CHANGES IN NUTRITIONAL STATUS AFTER DEEP BRAIN STIMULATION OF THE NUCLEUS BASALIS OF MEYNERT IN ALZHEIMER’S DISEASE – RESULTS OF A PHASE I STUDY


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Abstract: Objective: The progression of Alzheimer’s disease (AD) is associated with impaired nutritional status. New methods, such as deep brain stimulation (DBS), are currently being tested to decrease the progression of AD. DBS is an approved method in the treatment of Parkinson’s disease, and its suitability for the treatment of AD patients is currently under experimental investigation. To evaluate the advantages and disadvantages of this new treatment, it is important to assess potential side effects of DBS regarding the nucleus basalis of Meynert; this new treatment is thought to positively affect cognition and might counteract the deterioration of nutritional status and progressive weight loss observed in AD. This study aims to assess the nutritional status of patients with AD before receiving DBS of the nucleus basalis of Meynert and after 1 year, and to analyze potential associations between changes in cognition and nutritional status. Design: A 1-year phase I proof-of-concept study. Setting: The Department of Psychiatry and Psychotherapy at the University of Cologne. Participants: We assessed a consecutive sample of patients with mild to moderate AD (n=6) who fulfilled the inclusion criteria and provided written informed consent. Intervention: Bilateral low-frequency DBS of the nucleus basalis of Meynert. Measurements: Nutritional status was assessed using a modified Mini Nutritional Assessment, bioelectrical impedance analysis, a completed 3-day food diary, and analysis of serum levels of vitamin B12 and folate. Results: With a normal body mass index (BMI) at baseline (mean 23.75 kg/m²) and after 1 year (mean 24.59 kg/m²), all but one patient gained body weight during the period of the pilot study (mean 2.38 kg, 3.81% of body weight). This was reflected in a mainly stable or improved body composition, assessed by bioelectrical impedance analysis, in five of the six patients. Mean energy intake increased from 1534 kcal/day (min 1037, max 2370) at baseline to 1736 kcal/day (min 1010, max 2663) after 1 year, leading to the improved fulfillment of energy needs in four patients. The only nutritional factors that were associated with changes in cognition were vitamin B12 level at baseline (Spearman’s rho = 0.943, p = 0.005) and changes in vitamin B12 level (Spearman’s rho = -0.829, p = 0.042). Conclusion: Patients with AD that received DBS of the nucleus basalis of Meynert demonstrated a mainly stable nutritional status within a 1-year period. Whether DBS is causative regarding these observations must be investigated in additional studies.

Key words: Deep brain stimulation, nutritional status, Alzheimer’s disease, body weight change, body composition.

Introduction

The first study to use deep brain stimulation (DBS) as a therapy was published in 1987 by Benabid et al., who treated Parkinson’s disease by stimulating specific thalamic core structures. Today, DBS is an established and approved method in the treatment of Parkinson’s disease, with increased evidence of a benefit during the early stages (1). Since the first studies in Parkinson’s disease, this method has been extended to a series of other target structures and indications. The latest research indicates that DBS might have promising effects for Tourette syndrome, major depression, addiction, and Alzheimer’s dementia (2-5). Research into the influence of DBS of the subcallosal cingulate on eating behavior has been conducted in patients with anorexia nervosa (6). A partial influence on metabolic profile was found in a recent translational study that revealed alterations in blood glucose and plasma glucagon concentrations during DBS of the nucleus accumbens in rats (7).

There are several nutrition-associated factors that seem to influence the development of Alzheimer’s disease (AD), such as the intake and blood levels of fatty acids, B vitamins, and antioxidants, as well as body weight. A decrease in cognitive capabilities is often associated with a decrease in body weight (8, 9). At the same time, weight loss and malnutrition in AD are associated with several adverse outcomes, such as higher...
incidence of behavioral disorders (10); decrease in quality of life (17); and increased dependency (11, 12), morbidity (16), and mortality (13). Weight loss has often already occurred before AD is diagnosed (14). Therefore, some researchers suggest that a 1-year weight change may serve as an early prognostic indicator for cognitive changes (15).

The causes of weight loss in AD are still unclear (16) and seem to be related to the stage of the disease. Potential causes include the atrophy of brain regions associated with eating behavior (mesial temporal cortex), metabolic disturbances, and feeding behaviors (17). Aside from changes in energy balance owing to cognitive and motor causes, damage of the central nervous system (as is found in patients with dementia) might also influence food intake through dysfunctions in the hunger/satiety system (18).

