

Original Article

Evaluation of commonly used nutritional assessment methods in hip fracture patients

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Abstract

Objective: Malnutrition is a common problem in hip fracture patients. The prevalence of malnutrition and available nutritional markers for use for nutritional assessment in this population group was investigated. **Methods:** This is a case control study including 214 patients with a hip fracture from "KAT" Hospital in Athens, Greece, and 108 controls from three Elderly Open Protection Centers. Main outcome measures were anthropometric [Body Mass Index (BMI), triceps skinfold thickness (TST) and mid-arm muscle circumference (MAMC)] and biochemical parameters (serum albumin and serum cholesterol). Mini Nutritional Assessment (MNA) was used for malnutrition assessment. **Results:** Based on MNA score only, we found 19.5 % vs. 0.9% malnourished, 54.6% vs. 32.4% at risk and 25.9% vs. 66.7% well-nourished, in hip fracture group and controls, respectively. All anthropometric parameters of malnutrition were significantly lower in the hip fracture patients compared to controls (p value <0.05). Serum albumin and serum-cholesterol levels correlated negatively significantly with s-CRP levels ($R^2=0.247$, $p<0.001$ and $R^2=0.06$, $p<0.001$, respectively) in the hip fracture group. **Conclusions:** Hip fracture patients are often malnourished. MNA application may be helpful in identifying malnourished hip fracture patients. Moreover, serum cholesterol may be a useful marker of malnutrition in hip fracture patients.

Keywords: Hip fracture, Malnutrition, Mini Nutritional Assessment, Anthropometry, Biochemical markers

Introduction

According to the European Society for Clinical Nutrition and Metabolism (ESPEN) "malnutrition due to starvation, disease or ageing can be defined as a state resulting from lack of uptake or intake of nutrition leading to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease"¹. Nutritional care includes assessment of nutrient balance, anthropometry with measurements such as Body Mass Index (BMI), triceps skinfold thickness (TST) and mid arm muscle circumference (MAMC), functional and biochemical variables such as serum albumin and serum cholesterol and clinical signs and symptoms expressed by the patient, according to Nutritional Care Process (NCP)^{2,3}.

Prevalence of malnutrition in the elderly varies largely, as result of the variety in criteria used and different health care settings. Prevalence of malnutrition in the community,

acute care setting, and residential care setting are estimated at about 5-30%, 25-60% and 15-70% respectively⁴. As result of the various physiological, social and economic parameters, often referred to as the "nine d's" (dementia, dysgeusia, dysphagia, diarrhoea, depression, disease, poor dentition, dysfunction, and drugs)⁴, older adults are especially vulnerable to both starvation-related and disease-related undernutrition. Whereas starvation-related undernutrition is caused by insufficient intake only, chronic and acute disease-

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related undernutrition are accompanied by mild to moderate or marked inflammation activity respectively⁵.

Malnutrition is associated with many adverse outcomes including depression of the immune system, impaired wound healing, muscle wasting, longer lengths of hospital stay, higher treatment costs and increased mortality⁶. Malnutrition in hip fracture patients is associated with adverse rehabilitation outcomes⁷⁻¹¹. Moreover, malnourished individuals in all settings use more healthcare resources and experience poor life quality¹². Referral rates for dietetic assessment and treatment of malnourished patients have proven to be suboptimal, thereby increasing the likelihood of developing such aforementioned complications⁶.

“Improving systematic screening, assessment and treatment of malnutrition would result in better nourished patients and this would lead to reduced complications, admissions and length of stay” according to National Institute for Health and Care Excellence (NICE) Clinical Guideline 32¹³ Specifically, after a hip fracture determination of nutritional status is important since appropriate post-operative nutritional care enhances rehabilitation outcome and reduces unfavorable outcomes such as death or other complications^{7,14,15}.

The aims of the study were: a) to explore the nutritional status of hip fracture patients using the MNA score, BMI, MAMC, TST, and biochemical markers of nutritional status and b) to determine the most appropriate nutritional markers to apply to hip fracture patients. For this purpose we compared the nutritional status of 214 hip fracture patients with community dwelling controls living in Greece, which is a South European country with Mediterranean diet habits.

