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HOW TO DESIGN NUTRITIONAL INTERVENTION TRIALS TO SLOW COGNITIVE DECLINE IN APPARENTLY HEALTHY POPULATIONS AND APPLY FOR EFFICACY CLAIMS: A STATEMENT FROM THE INTERNATIONAL ACADEMY ON NUTRITION AND AGING TASK FORCE

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Abstract: Interventions are crucial as they offer simple and inexpensive public health solutions that will be useful over the long term use. A Task Force on designing trials of nutritional interventions to slow cognitive decline in older adults was held in Toulouse in September 2012. The aim of the Task Force was to bring together leading experts from academia, the food industry and regulatory agencies to determine the best trial designs that would enable us to reach our goal of maintaining or improving cognitive function in apparently healthy aging people. An associated challenge for this Task Force was to determine the type of trials required by the Public Food Agencies for assessing the impact of nutritional compounds in comparison to well established requirements for drug trials. Although the required quality of the study design, rationale and statistical analysis remains the same, the studies designed to show reduction of cognitive decline require a long duration and the objectives of this task force was to determine best design for these trials. Two specific needs were identified to support trials of nutritional interventions: 1- Risk- reduction strategies are needed to tackle the growing burden of cognitive decline that may lead to dementia, 2- Innovative study designs are needed to improve the quality of these studies.

Key words: Cognitive decline, aging, design nutritional intervention trials, efficacy claims.

Introduction

Diet and nutrition are important factors in the promotion and maintenance of good health throughout the entire life course. Their role as determinants of chronic disease is well established and they therefore occupy a prominent position in global disease prevention activities (1). Alzheimer's disease (AD) and other dementias are among the most burdensome age-related chronic diseases. Thus, risk management strategies are urgently needed to tackle the growing burden of cognitive decline in the elderly.

Nutritional status has been implicated as one of the many potential risk factors for cognitive decline in elderly people. Nutritional interventions are of interest because they are usually safe, relatively inexpensive in comparison to pharmacologic intervention, and provide some unique opportunities for long-term use. A Task Force on designing trials of nutritional intervention for cognitive decline in older adults was held in Toulouse in September 2012. The aim of the Task Force was to bring together a limited number of leading experts from academia, the food industry, and regulatory agencies to determine the best trial designs for identifying nutritional interventions that would enable us to reach our goal of maintaining or improving cognitive function with aging. Like trials of pharmacologic interventions, nutritional studies require clarity of rationale, appropriately selected trial designs, and rigorously applied statistical analysis. However, different types of data may be required to establish the impact of foods or supplements on cognition. The objective of this report is to provide an overview of the current landscape in the field and provide a summary of the discussion and outcomes of the meeting. Ultimately, the Task Force hopes to establish specific recommendations that will expedite the development of nutritional interventions in the elderly population.

The role of food in maintaining or improving cognitive functions with age

AD is the most frequent cause of dementia in older persons. The main risk factors for late-onset AD (i.e., age and the presence of the ApoEε4 allele) are not modifiable. The identification of nutritional factors associated with increased risk of cognitive decline may consequently represent an opportunity to develop novel risk reduction strategies. Several

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epidemiological studies (2-4) and clinical trials (5-7)) have reported strong links between nutritional status and cognitive health in older persons, suggesting that specific nutrients may play a role of lowering the risk of cognitive decline, especially in frail elderly people at risk of nutritional deficiencies and incident AD. These studies were initially focused on specific deficiencies of micronutrients involved in neuroprotection and/or regulation of the oxidative status (8-15). For example, the protective effect of fish oil consumption has been attributed to its high content of long-chain omega-3 polyunsaturated fatty acids (PUFA), in particular docosahexaenoic acid (DHA) (16). Longitudinal and cohort studies also show an association between diabetes, hyperhomocysteinemia, hypercholesterolemia, low intake of n-3 fatty acids and oxidative stress with the risk of dementia. Nevertheless, evidence is still controversial, with epidemiologic studies failing to demonstrate a relationship between omega-3 PUFA intake and risk of dementia or cognitive decline. The most consistent evidence is available for longer-chain omega-3 fatty acids (often measured as fish consumption), with several longitudinal studies showing an association with reduced risk for cognitive decline (17). Another example might be provided by results from the Three-City (3C) study, which analyzed the relationship between fat- or antioxidant-rich dietary components and the risk of dementia in older persons. Authors found that the frequent consumption of fruits, vegetables, fish, and omega-3 rich oils may play a role at decreasing the risk of dementia, especially in ApoEε4-non carriers (2).