This study aims to assess the nutritional status of AD patients before and 1 year after implantation of DBS electrodes to analyze potential associations between changes in cognition and nutritional status. Primary emphasis is placed on nutritional status according to the modified Mini Nutritional Assessment (m-MNA), body weight, body composition, blood levels of vitamin B12 and folate, and energy requirements.

**Methods**

Six patients (4 female) aged 57 to 78 years (mean ± standard deviation: 69.2 ± 7.5 years) were enrolled at the University Hospital of Cologne and had been diagnosed with mild to moderate AD. Details on the methods have been described earlier (19). Nutritional status was assessed using the modified Mini Nutritional Assessment (m-MNA), body weight and body mass index (BMI), body composition measured by bioelectrical impedance analysis (BIA), fulfillment of energy needs, and blood levels of vitamin B12 and folate.

**ADAS-cog**

The Alzheimer’s Disease Assessment Scale (ADAS), developed by Mohs et al. (20) in 1983, is a two part instrument developed to assess cognitive and non-cognitive symptoms of AD. For this study, we employed the ADAS cognitive subscale (ADAS-cog), which includes seven performance items and four items rated by the examiner: memory, orientation, language, and praxis. The scores range from 70 (severe impairment) to 0 (no impairment). The Mini Mental State Examination (MMSE), the trail making task, the Stroop task, the verbal fluency test, subtests of the Wechsler Memory Scale (visual reproduction, figural memory, digit and spatial span), subtests of the Wechsler Adult Intelligence Scale (digit-symbol test, Mosaic test), and psychopathological tests (BDI-II and HAM-D) were performed in addition to the ADAS-cog. The results of these tests have been described earlier (19). Because of its higher sensitivity to detect cognitive changes, ADAS was chosen to analyze potential associations with patients’ nutritional status.

**m-MNA**

Nutritional assessment was conducted at baseline before implantation of the DBS electrodes and after 1 year. Nutritional risk was assessed using the m-MNA (21, 22) consisting of BMI, weight change within the last 3 months, mobility, dependency in food intake, number of consumed main dishes per day, fluid intake, and the subjective rating of general health status compared with healthy peers. Patients were classified as well nourished (12.5-15.0 points), at risk for malnutrition (9.0-12.0 points), or malnourished (8.5 points).

**BMI and weight change**

Height, BMI, and body composition were assessed in order to analyze changes in body weight and body composition. Body weight was measured in the morning on an empty stomach in light clothing without shoes. For the patient aged <65 years, BMI was categorized according to the World Health Organization’s classifications, as underweight (< 18.5 kg/m²), normal weight (18.5 - 24.99 kg/m²), or overweight/obese (> 25.0 kg/m²). For all other patients (>65 years), normal weight was defined as BMI between 21 kg/m² ( ) and 30 kg/m² (24).

**Body composition**

Body composition was assessed using BIA. We used the Nutriguard-M impedance analyzer (DataInput) with Bianostic AT double size electrodes for BIA. The measurement was conducted in the morning on an empty stomach. Subsequently, body composition was calculated using the program NutriPlus© 5.4.1. Total body water (TBW) was calculated as height²/resistance. Lean body mass (LBM)/fat-free mass (FFM) includes organs, bones, and the central nervous system, and was calculated as 73% of TBW (25). Fat mass (FM) was calculated as the difference between lean body mass and body weight (25). Body cell mass includes skeletal muscle mass, heart muscle, smooth muscle, internal organs, the gastrointestinal tract, blood, glands, and the nervous system, and was calculated as FFM × phase angle × correction variable (25).

**Energy needs and food intake**

To analyze the fulfillment of energy needs, resting energy expenditure was calculated with 20 kcal/kg body weight/day (26) adding a physical activity level (PAL) of 1.4 (27). Because of the patients’ mild cognitive impairment, there was a high risk of misreporting if the study participants had kept their own food diaries. Therefore, the spouse/partner was asked to write down all food and drink consumed during two weekdays and one weekend day in a prepared form. As the spouses/partners accompanied the study participants all day, the reported intake can be assumed to be as accurate as possible. We used DGE PC Professional to analyze patients’ nutrient intake.