Methods

Study design

Among 480 patients >65 years, with no proven malignancy, with a GFR >30 ml/1,73m²/min who were admitted to “KAT” hospital in Athens, Greece in a 14 month period with a low energy, non pathologic hip fracture (femoral neck and intertrochanteric), 240 were randomly selected (odd numbers) for this study. 26 patients did not accept to participate in the study. The final hip fracture sample was 214 patients. From them, 158 were female and 56 were male. As a control group, 108 community dwelling male and female >65 years old without a history of hip fracture were recruited by a continuous list of membership from three Elderly Open Protection Centers located in the same district area as our hospital. From the total 108 controls participating in the study 84 were female, and 24 were male.

The participation in the study was voluntary and all subjects or/and their carers (in case of severely confused patients) gave their informed consent. The study was conducted in accordance with the World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects and the ethical approval for the study was granted by the Ethics Committee of the Hospital and the

Elderly Open Protection Center’s supervisors.

To accurately evaluate the nutritional status of the hip fracture patients and controls anthropometric, biochemical measurements and the MNA score were used.

Anthropometric measurements and MNA screening tool were administered and recorded by the same dietitian in order to elicit information regarding participants’ nutritional status.

Anthropometry

TST was measured using a Harpenden skinfold calliper and the mid arm muscle circumference (MAMC) measurements were taken at the same mid point as the TST with a non-elastic tape according to standard techniques. Recumbent knee height was measured in the elderly and height was estimated according to Chumlea’s equations: $64.19 - (0.04 * \text{age}) + (2.02 * \text{knee height})$ for men and $84.88 - (0.24 * \text{age}) + (1.83 * \text{knee height})$ for women¹⁶. Body weight was measured in both hospital and home-living group using an electronic wheelchair, to the nearest 0.05 kg. BMI was calculated with the equation $\text{BMI} = \text{body weight} / \text{height}^2$ (kg/m²). In the hip fracture group the body weight measurement was performed after the stabilization of the fracture to protect patients from pain and discomfort. The rest of anthropometric assessment was performed during the 24h after admission.

Biochemistry

Venous blood sampling was performed prior to operation, during the 24h after admission. Plasma was separated and stored at -20°C until analysis. S-alb concentration was analyzed with a quantitative immune-nephelometric method CV 1,71 (Roche/Hitachi902 Boehringer Mannheim Scandinavia AB). The reference interval for albumin is 3.5-5.2 gr/dl. C-reactive protein (CRP) concentration was analyzed with a particle-enhanced immunoturbidimetric assay based upon the reaction whereby increased immunoturbidity occurs when CRP binds with the anti-human CRP antibody CV 4.61 (Roche/Hitachi902 Boehringer Mannheim Scandinavia AB). CRP was measured to assess the level of inflammation or tissue destruction as these also affect albumin levels. CRP levels are raised after trauma but normalize on recovery. Serum creatinine concentration was analyzed with a kinetic colorimetric assay CV2.3 (Roche/Hitachi902 Boehringer Mannheim Scandinavia AB). GFR was calculated by the equation: $175 * \text{standardized SCr}^{1.154} * \text{age}^{-0.203} * 0.742$ (if female). Serum cholesterol concentration was analyzed with an enzymatic colorimetric test CV 1.7 (Roche/Hitachi902 Boehringer Mannheim Scandinavia AB).

The cut-off values for malnutrition for biochemical measurements were arbitrarily defined as 3.5 mg/dl for s-alb and 160 mg/dl for s-chol. Since in Greece there are no national data for MAMC and TST, we followed the recommendations of World Health Organization (WHO)¹⁷. Reference data from National Health and Nutrition Examination Surveys

Anthropometric & Biochemical Parameters	Normal
MAC	>10 th of reference population
TST	>10 th of reference population
S-alb	>3.5 mg/dl
S-chol	>160 mg/dl

Table 1. Anthropometric and biochemical cut-off values.