Large clinical trials have also been conducted to test the effects of nutritional supplements on the progression of cognitive decline. For example, a multicenter, randomized, double-blind placebo controlled clinical trial of antioxidants (600 mg vitamin E, 250 mg vitamin C and 20 mg β-carotene daily) failed to show any slowing of cognitive decline in the treatment group (18). Another multi-center trial of Docosahexaenoic acid (DHA) supplementation in individuals with mild to moderate AD showed no effect on cognitive or functional decline (16). Few trials have tested the effect of nutritional supplementation on the risk of cognitive decline in non-demented individuals. One example is the PREADVISE trial, which investigated the effect of anti-oxidants (daily doses of 400 IU vitamin E/ or placebo and 200μg selenium/or placebo) in decreasing the risk of AD among men enrolled in an even larger prostate cancer prevention study (19) . Ginkgo biloba extract was also recently investigated as a preventive treatment for AD (20). Despite failing to meet the primary outcome of a reduction in the number of subjects converting to AD, some possible protective effects were observed. These subtle benefits must be confirmed in the population subgroup that took gingko biloba extract for at least 4 years (20). Additional studies have further investigated the effectiveness of nutrients, including omega 3 fatty acids, DHA, vitamin E, vitamin C, and coeznyme Q, using more specific neuropsychologic measures and CSF biomarkers as outcomes, with little success (21-23). Two trials that have shown apparent benefits tested an oral ketogenic compound, AC-1202, in subjects with probable AD (24) and a medical food called Souvenaid® in subjects with mild AD (25). Souvenaid contains a specific nutrient combination patented under the name Fortasyn™ Connect, which is designed to stimulate synapse formation.

The possibility that nutritional intervention may protect against cognitive decline is an inviting prospect and data supporting a potential effect of dietary patterns are regularly published. However, long-term, large-scale randomized trials are still sparse.

European Food Safety Authority (EFSA) guidelines for claims on cognitive function

The European Food Safety Authority's Panel on Dietetic Products, Nutrition, and Allergies (NDA) issued a guidance in 2012 regarding scientific requirements to support health claims related to nervous system function for foods or food constituents such as vitamins (26).

The guidance addresses two key issues related to the substantiation of health claims: First, that health claims should only be permitted when the food or food constituent is shown to have a beneficial physiologic effect, and second, that the studies must have been well designed and executed and carried out in an appropriate study population; and that outcome measures utilize established and validated diagnostic tools, including measures of neural activity as supportive evidence of a neuropsychological benefit. A beneficial physiologic effect in the nervous system is defined as maintenance or improvement of a psychological, perceptual, psychomotor, or physiologic regulatory function; or a reduction in a disease risk factor.

With respect to the study population, the guidelines supported studies in well characterized subjects with mild cognitive decline, with extrapolation to more cognitively impaired patients considered on a case-by-case basis.

What is recommended in order to obtain nutrition claims?

The role of public agencies is to formulate guidelines to support the implementation of public health policies in the apparently healthy population. For example, the EFSA was established to develop procedures and guidelines related to food safety, and has also issued guidances related to nutrition and health claims of foods. Related to the work of the Task Force, these regulations provide definitions of nutrition references, based on nutritional requirements in order to evaluate the relationship of food consumption to age-related metabolic modifications and the nutrition of elderly people in frailty or pathological contexts (see Text box).