**Status of vitamin B12 and folate**

Serum levels of vitamin B12 and folate were assessed before surgery and after 1 year of chronic stimulation.
Micronutrients are thought to be associated with impaired cognitive function and AD (28, 29). Furthermore, elderly individuals are at risk of vitamin B12 and folate deficiencies (30, 31). Serum levels of vitamin B12 and folate were analyzed using electroluminometric immune assays. Normal levels were defined as 191 – 663 ng/l for vitamin B12 and 4.6 - 18.7 µg/l for serum folate.

Statistics

Correlations between changes in cognition and nutritional status were assessed using Spearman’s rho rank correlation coefficient. Thus, monotone association between any two at least ordinal variables is measured. Note, the relationship between two variables X and Y is monotone if x1 < x2 implies y1 ≤ y2 (monotone rising) [or y1 ≥ y2 (monotone falling)]. A correlation >0.5 in absolute value was considered potentially relevant, although statistical significance was claimed only for corresponding p-values < 0.05. A correction due to multiple testing was not applied, in order to avoid further reduction in power. Of course, the sample size (n=6) was far too low to detect relevant correlation and effect with reasonable power. For example, n=29 patients are required to detect a correlation of 0.5 with 80% power (two-sided type I error 5%). This proof-of-concept study primarily served to obtain a first impression of whether or not AD patients might benefit from DBS. Larger trials must definitely follow to confirm any finding. All calculations were completed with SPSS software (IBM Corp., Armonk, NY).

Ethics and informed consent

Written informed consent was obtained from patients and relatives, respectively. The ethics committee of the Medical Faculty of the University of Cologne and the governmental authority each approved the study. Details of the procedure have been described earlier (19).

Results

Patients’ characteristics are listed in Table 1. After 12 months of nucleus basalis of Meynert stimulation, Patients 3 and 5 worsened by 19 and 8 points; Patients 1, 4, and 6 remained stable (changes of +1, -1, ±0 points), and Patient 2 improved by 9 points. The mean ADAS-cog increased by 3 points (min -9, max 19) during the 12-month observation period, which shows a decrease in cognitive function. This change in ADAS-cog demonstrates only a slight and clinically irrelevant progression of AD.

m-MNA

The mean score for nutritional status according to m-MNA at baseline was 13.2 points (min 11.5, max 14.5), which is defined as well nourished. After 1 year, the mean score decreased by 0.3 points to 12.9 points (min 10.5, max 15.0), which was associated to a potentially relevant extent with

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td>BMI at baseline, kg/m²</td>
<td>28.1</td>
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<td>20.2</td>
<td>24.4</td>
<td>22.4</td>
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<tr>
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<td>24.7</td>
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<td>1.6</td>
<td>1.0</td>
<td>1.3</td>
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<td>Body weight at baseline, kg</td>
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<td>61.5</td>
<td>56.2</td>
<td>55.0</td>
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<td>62.0</td>
<td>59.3</td>
<td>58.0</td>
<td>75.9</td>
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<td>3.1</td>
<td>4.4</td>
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<td>13.5</td>
<td>11.5</td>
<td>14.5</td>
<td>14.0</td>
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<tr>
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<td>14.0</td>
<td>11.0</td>
<td>10.5</td>
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<td>-1.0</td>
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<td>595</td>
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<td>274</td>
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<td>-196</td>
<td>74</td>
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<td>11</td>
<td>15.9</td>
<td>17.7</td>
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<tr>
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<td>12.3</td>
<td>13.9</td>
<td>14.7</td>
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<td>1574</td>
<td>1540</td>
<td>2114</td>
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<td>1660</td>
<td>1663</td>
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<td>1010</td>
<td>1263</td>
<td>1753</td>
<td>2663</td>
</tr>
<tr>
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<td>-622</td>
<td>81</td>
<td>-503</td>
<td>256</td>
<td>-1057</td>
</tr>
<tr>
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<td>97</td>
<td>-346</td>
<td>-650</td>
<td>-400</td>
<td>-451</td>
<td>440</td>
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</table>
changes in ADAS-cog (Spearman’s rho = -0.600, p = 0.208). However, the ranking of the changes in cognition of Patients 3, 5, and 6 corresponded to the ranking of their changes in nutritional status. Patient 3, who exhibited the greatest decrease in nutritional status according to the m-MNA, simultaneously experienced the strongest decrease in ADAS-cog (m-MNA -2.5 points, ADAS-cog -19 points) (Table 1).