Variables	Hip fracture group (N=214) Mean±SD	Control group (N=108) Mean±SD	p-value
Age (years)	80.47±7.20	79.03±8.86	N.S.
BMI (kg/cm ²)	26.52±4.9	28.24±4.46	<0.005
MAC (cm)	29.43±4.75	30.75±4.06	<0.05
TST (mm)	17.17±7.15	19.38±6.53	<0.05
S-alb (gm/dL)	3.87±0.54	4.40±0.3	<0.0005
S-chol (mg/dL)	174.66±39.3	211.86±41.05	<0.0005
MNA score	20.62±4.22	24.40±2.8	<0.0005

Table 2. Comparisons between hip fracture patients and controls.

(NHANES III) were used to define normal values¹⁸. MAMC and TST values lower than the 10th percentile of the recordings of the NHANES population for each age decade and sex were defined as subnormal (Table 1).

Mini Nutritional Assessment

The MNA is a sensitive, specific and reproducible tool specifically developed for use in elderly people to detect risk of malnutrition before severe change in serum proteins occurs in geriatric patients¹⁹. The MNA is the most well validated screening tool for the elderly. The original validation study on the full MNA demonstrated that MNA had a sensitivity of 96%, specificity of 98% and positive predictive value of 97% compared to clinical status²⁰. It consists of 18 items divided into four parts: anthropometric measurements (calf and arm circumferences and BMI), general assessment (lifestyle, medications, and mobility), dietary questionnaires (number of meals, fluid and food intake, and autonomy of feeding) and subjective assessments (self-perception for health and nutrition). MNA has been officially translated in Greek; therefore its version was used in our study²¹. The item E of the questionnaire regarding participants' neuropsychological problems was completed by the dietitian's subjective impression and the mental state was assessed either from the patients' medical records, or by the nursing staff and the carers' reports. For the participants who were severely confused, the answers to

non measurable items were checked for accuracy with the carer and/or nursing staff. The scoring system ranges from 0 to 30. A score of less than 17 points indicates malnutrition, 17-23.5 points indicate a risk for malnutrition while score of >23.5 points indicates that the person is well nourished. The MNA was performed during the 24h after admission.

Statistical methods

Data is expressed as mean±standard deviation (S.D.) or median (in case of violation of normality) for continuous variables and as percentages for categorical data. The Kolmogorov-Smirnov test was utilized for normality analysis of the parameters.

Continuous variables were analyzed using the independent samples t-test and Mann-Whitney test (in case of violation of normality). Categorical data were analyzed using Chi-square (χ^2) test and Fisher's exact test.

All tests are two-sided, statistical significance was set at $p<0.05$. All analyses were carried out using the statistical package SPSS v13.00 (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Ill., USA).

Results

The mean age of the hip fracture patients was 80.47 years (± 7.20). From the 214 hip fracture patients, 158 (74%) were female and 56 (26%) were male. 81 (38%) patients had a femoral neck fracture and 133 (62%) patients had an

	MNA Score		
	PEM (<17)	At risk for PEM (17-23.5)	Well-nourished (>23.5)
Hip fracture patients N=214	19.5%	54.6%	25.9%
Controls N=108	0.9%	32.4%	66.7%

Table 3. Classification of hip fracture patients and controls for PEM according to MNA total score.

intertrochanteric fracture. From the control group (N=108), 84 (77.5%) were female and 24 (22.5%) were male. The mean age of the controls was 79.03years (± 8.86). There were no statistically significant differences in the mean age and gender distribution of the two study groups.

Regarding the BMI values, for the hip fracture group underweight (<20 kg/m²) was 8.8% of the patients, 28% (20-25 kg/m²) were normal, 42.4% of the patients were overweight (25-30 kg/m²) and 20.8% of them were obese (>30 kg/m²). For the controls, underweight (<20 kg/m²) was only 0.8% of the patients, 20.7% (20-25 kg/m²) of the patients had a normal weight range, 52.3% were overweight (25-30 kg/m²) and finally 26.1% of the patients were obese (>30 kg/m²).

All anthropometric and biochemical parameters of malnutrition were significantly lower in the hip fracture patients compared to controls (Table 2).

