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NUTRITIONAL PREDICTORS OF COGNITIVE IMPAIRMENT SEVERITY IN DEMENTED ELDERLY PATIENTS: THE KEY ROLE OF BMI

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Abstract: *Introduction:* The body mass index (BMI) is commonly used to assess nutritional status and the Mini Mental State Examination (MMSE) is a validated tool for assessing cognitive status in elderly people. Nutritional and cognitive aspects are closely related in dementia. *Objectives:* To establish whether BMI predicts cognitive decline in demented patients and whether an "alarm" BMI cut-off exists for declining MMSE scores. *Subjects and methods:* 82 elderly demented patients underwent clinical, bio-chemical and functional assessment. *Design:* Transversal study. *Results:* The mean BMI was 26.08±4.48 kg/m^2 and the mean MMSE 18.68±5.38. Patients with BMI<25 kg/m^2 had significantly lower MMSE scores (16.5±5.53 vs 20.38±4.64; p 0.001), fat-free mass (FFM; 27.76±8.99 vs 37.38±10.58 kg; p<0.001), fat-free mass index (FFMI; 11.52±3.03 vs 14.67±2.89 kg/m^2; p<0.001), and fat mass (FM; 24.90±6.89 vs 36.86±6.77 kg; p<0.001), as well as lower Mini Nutritional Assessment (MNA) scores (23.80±2.50 vs 25.00±2.29; p=0.03) and higher vitamin B12 levels (460.95±289.80 vs 332.43±82.07 pg/ml; p=0.01). In the sample as a whole, MMSE scores significantly correlated with scores for MNA (r=0.27, p=0.01), FFM (r=0.27, p=0.01), BMI (r=0.19, p=0.05), ADL (r=0.28, p=0.01) and instrumental activities of daily living (IADL; r=0.34, p=0.002). On multiple logistic regression, BMI<25 kg/m^2 was independently associated with the risk of moderate-severe cognitive impairment (OR=2.96; 95% CI; 1.16-7.55) and female gender was independently associated with severity of dementia (OR=3.14; 95% CI; 1.09-9.03). *Conclusion:* BMI seems to indicate global health status in elderly demented people and a BMI of 25 kg/m^2 can be considered an "alarm" cut-off, lower values coinciding with a worse cognitive status based on MMSE scores.

Key words: Body mass index, cognitive fonction, dementia, Mini Mental State Examination.

Introduction

Nutritional problems are common in elderly demented patients, leading to disability, co-morbidities and mortality, and the potential role of nutrition in preventing cognitive impairment is currently attracting interest.

The body mass index (BMI) is a useful, reproducible method for assessing nutritional status. The cut-off distinguishing underweight from normal conditions differs in the elderly from the one recommended for younger adults (1). For older people, a BMI of 24 kg/m^2 or lower correlates with a higher risk of death (2) and is also indicative of malnutrition, and subjects with a BMI of 25 kg/m^2 or more carry a lower risk of developing dementia than those with a BMI between 20 and 24.9 kg/m^2 (3).

The Mini Mental State Examination (MMSE) is a validated and simple method giving a score that indicates the cognitive status of elderly people; it is used in the diagnosis and follow-up of demented patients.

Nutritional and cognitive status correlate closely via the fat-brain axis (4). Accelerated weight loss sometimes precedes the onset of cognitive impairments and it has also been associated with dementia severity and a faster progression of the disease (5, 6). Chu et al. suggested that a low late-life BMI could be a preclinical marker of mild cognitive impairment (MCI) and Alzheimer's disease (AD) (7); and Cronk et al. found a lower baseline BMI associated with a faster cognitive decline in MCI (8). The relationship between BMI and cognitive status would suggest either that body composition influences the rate of cognitive decline, or that factors related to cognitive impairment influence body composition.

BMI is calculated from a person's height and weight, and therefore both fat mass (FM) and fat-free mass (FFM), which can be estimated using bio-impedance. Buffa et al. assessed the nutritional status of patients with Alzheimer's disease using bioelectrical impedance vector analysis, concluding that the disease is characterized by a tendency to malnutrition developing in the severe stage (9). Other studies confirmed that weight loss is due to the loss of fat mass first, then of lean mass (10, 11).

As mentioned above, many studies have dealt with the role of BMI and its components in early dementia, but few have specifically considered the relationship between BMI and MMSE score (12, 13).

Our study aimed to assess whether BMI predicted the severity of cognitive decline in a group of demented patients, and whether an "alarm" cut-off BMI correlates with a decline in MMSE score.