BMI and weight change

Patients’ mean BMI at baseline was 23.75 kg/m² (min 20.20, max 28.13), which is within the range of normal for BMI. After 1 year, all patients exhibited increases in body weight except for Patient 1, whose ADAS-cog remained stable. Patients’ mean change in body weight was +2.38 kg, +3.81% of body weight (min -1.30 kg, -1.60%, max +4.40 kg, +8.00%), which led to a mean BMI of 24.59 kg/m² (min 21.82, max 27.68). The change in body weight was not relevantly associated with changes in ADAS-cog (Spearman’s rho = -0.086, p = 0.872).

Body composition (Table 2)

Patients exhibited a clinically normal hydration status, which is necessary to obtain correct BIA results. The mean phase angle at baseline was 5.7° (min 5.0, max 5.9), which is within the normal range of 4.7 – 6.4°. There was a potentially relevant correlation between phase angle and changes in ADAS-cog (Spearman’s rho = -0.696, p = 0.125) and a statistically significant correlation between phase angle and nutritional status (Spearman’s rho = 0.870, p = 0.024). There was no relevant correlation between changes in ADAS-cog and changes in TBW (Spearman’s rho = 0.257, p = 0.623). After 1 year, three patients (Patients 3, 4, and 6) exhibited increased FFM, three patients exhibited decreased FFM, and only one patient exhibited a decrease in body fat.

Energy requirements and food intake

The mean energy requirement at baseline was 1888 kcal/day (min 1540, max 2276), and the mean energy intake was 1534 kcal/day (min 1037, max 2370). The four patients with improved or stable ADAS-cog (Patients 1, 2, 4, and 6) did not fulfill their energy needs at baseline. Patients 3 and 5, who exhibited decreases in cognitive function, each had a positive energy balance at baseline (Table 1). After 1 year, due to weight gain, mean energy needs increased to 1954 kcal/day (min 1660, max 2240), and mean energy intake increased to 1736 kcal/day (min 1010, max 2663). There was a change in the fulfillment of energy requirements. The respective energy balances of Patients 3 and 5, who exhibited decreased cognitive function, changed from positive to strongly negative. All other patients increased their energy intake, resulting in a positive energy balance in Patients 1 and 6 and a less negative energy balance compared to baseline in Patients 2 and 4 (Table 1). There was a significant correlation between changes in energy intake and changes in nutritional status according to the m-MNA (Spearman’s rho = 0.829, p = 0.042), as well as a potentially significant correlation between changes in energy intake and changes in cognition (Spearman’s rho = 0.543, p = 0.266) (Figure 1).

Levels of vitamin B12 and folate

The mean serum level of vitamin B12 at baseline was 344 ng/l (min 101, max 595), which is within the normal range of 191 – 663 ng/l. Only Patient 2 had a reduced vitamin B12 blood

| Body compartment: ◊ below normal range, ▲ above normal range |
level of 101 ng/l. After 1 year, the vitamin B12 levels increased for Patients 2, 4, and 5 and decreased in the remaining patients, still resulting in a mean level of 327 ng/l (min 198, max 557) for all patients, well within the normal range. There was a significant correlation between changes in ADAS-cog and vitamin B12 level at baseline (Spearman’s rho = 0.943, p = 0.005), as well as between changes in ADAS-cog and changes in vitamin B12 levels (Spearman’s rho = -0.829, p = 0.042) (Figure 2).

The mean folate serum level at baseline was 12.5 µg/l (min 5.3, max 17.7), which is within the normal range of 4.6-18.7 µg/l. After 1 year, folate level increased in five patients. Only Patient 6, who had a stable ADAS-cog, exhibited a decrease of 11.5 µg/l (Table 1). There was no detectable relevant correlation between changes in folate blood level and ADAS-cog (Spearman’s rho = 0.086, p = 0.872).

Discussion

This is the first study to examine the nutritional status of patients with AD who received DBS of the nucleus basalis of Meynert for a 1-year period. To date, two clinical studies and one single case study of DBS in AD have been published. None of these studies assessed nutritional status and weight change.