Based on MNA score 19.5% of hip fracture patients were classified as malnourished, 54.6% as at risk of malnutrition and 25.9% as well nourished, while from the control group, 0.9% of controls were classified as malnourished, 32.4% as at risk of malnutrition and 66.7% as well nourished (Table 3).

Regarding s-CRP levels, they were significantly higher in the hip fracture group (median=16.40 (0.70-372.60)) than the reported serum CRP levels of the control group (median=1.40 (0.10-22.00)) ($p < 0.0005$) (Table 2).

In the bivariate analysis, s-alb levels correlated negatively significantly with s-CRP levels (partial correlation, $R^2=0.247$, $p < 0.0005$) in the hip fracture group while there was not revealed any statistically significant correlation in the control group. Similarly, low s-chol levels were negatively correlated with s-CRP levels in the hip fracture while there was no difference in the non-fracture elderly (partial correlation, $R^2=0.06$, $p < 0.0005$).

Discussion

The present study investigated the nutritional status of elderly hip fracture patients compared to controls using anthropometric, biochemical markers and MNA score.

Our findings showed that the two biochemical markers of malnutrition (s-alb and s-chol) were lower in the hip fracture patients than in the controls. Similarly, other researchers found lower s-alb levels in the hip fracture patients compared to controls²². Furthermore, as shown in other studies, low s-alb levels are associated with morbidity and mortality in

hip fracture patients²³. S-alb is a widely used biochemical marker of malnutrition in hip fracture patients, although it could also be attributed to acute phase or immediate response patterns (naturally occurring after trauma) that compromise albumin production^{24,25}. In our study, S-alb was correlated ($p < 0.0005$) with s-CRP which is an indication of inflammation, confirming the hypothesis that the low s-alb in hip fracture patients can be attributed to trauma and not only to malnutrition. Consequently, our findings support the hypothesis that S-alb is a poor malnutrition indication in hip fracture patients and should not be routinely used as part of nutritional assessment in this patient group.

Regarding our findings, s-chol was significantly lower in the hip fracture patients than in the control group, consistent with previous research studies^{26,27}. The lower levels of s-chol in hip fracture patients compared to controls, support the hypothesis that hip fracture patients are more likely to be malnourished than healthy controls. Low levels of s-chol could be caused not only by malnutrition but also by inflammation as well²⁸. In our bivariate analysis that was conducted, statistically significant correlation was found between s-chol and s-CRP ($p < 0.0005$). Nevertheless, only approximately 6% of the variability of s-chol could be explained by CRP in the hip fracture patient group. This finding is consistent with a recent systematic meta-analysis of malnutrition biomarkers among older adults that showed that total cholesterol is a useful biomarker of malnutrition in older adults not only in stable non-hospitalized but also hospitalized in acute care settings older adults²⁵. Consequently, our findings support the hypothesis that s-chol is a malnutrition indication in hip fracture patients and could be routinely used as part of nutritional assessment in this patient group-taken into consideration that only a small part of its variance is attributed by inflammation.

Anthropometric variables were statistically significantly different between the two groups. BMI was significantly lower in the hip fracture patients than in the control group. Our findings are in accordance with previous research where low BMI levels were previously described in elderly with a hip fracture when compared with aged-matched elderly controls²⁶. Nevertheless, the mean of BMI in both groups was >25 kg/m². Based on MNA score -that is a validated nutrition screening tool -19.5% of hip fracture patients were classified as malnourished, 54.6% as at risk of malnutrition and 25.9% as well nourished, while