EFSA expectations regarding food/nutritional claims

Characterization of the food (this word encompasses any situation: a food, a part of a food, an ingredient, an extract, a purified natural or synthetic molecule); this characterization should be done in relation to the claim, not in an absolute way: thus it may be enough to have standardized the food for something which is considered as the active part for the claimed effect, taking into account as appropriate the content of other elements for which approved claims exist. This characterization is needed in order to check that any provided study for substantiation can actually apply to the proposed food. In case of positive outcome for the claim substantiation, this characterization will also be important for defining the conditions of use of the claim and, ultimately, will allow the possibility of control for control authorities. The applicant can choose to apply for a product-specific claim, the product being characterized by e.g. a fixed combination of nutrients and/or a specific manufacturing process: the claim substantiation should be based on studies performed with this specific product; studies performed with individual nutrients or other foods claimed to be similar can only be used as supportive evidence.

Characterization of the target population for the claim, leading to the issue of the possible difference between the target population and the study population. Given the constant interdiction of medicinal or therapeutic claims for foods (including dietary supplements), the target population should be an apparently healthy population, even if this population is at increased risk of a specific disease or affected by functional impairment. From the example of cholesterol-lowering food due to phytosterol content, it clearly appears that it is a matter of wording at the basis of the classification: food containing phytosterol targets people who want to maintain or reduce their blood cholesterol and do not explicitly target people with hypercholesterolemia (requiring a clinical diagnosis).

At the preliminary approach, the absence of interference (at the mechanistic level) between the drug and the food allows the inclusion of subjects using drugs in the study group. However, it would be safe to balance the groups on this aspect in order to avoid/limit any bias or uncertainty from this possible confounding factor. In any case, there is a continuum between healthy people and overtly diseased people and placing the boundary may always be questioned.

A third issue will have to be considered in the future, and at present can only be mentioned: in order to support a claim, the food should comply with a nutrient profile, according to article 4 of the claim regulation. Such point is aimed at avoiding that a food with a high content of potentially deleterious nutrients (e.g. fat, saturated fat, sugars, trans fatty acid, salt) may be promoted by simply adding 15 % of the RDA of specific vitamins or minerals.
The regulation does not contain the possibility of exemptions for health claims and risk reduction claims. Since, to date, nutrient profiles are not yet defined, this aspect leaves some uncertainty when considering multi-nutrient foods.

Design of nutritional intervention trials targeting cognitive decline

Nutritional intervention trials that target cognitive decline are complicated by the multiple and poorly understood pathways through which nutrition affects cognition, the multiple domains of cognition that may be affected, and individual differences in the ability to cope with neuropathology and the influence of cognitive reserve on coping. Given the heterogeneous manifestations of cognitive decline and the wide spectrum of underlying pathophysiological mechanisms, the Task Force recommended consideration of alternative and adapted designs (e.g., multidomain interventions) (27). The Task Force also identified other design considerations related to the target population and sample size, length of the trial, and selection of endpoints/outcome measures, including biomarkers:

Target population

The EFSA guidelines supported studies in well characterized subjects with mild cognitive decline, indicating that extrapolation of the results to a larger target group may be considered on a case-by-case basis. A number of issues were identified related to the selection of the study population in order to facilitate extrapolation. In selecting a target population, the study team must take into account the intervention to be tested, the study design, and the study outcome. Several target populations may be proposed, each with specific advantages and limitations:

- The recruitment of pre-frail and frail older persons (defined according to the phenotype proposed by Fried and colleagues in the Cardiovascular Health Study (28)) with cognitive impairment (e.g., CDR equal to 0.5) may represent an interesting population since frail elders are at increased risk of having both nutritional deficiencies and dementia. In fact, the malnutrition component included in the frailty phenotype (i.e., weight loss) may enhance the possibility of implementing a nutritional intervention.
- Individuals with Mild Cognitive Impairment (MCI) may be an interesting target population, although it might be difficult to recruit these people because an evaluation in a memory center is usually needed
- PET amyloid positive individuals represent approximately 20 to 30% of older adults aged over 70 years. As they are thought to be at high risk of developing AD, they could represent a good target population although PET imaging would add substantial cost to the study..
- Other biomarkers may also be used to select appropriate study subjects.
- APOEε4 is an important risk factor for AD, and older adults who are carriers of this allele may represent a good target population for nutritional studies. Even if not used as an inclusion criteria, the presence of an APOE4 allele could be a confounding factor that needs to be taken into account in balancing study groups.
- Other populations at high risk of cognitive decline may also represent appropriate subjects, for example those with a family history of AD.