In contrast to earlier findings that revealed malnutrition and a risk for malnutrition in 0-6% and 19-36% of community-dwelling older people with dementia, respectively (32), all six patients included in this study were well-nourished. In 2012, Saragat et al. found a significant association between MNA and psycho-cognitive indicators (MMSE, Geriatric Depression Scale (GDS)) in the control group, but not in AD patients (33). This finding is in contrast to those of previous studies, which demonstrated a strong connection between nutritional status and cognition (34-36), and also suggested that nutritional status according to the MNA is a predictor of dementia progression according to the MMSE (37). In our study population, we observed a potentially relevant correlation between ADAS-cog and nutritional status assessed by m-MNA, although statistical significance was not reached (Spearman’s rho = -0.600, p = 0.208). This finding might be due to the slight, clinically non-relevant change in cognition in our study population. A clearer picture is observed regarding the changes of body weight.

As previously mentioned, AD is associated with weight loss (8, 38). In contrast, there was no correlation between changes in cognition and body weight in our study group. Five patients exhibited weight gain after 1 year; only one patient, whose cognition remained stable, lost weight (1.3 kg, 1.6% of body weight). This weight loss was reflected in decreases in FM and FFM. There are several possible reasons for a stable body weight and a lack of correlation between weight change and changes in cognition: a) changes in ADAS-cog were too small to cause any changes in weight loss; b) the study period was too short to observe any significant changes in body weight; c) the study population was too small to observe a statistically significant correlation between ADAS-cog and weight change; d) DBS influenced regions of the brain, which in turn stabilized patients’ eating behaviors; e) the contact persons (spouses) of the study patients may have provided additional attention to the necessity of adequate nutrition; f) the need to write a 3-day food diary at the beginning of the study might have increased spousal awareness regarding food intake; and/or g) the caregiver or partner did not perceive the support as stressful, which can also influence weight changes in AD patients (12, 37, 39).

Although not statistically significant, our study group did exhibit a trend toward improved energy intake in patients
with an improvement in cognition or stable cognitive status. Interestingly, the only two patients that exhibited a positive energy balance at baseline simultaneously experienced the largest reduction in cognition, which appears to have led to a drastic decrease in energy intake after 1 year. In contrast, all other patients exhibited increases in energy intake, which led to better fulfillment of energy needs after 1 year. Certainly, the fact that a 3-day food diary is only a snapshot of the eating behavior must be taken into consideration. Furthermore, it is surprising that five of the six patients exhibited weight gain, while three indicated a negative energy balance at baseline and four indicated a negative energy balance after 1 year. Possible reasons for this observation could be metabolic alterations, as shown in rats during DBS of the nucleus accumbens (7); underreporting of food intake; and/or lower energy expenditure than estimated.

Given that other studies demonstrated a close relationship between phase angle and both nutritional and functional status (40), it appears to be useful as a screening tool for the identification of risk in AD patients that also have impaired nutritional and functional status. In the present study, the phase angle measured by BIA increased after 1 year in all patients except one, allowing the assumption that nutritional status and functional status were stable or improved in five of the six patients. The increase in mean body weight and the mainly stable FFM and FM also support this conclusion. Although the reliability of assessing the body composition of older people using BIA is debatable, it is still a very useful and commonly used method to estimate FFM (41) and FM (42) in this age group.

The role of B vitamins in the development and treatment of cognitive impairment is controversial (43-46). Although all of the patients in our study population except one exhibited vitamin B12 levels within the normal range at baseline and after 1 year, suggesting that there was no deficiency, there are significant correlations between the nutritional status and vitamin B12 levels at baseline, and between cognitive changes and variation in vitamin B12 levels. One reason that our findings differ from those of previous studies that analyzed the association between B vitamins and cognition might be that such effects can only be determined in the longer term. In a review of long-term studies, Hinterberger and Fischer (28) showed that 11 of 14 epidemiologic studies with observation periods between 4 and 9.3 years reported that at least one of the parameters folate, vitamin B12, and homocysteine had a significant, independent, and beneficial impact on cognition. Furthermore, six of seven randomized controlled trials with B vitamin intervention periods of between 2 and 5.4 years report about cognitive benefits of the supplemented groups for those subjects with low folate intake or high homocysteine levels (28).

**Limitations**

This is a pilot project using an invasive therapy method. Thus, the number of patients assessed in this preliminary work was small. The small group size of only six patients notably diminishes its statistical power and renders generalization of the results questionable. Although it is still the most commonly used method to assess body composition, the reliability of BIA results in older adults is debatable, and results should be interpreted with caution.

