| TOTAL FAT<br>of which: saturates | 55 g<br>45,7 g | 22 g<br>18,3 g | 34%<br>91% |
| CARBOHYDRATE<br>of which: sugars | 23,8 g<br>11,9 g | 9,5 g<br>4,8 g | 3% |
| FIBER | 11,4 g | 4,6 g | 18% |
| PROTEIN | 9,4 g | 3,7 g | 7% |
| SODIUM | 21,5 mg | 8,6 mg | 0,4% |

°Reference Intake of an average adult (8400 kJ/2000 kcal)

***EXTRA-VIRGIN OLIVE OIL***

100% italian product, 12 ml

Nutrition Information:

| TYPICAL VALUES | 100 ml | Serving size:12 ml |
|---|---|---|
| ENERGY | 3389 kJ<br>824 kcal | 407 kJ<br>99 kcal |

| | | |
|---|---|---|
| TOTAL FAT<br>of which: saturates | 91,6 g<br>14 g | 11 g<br>1,7 g |
| CARBOHYDRATE<br>of which: sugars | 0 g<br>0 g | 0 g<br>0 g |
| PROTEIN | 0 g | 0 g |
| SALT | 0 g | 0 g |

°Reference Intake of an average adult (8400 kJ/2000 kcal)

***NUT CLUSTERS***

INGREDIENTS: almond flour, macadamia nuts, coconut flower nectar, pecan nuts, desiccatedcoconut, flaxseed protein, coconut oil, vanilla extract, salt.

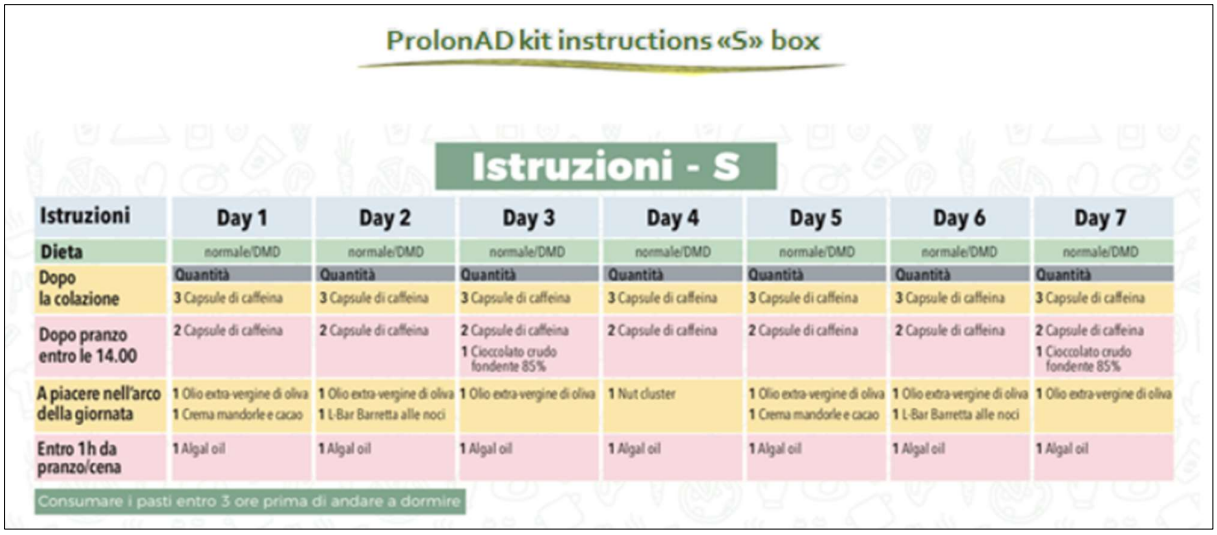
Allergy advice: for allergens, see ingredients in bold.NET WT 45 g

Nutrition Information:

| TYPICAL VALUES | 100 g | Serving size:45 g | %RI°<br>serving size 45 g |
|---|---|---|---|
| ENERGY | 664 kcal | 299 kcal | |
| TOTAL FAT<br>of which: saturates | 52 g<br>12,3 g | 23,4 g<br>5,5 g | 36%<br>28% |
| CARBOHYDRATE<br>of which: sugars | 31,7 g<br>11,9 g | 14,2 g<br>5,3 g | 5% |
| FIBER | 10,9 g | 4,9 g | 20% |
| PROTEIN | 12,1 g | 5,5 g | 11% |
| SODIUM | 7,8 mg | 3,5 mg | 0,2% |

°Reference Intake of an average adult (8400 kJ/2000 kcal)

(d) This table refers to a 7-day cycle which is repeated identically throughout the experiment.



APPENDIX B

The placebo diet (the kit "B") assigned to patients in the control arm consisted of replacing lunch or dinner with a meal (of about 600-800 Kcal) based on pasta or rice with vegetables and olive oil for 5 days a month, without supplements.. Meal replacements are as follows:

### *(a) RISOTTO WITH ASPARAGUS (PLACEBO)*

INGREDIENTS: parboiled rice, rice flour, dried and freeze dried asparagus, salt, tapiocastarch, potato maltodextrin, yeast extract, flavors, sugar, dried onion, dried parsley. NET WT 75 g.