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Subjects and Methods

Subjects

Subjects over 65 years old attending the Alzheimer's Assessment Unit at the Geriatrics Clinic of Padua University with a diagnosis of dementia were eligible for the study. Dementia was diagnosed according to the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association) (14) for AD, and the NINDS-AIREN (National Institute of Neurological Disorders and Stroke, and Association Internationale pour la Recherche et l'Enseignement en Neurosciences) clinical criteria (15) for vascular dementia. All subjects underwent multidimensional geriatric assessment, including medical examination, biochemical tests, neuroimaging (brain CT or MRI), MMSE and other scores, i.e. ADL (activities of daily living), IADL (instrumental activities of daily living), NPI (Neuropsychiatric Inventory) and GDS (Geriatric Depression Scale).

The exclusion criteria were: neoplastic, kidney, liver or severe heart diseases and their treatment, major disabilities or bedridden status. Subjects who had past or present medical, psychiatric or iatrogenic conditions that can cause cerebral dysfunction were also excluded. Among 149 patients, 82 patients fulfilled these criteria and entered the study.

The study was designed in accordance with the Helsinki Declaration and all participants were fully informed about the nature, purpose and procedures of the study, and gave their written informed consent.

Methods

Patients underwent a global clinical assessment and performed the following tests:

- cognitive evaluation using the MMSE score (16) and disease severity by Clinical Dementia Rating (CDR) (17);
- functional evaluation based on ADL (18) and IADL (19) indexes;
- affective and behavioral status based on the GDS (20) and NPI (21);
- body weight and stature were measured to the nearest 0.1 kg and 0.1 cm with a standard balance and stadiometer (Seca; Germany) with subjects wearing light clothing and no shoes. Their BMI was calculated as their weight in kilograms divided by the square of their stature in meters;
- the Mini Nutritional Assessment score (MNA) (22);
- blood samples were drawn by peripheral venipuncture after 30 minutes of supine rest. Serum concentrations of folate (Advia Centaur Folate; Chiron Diagnostics, USA) and vitamin B12 (Advia Centaur VB12; Chiron Diagnostics) were immunoassayed, the lymphocyte count was determined using Xowcytometry (ADVIA® Hematology system, Siemens), and albumin by nephelometric immunoassay;
- bioelectrical measurements (resistance and reactance) were obtained at a standard frequency (50 kHz and 800 mA; BIA 109 Akern-RJL), with subjects lying comfortably with their limbs abducted from the body. Tetrapolar electrodes were placed according to the method proposed by Lukaski (23). FM and FFM were calculated with NutriPlus software (rel. 5.1) by Data-Input-GmbH. The FM index (FMI) and the FFM index (FFMI) were calculated as the ratio of FM and FFM to the square of the subject's height in meters.

Statistical analysis

Statistical analyses were performed using the SPSS for Windows, rel. 17.0 (SPSS Inc. Chicago). The results are expressed as means ± standard deviation (SD) or percentages. The two-tailed t-test was used for unpaired data, the chi-square test to identify differences between patients with a BMI below and above 25 kg/m^2 (representing the 50th percentile of the BMI values distribution). Pearson's correlation coefficients between assays were determined. A p value <0.05 was considered significant for each two-sided test. The association between different factors and MMSE scores was explored using a multiple logistic regression model, adopting 19 (the 50th percentile of the MMSE score distribution) as the MMSE score cut-off indicating the severity of cognitive deterioration (dependent variable).

Results

Table 1 shows the demographic features of the sample as a whole and by BMI (below or above 25). The mean age was 78.16±5.74 years, the mean weight 65.13±9.90 kg, the mean BMI 26.08±4.48 kg/m^2 and the mean MMSE score 18.68±5.38. No differences were found between the two groups except for living status: fewer subjects with a BMI<25 kg/m^2 lived alone than among the subjects with a BMI≥25 kg/m^2 (p=0.09).

Table 1
Demographic features of patients by BMI

	Whole sample (n=82)	BMI <25 (n=36)	BMI ≥25 (n=46)	p
Age (years)	78.16±5.74	78.78±5.80	77.67±5.72	0.39
Male gender (%)	24/82 (29%)	15/46 (33%)	9/36 (25%)	0.46
Education (years)	6.30± 3.70	6.15±3.90	6.42±3.60	0.26
Living status (% alone)	27%	18%	38%	0.09
Marital status (% married)	14%	17%	11%	0.82

As shown in Table 2, subjects with a BMI<25 kg/m^2 had significantly lower nutritional mean parameters, e.g. FFM (27.76±8.99 vs 37.38±10.58 kg; p<0.001), FFMI (11.52±3.03 vs 14.67±2.89 kg/m^2; p<0.001), and FM (24.90±6.89 vs 36.86±6.77 kg; p<0.001). They also had a lower MNA score (23.80±2.50 vs 25.00±2.29; p=0.03), but higher vitamin B12 levels (460.95±289.80 vs 332.43±82.07 pg/ml; p=0.01). The proportion of people at risk of malnutrition (MNA scores 17 to 23.5) was 26% in the group with BMI≥25 kg/m^2 and 44% in the other group, and nobody had a MNA score lower than 17 (Table 3). Subjects with severe dementia were more numerous

in the BMI<25 group (22% vs 2%), while those with mild-moderate dementia were in higher numbers in the BMI≥25 group (Table 3).