Sample size

Sample size calculations must be conducted for the primary outcome of the trial in order to guarantee its optimal design. Large sample sizes are likely to be needed given the heterogeneity of the decline observed across older persons

Length of the trial

Symptomatic trials must be between 6 and 12 months in duration in order to be able to observe a decline in the placebo group. Disease modifying trials must be at least 18 months to really be able to have an effect on the disease course. (29-33). Preventive trials may require 3 to 5 years of follow-up. Although long-term randomized controlled trials (RCTs) are the ideal approach, in many cases the barriers to implementing such studies may make them unrealistic. For this reason, RCTs might aim to identify individuals at high risk of cognitive decline to make trials more efficient and economical.

Other issues to consider in planning the length of a trial include:

- The intensity, duration, and timing of the exposure, should be taken into account. Exposures may be more influential and interventions more effective during specific times and in the presence of specific conditions.
- Given the usual long subclinical, prodromal period of neurodegenerative diseases, trials need to consider extended periods of follow-up.

Endpoints/Outcomes

The choice of outcome measures depends on the expected effects of the intervention. Since multidomain interventions may be necessary, multiple outcome measures may also be needed. The choice of outcome should also be adapted to the population under study. Studies should test the hypothesized effects of a nutritional intervention on appropriate outcome measures (i.e. cognition) by using validated, reliable and accurate psychometric tests, as well as markers of specific pathways.

Some domains (such as memory) may be considered as more "clinically relevant", and as such, particularly important. Subjective memory complaint may represent a key feature for preventive trials on cognitive decline because associated with an increased risk for dementia. Moreover, this symptom may be easily detected by healthcare professionals (facilitating the potential participants recruitment), and has already been used in large trials. A good test of episodic memory is the Free and Cued Selective Reminding Test (FCSRT), which has shown to be predictive of memory changes in AD (34). Batteries of tests covering multiple cognitive domains have been developed and validated over the years (e.g., the Neuropsychological Test Battery (29) or the Clinician Dementia Rating scale (30).

Biomarkers (both CSF and imaging) may also be used as secondary outcome measures, and may be measured only in a subgroup of the total population (31-33, 35, 36). They may be especially useful when anticipating a disease modifying effect or in preventive trials.

The modification of a risk factor for a disease, rather than the direct action on the disease itself may also be the subject of a claim. In the absence of a well-established risk factor for dementia or cognitive decline (such as the high level of LDL-cholesterol or blood pressure which are well established for cardiovascular disease), there should be a demonstration of both the reduction of the risk factor and of the disease itself.

Other important considerations when selecting outcome measures include:

- tests (especially those used in prevention trials) should be sufficiently sensitive to changes.
- For the EFSA, it is the responsibility of the applicant to demonstrate that the test chosen has been validated for the purpose (i.e. cognitive decline) in the specific population.
- In the statistical treatment of the results, the consideration of multiple outcomes should be done using appropriate statistical corrections.
- Other factors that may need to be assessed as covariates include nutritional status, physical exercise and cognitive activity.

Conclusion

Nutrition is a domain that should be more fully explored as a determinant of cognitive impairment in the older persons. Moreover, links between nutrition and physical and cognitive frailty make this an area of particular interest for nutrition intervention (37-39).

The efficacy of nutritional interventions on cognition should be tested using recommendations that mirror those already established for the design of pharmacological trials. For example, the selection of a target population, study design, and the study outcome for appropriate the tested intervention is very important. With regard to the study design, large sample sizes will most likely be needed. For symptomatic treatments, trials of between 6 and 12 months in duration will be required in order to detect a decline in the placebo group, while preventive trials may require 3 to 5 years of follow-up.

The EFSA reports that of 2,927 consolidated health claims for different ingredients examined, only 241 passed muster. This high rejection rate in an industry that has lobbied against legislation requiring stricter approval standards and costly quality control (40) prompted the members of this Task Force to propose ambitious and robust trials aimed at obtaining similar success to those obtained in the past for cardiovascular diseases and osteoporosis.

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