Nutrition Information:

| TYPICAL VALUES | 100 g | Serving size:75 g | %RI°<br>serving size 75 g |
|---|---|---|---|
| ENERGY | 1574 kJ<br>372 kcal | 1181 kJ<br>279 kcal | 14%<br>14% |
| TOTAL FAT<br>of which: saturates | 3,1 g<br>1,4 g | 2,3 g<br>1,1 g | 3%<br>5% |
| CARBOHYDRATE<br>of which: sugars | 74,6 g<br>5,1 g | 65 g<br>3,8 g | 22%<br>4% |
| FIBER | 6,5 g | 4,9 g | 20% |
| PROTEIN | 8,2 g | 6,2 g | 12% |
| SALT | 3,3 g | 1,7 g | 29% |

°Reference Intake of an average adult (8400 kJ/2000 kcal)

### *RISOTTO WITH TOMATO (PLACEBO)*

INGREDIENTS: parboiled rice, dried tomato, sugar, corn starch, rice flour, salt, potato maltodextrin, yeast extract, onion, flavourings, dried basil, tumeric. NET WT 75 g

Nutrition Information:

| TYPICAL VALUES | 100 g | Serving size:75 g | %RI°<br>serving size xx g |
|---|---|---|---|
| ENERGY | 1520 kJ<br>359 kcal | 1140 kJ<br>269 kcal | 14%<br>13% |
| TOTAL FAT<br>of which: saturates | 1,2 g<br>0,3 g | 0,9 g<br>0,2 g | 1%<br>1% |
| CARBOHYDRATE | 76,7 g | 57,5 g | 22% |
| FIBER | 5,2 g | 3,9 g | 16% |
| PROTEIN | 7,6 g | 5,7 g | 11% |
| SALT | 3,5 g | 3,5 g | 44% |

°Reference Intake of an average adult (8400 kJ/2000 kcal)

**PASTA PARMIGIANA (PLACEBO)**

INGREDIENTS: Durum wheat pasta 79%, cheese powder 7.5% (cheese, whey, flavourings salt), skimmed milk powder, rice flour, salt, lactose, corn starch, dried onion, yeast extract, flavourings, dried parsley. Allergy advice: for allergens, see ingredients in bold.NET WT 87,5 g

Nutrition Information:

| TYPICAL VALUES | 100 g |
|---|---|
| ENERGY | 1519 kJ<br>359 kcal |
| TOTAL FAT<br>of which: saturates | 2,8 g<br>1,5 g |
| CARBOHYDRATE<br>of which: sugars | 67,1 g<br>9,8 g |
| FIBER | 4,5 g |
| PROTEIN | 11,8 g |
| SALT | 5,76 g |

**PASTA CARBONARA (PLACEBO)**

INGREDIENTS: durum wheat pasta 81.1%, skimmed milk powder, cheese powder 2.6% (cheese, whey, flavourings, salt), lactose, rice flour, salt, corn starch, flavourings, dehydrated onion, yeast extract, whole egg powder 0.5%, paprika, dehydrated parsley, turmeric. Allergy advice: for allergens, see ingredients in bold.NET WT 87,5 g

Nutrition Information:

| TYPICAL VALUES | 100 g |
|---|---|
| ENERGY | 1427 kJ<br>337 kcal |
| TOTAL FAT<br>of which: saturates | 1,8 g<br>0,9 g |
| CARBOHYDRATE<br>of which: sugars | 66 g<br>9,2 g |
| FIBER | 6 g |
| PROTEIN | 11,2 g |
| SALT | 2,07 g |

*PASTA WITH SEAFOOD (PLACEBO)*

INGREDIENTS: Durum wheat pasta 80.2% dried and freeze-dried molluscs and crustaceans 3% (shrimps, clams), dried tomato, rice flour, salt, corn starch, skimmed milk powder, dried carrot, flavourings, yeast extract, fish stock (salt, fish and dried crustaceans, lactose, vegetable extract, sunflower oil, dried vegetables (celery), white wine, natural flavors, spices), dried white wine, dried garlic, dried parsley. Allergy advice: for allergens, see ingredients in bold.NET WT 87,5 g

Nutrition Information:

| TYPICAL VALUES | 100 g |
|---|---|

| | |
|---|---|
| ENERGY | 1453 kJ<br>343 kcal |
| TOTAL FAT<br>of which: saturates | 1,6 g<br>0,6 g |
| CARBOHYDRATE<br>of which: sugars | 64,7 g<br>8 g |
| FIBER | 6,1 g |
| PROTEIN | 14,5 g |
| SALT | 3,6 g |

*PLACEBO BAR*

INGREDIENTS: dates, coconut flakes, cashews, cacao powder.NET WT 50 g

Nutrition Information:

| TYPICAL VALUES | 100 g |
|---|---|
| ENERGY | 1495,3 kJ<br>367,9 kcal |
| TOTAL FAT<br>of which: saturates | 19,92 g<br>11,86 g |
| CARBOHYDRATE<br>of which: sugars | 43,5 g<br>39,14 g |
| FIBER | 8,26 g |
| PROTEIN | 6,28 g |
| SODIUM | 10,2 mg |