Table 2
Biochemical and nutritional features of patients by BMI

	Whole sample (n=82)	BMI <25 (n=36)	BMI ≥25 (n=46)	p
Lymphocytes (cell/mm³)	5.04±25.07	8.41±36.08	1.89±0.71	0.32
Folates (ng/ml)	5.36±3.39	5.86±3.97	4.95±2.80	0.26
Vitamin B12 (pg/ml)	391.34±213.57	460.95±289.80	5332.43±82.07	0.01*
Albumin (g/dl)	39.93±5.27	40.11±6.05	39.78±4.62	0.79
Fat-free mass (FFM) (kg)	33.16±10.96	27.76±8.99	37.38±10.58	0.001**
Fat-free mass index (FFMI) (kg/m²)	13.28±3.33	11.52±3.03	14.67±2.89	0.001**
Fat mass (FM) (kg)	31.27±8.83	24.90±6.89	36.86±6.77	0.001**
Fat mass index (FMI) (kg/m²)	12.79±3.55	10.49±2.81	14.58±3.00	0.001**
Fat mass %	51.07±10.02	52.22±11.62	50.16±8.59	0.36

Table 3
Percentage of patients with mild, moderate and severe cognitive impairment on MMSE and MNA-based nutritional status in the whole sample and by BMI

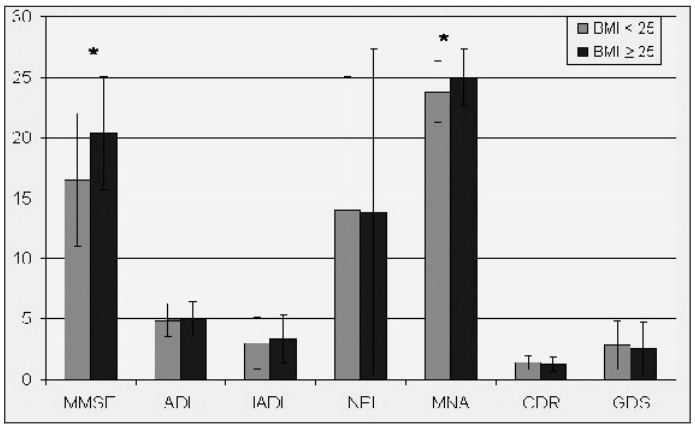
	Whole sample (n=82) % (Mean±SD)	BMI <25 (n=36) % (Mean±SD)	BMI ≥25 (n=46) % (Mean±SD)	p
Cognitive impairment (MMSE score)				
Mild (MMSE 21-23)	36% (24.20±2.39)	33% (25.04±2.36)	39% (22.92±1.88)	0.01
Moderate (MMSE 11-20)	52% (16.77±2.80)	45% (17.68±2.53)	59% (15.22±2.58)	0.004
Severe (MMSE 0-10)	11% (9.42±1.07)	22% (9.42±1.14)	2% (9.4)	NA
Nutritional status (MNA score)				
Normal (MNA>23.5)	65.9 % (25.96±1.32)	55.6% (25.67±1.34)	73.1% (26.13±1.29)	0.22
Risk malnutrition (MNA 17-23.5)	34.1% (21.6±1.28)	44.4% (21.47±1.40)	26.1% (21.78±1.15)	0.54
Malnutrition (MNA< 17)	0	0	0	NA

Finally, as shown in Figure 1, people with BMI<25 kg/m² had lower MMSE scores (16.5±5.53 vs 20.38±4.64; p 0.001) and more severe dementia as expressed by the CDR (1.44±0.58 vs 1.29±0.58; p=0.26). The result was the same when subjects were divided by type of dementia (Alzheimer's vs vascular, data not shown).

In the whole sample, MMSE scores correlated significantly with MNA scores (r=0.27, p=0.01), FFM (r=0.27, p=0.01) and BMI (r=0.19, p=0.05). No correlation was seen with lymphocytes, albumin, folates or vitamin B12. MMSE scores also correlated with scores for ADL (r=0.28, p=0.01) and IADL (r=0.34, p=0.002).

Subjects with a BMI≥25 kg/m² had MMSE scores that correlated significantly with IADL (r=0.35; p=0.01), as seen for patients with a BMI<25 kg/m² (r=0.33; p=0.05). The former group's MMSE scores also correlated significantly with their ADL (r=0.42; p=0.004) and MNA scores (r=0.40; p=0.006).