from the control group, 0.9% of controls were classified as malnourished, 32.4% as at risk of malnutrition and 66.7% as well nourished. Based on the well-accepted BMI cut-off of 18.5 kg/m² provided by World Health Organization (WHO) to define malnutrition only 8.8% of hip fracture patients were classified as malnourished, while from the control group, 0.8% of controls were classified as malnourished. Although MNA score incorporates BMI as an aid in screening for malnutrition, BMI did not perform as well in detecting malnutrition. Consequently, our results, support the use of higher BMI cut-off points to identify malnutrition in older adults. Specifically our results support the use of a cut-off of 22 kg/m² for subjects older than 70 years consistent to the recent ESPEN consensus that suggested using <22 kg/m² in subjects older than 70 years combined with unintentional weight loss in order to warrant identification of all individuals that are at risk of malnutrition¹. A simple adoption of the well-accepted BMI cut-off of 18.5 kg/m² provided by World Health Organization (WHO) to define malnutrition in hip fracture patients whose mean age is 79 years would likely fail to identify some patients who are at risk of malnutrition. This suggestion is in accordance with a recent meta-analysis aimed at evaluating biomarkers associated with risk of malnutrition in older adults with or without acute illness in general²⁵.

Previous surveys exhibited that people with hip fracture have significantly lower MAMC and TST than healthy elderly controls which was also apparent in our study²⁹. MAMC and TST are quick, inexpensive and portable methods of assessing body composition and nutritional status in older adults³⁰. Contrary, body weight measurement and consequently BMI calculation is difficult in this patient group due to mobility restrictions. Consequently, it is of interest from a practice perspective point that MAMC and TST are useful indicators of nutritional status in older hip fracture patients.

MNA screening tool was also used to measure participants' nutritional status. Our findings are in agreement with Murphy's et al study³¹ where in 49 elderly orthopaedic patients, 16% of the group were diagnosed as malnourished, and 47% were at risk of undernourishment, according to the MNA classification. A multicenter prospective cohort study of hip fracture patients using MNA-Short Form also reached to similar conclusions. According to MNA-SF assessments, 51 (25.0%) patients were malnourished, 98 (48.0%) were at risk of malnutrition, and 55 (27.0%) were well-nourished before fracture³².

In conclusion, hip fracture patients are often malnourished. Various simple factors measuring malnutrition may be helpful for the health care professionals in assessing nutritional status and in improving perioperative nutritional care in patients with hip fracture. TST and MAMC measurement are such inexpensive, quick and portable measurements. Moreover MNA, a non-invasive clinical tool, identifies malnourished hip fracture patients earlier than biochemical markers and independently of trauma. Among biochemical

markers of malnutrition serum albumin should not be used in hip fracture patients because its variance can be attributed to trauma inflammation as well. Contrary serum cholesterol could be used as a biochemical indication of nutritional status in hip fracture patients taken into account that its variance is in a limited extend only attributed to trauma inflammation.

References

1. Cederholm, T, et al. Diagnostic criteria for malnutrition-An ASPEN Consensus Statement. *Clin Nutr* 2015;34(3):335-40.
2. Lacey, K and Pritchett, E. Nutrition Care Process and Model: ADA adopts road map to quality care and outcomes management. *J Am Diet Assoc* 2003;103:1061-1071.
3. Elia, M and Russell, C. Compating Malnutrition: Recommendations for Action. Report from the advisory group on malnutrition, led by BAPEN. 2009.
4. Agarwal, E, et al. Malnutrition in the elderly: a narrative review. *2013;76(4):296-302.*
5. White, JV, et al. Consensus statement of the Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *J Acad Nutr Diet* 2012;112(5):730-8.
6. Barker, L, Gout, B and Crowe, T. Hospital Malnutrition: Prevalence, Identification and Impact on Patients and the Healthcare System. *Int J Environ Res Public Health* 2011;8:514-27.
7. Bell, JJ, et al. Multidisciplinary, multi-modal nutritional care in acute hip fracture inpatients-results of a pragmatic intervention. *Clin Nutr* 2014;33(6):1101-1107.
8. van Wissen, J, et al. Mini Nutritional Assessment and mortality after hip fracture surgery in the elderly. *J Nutr Health Aging* 2016;20(9):964-8.
9. Gumieiro, DN, et al. Mini Nutritional Assessment predicts gait status and mortality 6 months after hip fracture. *BrJ Nutr* 2013;109(9):1657-61.
10. Goisser, S, et al. Malnutrition according to Mini Nutritional Assessment is associated with severe functional impairment in geriatric patients before and up to 6 months after hip fracture. *J Am Med Dir Assoc* 2015;16(8):661-7.
11. Nuotio, M, Tuomisen, P and Luukkaala, T. Association of nutritional status as measured by the Mini-Nutritional Assessment short form with changes in mobility, institutionalization and death after hip fracture 2016;70(3): 393-8.
12. Guest, JF, et al. Health economic impact of managing patients following a community-based diagnosis of malnutrition in the UK. *2011;30(4):422-29.*
13. National Institute for Health and Care Excellence (NICE). Nutritional support in adults: oral nutritional support, enteral tube feeding and parenteral nutrition. 2006. Clinical Guidelines 32.
14. Avenell, A, et al. Nutritional supplementation for hip fracture aftercare in the elderly. *Cochrane Database Syst Rev.* 2016;11:CD001880.
15. Hoekstra, JC, et al. Effectiveness of multidisciplinary nutritional care on nutritional intake, nutritional status and quality of life in patients with hipfractures: a controlled prospective cohort study. *Clin Nutr* 2011;30(4):455-61.
16. Grant, A and DeHoog, S. Nutritional assessment and support. Seattle: Grant/Dehoog, 1991. ISBN 0962767808.
17. Group, WHO Working. Use and interpretation of anthropometric indicators of nutritional status. *Bull World Health Organ* 1986; 64:929-41.