**Conclusion**

Stimulation of the nucleus basalis of Meynert seems to have no negative effect on the nutritional status of AD patients. Although stabilization of the nutritional status was not the aim of the present treatment study, results show that most of the parameters used to assess nutritional status were stabilized in five of six patients who received DBS of the nucleus basalis of Meynert. This finding is in accordance with results of the ADAS-cog test, showing only slight, clinically undetectable progression of AD. The only nutritional factor that was significantly associated with changes in cognition was vitamin B12 level. There were trends towards associations between change in cognition and change in nutritional status, as well as between change in cognition and change in energy intake. Additional investigations are needed to evaluate the potentially beneficial impact of DBS on the nutritional status of AD patients.

**Ethical standards:** The ethics committee of the Medical Faculty of the University of Cologne as well as the governmental authority approved the study. An independent data monitoring committee (IDMC) supervised the progress, safety and efficacy of the investigation. Patients were entering the study sequentially, with each further inclusion demanding a renewed authorization by the IDMC. An independent licensed physician assessed each patient’s ability to understand the research objectives and to give informed consent to treatment in a personal interview. As a standard, the MacArthur Competence assessment Tool for Treatment (MacCat-T) was applied.

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**References**


The image contains a page from a document with references and text discussing various topics related to aging, dementia, and nutritional status. Here is a brief summary of the key points:

1. **Systematic Reviews and Meta-Analyses**
   - Various systematic reviews and meta-analyses are cited, including those on B12 levels and cognitive impairment, and the effects of nutritional status on cognitive decline.

2. **Clinical Trials**
   - Trials such as the REAL.FR study and the IMPACT study are discussed, highlighting their contributions to understanding the impact of nutrition on cognitive health.

3. **Nutritional Assessment**
   - The importance of nutritional assessment tools, such as the Mini Nutritional Assessment (MNA), is emphasized.

4. **Dementia and Weight Loss**
   - The relationship between dementia and weight loss is explored, including the role of nutritional status in this context.

5. **Deep Brain Stimulation**
   - Deep brain stimulation (DBS) is mentioned as a treatment for Alzheimer's disease, with references to studies on its effectiveness.

6. **Nutritional Interventions**
   - The role of nutritional interventions in managing cognitive decline and dementia is discussed, with a focus on the potential benefits of B vitamins and fatty acids.

7. **Quality of Life**
   - The impact of nutrition on quality of life for dementia patients is highlighted, with references to studies showing improvements in cognitive function and mood.

8. **Longitudinal Studies**
   - Longitudinal studies are cited to support the ongoing research into the long-term effects of nutrition on aging and dementia.

9. **Epidemiological Studies**
   - Epidemiological studies are used to support the findings on the relationship between nutrition and cognitive health.

10. **Growth Hormone**
    - The role of growth hormone in relation to Alzheimer's disease is discussed, with references to studies suggesting a link between lower growth hormone levels and increased risk.

11. **Vitamin B12 Deficiency**
    - Vitamin B12 deficiency is highlighted as a significant risk factor for cognitive decline, with references to studies on its prevalence and impact.

12. **Bioimpedance Analysis**
    - Bioimpedance analysis is used as a tool to assess body composition, with references to studies demonstrating its effectiveness in predicting weight loss and cognitive decline.

13. **Cohort Studies**
    - Cohort studies are used to track the long-term effects of nutrition on cognitive health, with references to studies on the French REAL.FR cohort.

14. **BMI and Mortality**
    - The relationship between BMI and mortality is discussed, with references to studies showing that lower BMI is associated with increased risk of mortality.

15. **Clinical Nutrition**
    - The role of clinical nutrition in managing dementia is discussed, with references to guidelines and best practices.

16. **Cognitive Impairment**
    - Cognitive impairment is discussed in relation to nutrition, with references to studies on the impact of nutritional status on cognitive function.

17. **Clinical Relevance**
    - The clinical relevance of nutritional interventions is discussed, with references to studies showing improvements in cognitive function and quality of life.

18. **Future Directions**
    - The future directions in nutritional research are discussed, with references to emerging trends and potential areas for further study.

This summary provides a broad overview of the key points discussed in the page, highlighting the importance of nutrition in managing cognitive health and dementia.
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