Figure 1
Cognitive and functional parameters after dividing people for BMI =25



MMSE: Mini Mental State Examination; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; NPI: Neuropsichiatric Inventory; MNA: Mini-Nutritional Assessment; CDR: Cumulative Dementia Rating; GDS: Geriatric Depression Scale. *: p<0.05

On multiple logistic regression (Table 4), a BMI<25 kg/m² was independently associated with the risk of moderate-severe cognitive impairment, i.e. MMSE score <19 (OR=2.96; 95% CI; 1.16-7.55). Female gender was also independently associated with severity of dementia (OR=3.14; 95% CI; 1.09-9.03).

Table 4
Multiple logistic regression model exploring the odds ratio of BMI<25 kg/m² and gender on severity of dementia (MMSE score < 19)

Variables	B	SE	p	OR	95% CI lower limit	95% CI upper limit
Gender: female	1.14	0.54	0.034	3.14	1.09	9.03
BMI <25 kg/m²	1.09	0.48	0.023	2.96	1.16	7.55
Constant	-1.97	0.80	0.014	-	-	-

B: model coefficient; SE: standard error; OR: odds ratio; CI: confidence interval.

Discussion

Our study considered outpatients with an apparently good nutritional status and mild to severe cognitive decline.

For the whole sample, MMSE scores correlated with MNA scores and BMI. The correlation between MMSE and MNA scores had been reported in other studies (24-26), which found the MNA score useful for defining malnutrition (in demented people too). The MNA score has proved more accurate in frail patients (27). In our sample, the absence of under-nourished subjects may explain the weak relationship found between MNA scores and cognitive aspects; on the other hand, our patients were still fairly self-sufficient and had no important medical problems other than dementia.

The NPI score did not differ statistically between the BMI groups, probably because few patients had behavioral problems, though there were more patients with at least one

severe behavioral disorder in the BMI<25 group (4 cases vs 1).

The relationship between MMSE score and BMI had not been studied before; some authors suggest that BMI decreases before cognitive abilities deteriorate, due to neuropathological changes occurring years before the onset of clinical symptoms (28).

To establish whether there is a BMI cut-off that can distinguish people with a worse cognitive status, we divided our population between those with a BMI < or ≥ 25 kg/m^2, the former reportedly identifying subjects at risk of dementia among non-demented people (3). The MMSE scores differed significantly between the two groups and were lower for patients with BMI<25 kg/m^2, which emerged as an independent predictor of severe cognitive impairment (MMSE score <19) with three-fold odds by comparison with patients with a higher BMI. This confirms that BMI≥25 kg/m^2 is associated with a better health status in the elderly, and a BMI of 25 kg/m^2 can be considered an acceptable cut-off for demented people, pointing to a risk of more severe dementia. Among the nutritional parameters, BMI seems to be the most reliable predictor for globally assessing demented patients. Patients with BMI≥25 kg/m^2 had less severe dementia and a lower percentage malnutrition risk than those with BMI<25 kg/m^2 (though the difference was not statistically significant). Given the nature of our study, we cannot say whether cognitive impairment is a cause or a consequence of a worse nutritional status. Further longitudinal studies are necessary.

As expected, FM and FFM were statistically lower in patients with BMI<25 kg/m^2 (and therefore in patients with worse MMSE scores). Our data are consistent with those Wirth et al. found in elderly patients with an altered cognitive status (11). Although FM and FFM are the most accurate in nutritional assessments, they are hard to measure and less useful than BMI in predicting the severity of dementia.

Among the biochemical parameters, about two in three patients had a vitamin B12 deficiency. The Rotterdam Scan Study confirmed that a worse vitamin B12 status is associated with more severe white matter lesions (27). Like Karatela (29), we found lower vitamin B12 levels in patients with BMI≥25 kg/m^2, but the relationship between vitamin B12 and BMI is still unclear.

The first shortcoming of our study is that only demented patients were considered, there was no control group. Another limit relates to the MMSE's inability to detect certain cognitive functions affected early in the course of Alzheimer's disease or other dementias (it includes few memory and verbal fluency items, and no problem-solving or judgment items), its relative insensitivity to very mild cognitive decline (particularly in well-educated individuals), and its susceptibility to floor effects in tracking the progression of dementia in patients with moderate-severe cognitive impairment (30). The small size of our sample also prevents any generalization of our results.

In conclusion, BMI seems to be not only a good nutritional parameter but also an indicator of global health status in elderly demented people. In particular, a BMI=25 kg/m^2 can be considered an "alarm" cut-off below which cognitive status deteriorates.

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