18. Kurzmarski, MF, Kurzmarski, RJ and Najjar, M. Descriptive anthropometric reference data for older Americans. *J Am Diet Assoc* 2000;100:59-66.
19. Guigoz, Y. The Mini Nutritional Assessment (MNA). *J Nutr Health Aging* 2006;10(6):466-487.
20. Vellas, B, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition* 1999;15(2):116-22.
21. S.A., Societe des Produits Nestle. www.mna-elderly.com/forms/MNA_greek.pdf. [Online] [Cited: August 20, 2017].
22. Diaz de Bustamante, M, et al. Prevalence of malnutrition in a cohort of 509 patients with acute hip fracture: the importance of a comprehensive assessment. *Eur J Clin Nutr* 2017. Epub ahead of print.
23. Bajada, S, Smith, A and Morgan, D. Pro-operative nutritional serum parameters as predictors of failure after internal fixation in undisplaced intracapsular proximal femur fractures 2015;46(8):1571-6.
24. Cabrerizo, S, et al. Serum albumin and health in older people: Review and meta analysis. *Maturitas* 2015;81(1):17-27.
25. Zhang, Z, et al. Evaluation of Blood Biomarkers Associated with Risk of Malnutrition in Older Adults: A systematic review and meta-analysis. *Nutrients* 2017;9(8). pii: E829.
26. Lumbers, M, et al. Nutritional status in elderly female hip fracture patients: comparison with an age-matched home living group attending day centers. *Br J Nutr* 2001;85:733-740.
27. Formiga, F, et al. No correlation between mini-nutritional assessment (short form) scale and clinical outcomes in 73 elderly patients admitted for hip fracture. *Aging Clin Exp Res* 2005;17(4):343-6.
28. Ettinger, WH, et al. Evidence for inflammation as a cause of hypocholesterolemia in older people. *J Am Geriatr Soc* 1995;43(3):264-6.
29. Paillaud, E, et al. Nutritional status and energy expenditure in elderly patients with recent hip fracture during a 2-month follow up. *Br J Nutr* 2000;83(21):97-103.
30. Powell-Tuck, J and Hennessy, EM. A comparison of mid upper arm circumference, body mass index and weight loss as indices of undernutrition in acutely hospitalized patients. *Clin Nutr* 2003;22:307-12.
31. Murphy, MC, et al. The use of the Mini-Nutritional Assessment (MNA) tool in elderly orthopaedic patients. *Eur J Clin Nutr* 2000;54:556-562.
32. Inoue, T, et al. Pre-fracture nutritional status is predictive of functional status at discharge during the acute phase with hip fracture patients: A multicenter prospective cohort study. *Clin Nutr* 2017;36(5):1320-1325.