Progress in Nutrition 2020; Vol. 22, N. 1: 30-35 DOI: 10.23751/pn.v22i1.7951

Original article

Strong association between malnutrition, inflammation, and depression in elderly patients. A new novel geriatric complex based on malnutrition; MID complex?

İbrahim Halil Türkbeyler[1], Zeynel Abidin Öztürk[2], Zeynel Abidin Sayiner[3], Mehmet Gol[4], Eyüp Murat Efendioglu[1], Seyma Sahinbeyoglu[1]

[1]Ersin Arslan Education and Research Hospital, Department of Internal Medicine, Division of Geriatric Medicine, 27100 Sahinbey, Gaziantep, Turkey - E-mail: turkbeyler@mynet.com; [2]Gaziantep University, Faculty of Medicine, Department of Internal Medicine, Division of Geriatric Medicine, 27100 Sahinbey, Gaziantep, Turkey; [3]Gaziantep University Faculty of Medicine, Department of Internal Medicine Division of Endocrinology, 27100 Sahinbey, Gaziantep, Turkey; [4]Faculty of Medicine, Department of Physiology, Gaziantep University, 27100, Sahinbey, Gaziantep, Turkey

Summary. *Background/Aim:* The proportion of elderly individuals is increasing worldwide and geriatric syndromes (GS) are associated with a decreased life span. Malnutrition and depression are highly prevalent among the elderly and associated with poor clinical prognosis. This study investigated the frequency of inflammation and depressive symptom comorbidity in the context of a cause-and-effect relationship among elderly patients with malnutrition and/or malnutrition risk. *Material and Methods:* Participants in this cross-sectional study included 217 individuals aged 65 years and over. Comprehensive geriatric assessment was performed to participants. Malnutrition and depression were diagnosed according to the Mini-Nutritional Assessment (MNA-SF) Tool and Yesavage Geriatric Depression Scale (YGDS), respectively. Inflammation status were diagnosed according to the C-reactive protein (CRP) levels. *Results:* According to MNA-SF, 41 (18.9%) patients were malnourished, 82 (37.8%) at a risk of malnutrition, and 94 (43.3%) possessed normal nutrition. Among the malnourished patients, 51.2% experienced CRP elevation and 70.7% displayed symptoms of depression. Patients at risk of malnutrition experienced 39.0% CRP elevation, and 46.3% displayed depression symptoms. There was a statistically significant negative correlation between MNA-SF scores and YGDS and CRP (r: -0,201, p: 0,003, r: -0,495, p: 0,000, respectively). The incidence of inflammation-depression association in malnourished patients was 36.6%, 12.2% in those at risk for malnutrition, and 10.6% in those with normal nutrition. *Conclusion:* Physicians should be informed regarding the association among malnutrition, inflammation, and depression in geriatric patients.

Key words: malnutrition; inflammation; depression

Introduction

In comparison to the general population, the proportion of elderly individuals is increasing worldwide. According to data reported by the Turkey Statistical Institute, the geriatric population constitutes 8.2% of the total population in Turkey (1). In developed countries, the geriatric population has risen to 15%, and it is estimated that 22% of the world's population will be elderly by 2020 (2).

In elderly patients, geriatric syndrome (GS) refers to clinical conditions comprised of atypical symptoms and cannot be fully explained by a specific disease definition. In addition, Kane et al. have proven that GS is associated with a decreased life span (3).

Geriatric malnutrition is a major problem worldwide. Malnutrition is highly prevalent among the elderly and is associated with poor clinical prognosis, decreased functional status, and increased morbidity and mortality (4). Among patients diagnosed with

GS, the prevalence of geriatric malnutrition has been found to be 22.8% (5). Moreover, inflammation plays an important role in the development of GS and is thought to be related to malnutrition (6). Depression is a common health problem among elderly individuals which impacts several functions, leads to public health expenditure, and increases mortality rates (7). According to a recent meta-analysis, the prevalence of major depression ranged from 4.6% to 9.3%, and the prevalence of all depressive symptoms ranged from 4.5% to 37.4% among individuals aged 75 years and older (8). In several other studies, the role of inflammation in the etiopathogenesis of depressive disorders has been supported in different ways. In recent years, findings supporting the elevation of proinflammatory cytokine levels in patients diagnosed with depressive disorders has increased (9).

This study investigated the frequency of inflammation and depressive symptom comorbidity in the context of a cause-and-effect relationship among elderly patients with malnutrition and/or malnutrition risk.

Material and Methods

Subjects

Participants in this cross-sectional study included 217 individuals aged 65 years and over who had been admitted for routine medical care to the outpatient clinic of the Department of Internal Medicine, Division of Geriatric Medicine at Gaziantep University Hospital. All patients were administered comprehensive geriatric assessment tests via a one-on-one interview method. Patient demographics were also recorded during this interview, including age, sex, height, weight, marital status, household size (including spouse, children, and relatives), educational status, exercise habits, comorbidities (diabetes mellitus, cardiovascular diseases, neuropsychiatric diseases, musculoskeletal diseases, and respiratory system diseases) and polypharmacy status (currently using ≥4 drugs). Patients excluded from this study were those under 65 years of age; those with active malignancy or a gastrointestinal pathology directly causing malnutrition; those residing in nursing homes; those with visual or hearing problems potentially complicating the interview; those with schizophrenia, mental retardation, and/or bipolar disorder; and those with a Mini-Mental State Examination (MMSE) score less than 17. All participants provided informed consent, and the procedures followed throughout the course of this study were in accordance with the institutional ethical standards of the responsible committee on human experimentation. The study protocol was approved by the Gaziantep University Local Research Ethics Committee.

Comprehensive Geriatric Assessment Tests

Patients were administered a standardized comprehensive geriatric assessment, and detailed patient histories were recorded using several clinical testing modalities including the 15-question Yesavage Geriatric Depression Scale (YGDS) (10), MMSE (11), Barthel Index of Daily Living Activities (12), Lawton-Brody Instrumental Activities of Daily Living Scale (13), and an abbreviated form of the Mini-Nutritional Assessment (MNA-SF) Tool (14). MMSE assesses five different areas in cognitive functions such as orientation, registration, attention and calculation, recalll and language. Moreover, GDS scores of 5 and over indicate depression. The nutritional status of participants was determined by utilizing the MNA-SF, which is a simple and validated screening tool for nutritional risk. Scores ≤7 indicate malnutrition, those 7-11 indicate malnutrition risk, and those >12 designate normal nutritional status.

Blood Samples

Blood samples were obtained between 8:30 and 10:00 a.m. from the antecubital veins of all subjects, who had fasted for at least eight hours prior. The results of laboratory tests consisting of complete blood count analysis (CBC), erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP) were analyzed via a hospital auto-analyzer. Moreover, CBC analysis was performed via a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer within 2 hours.

Statistical Analysis

SPSS 17.0 software for Windows was utilized for statistical analysis. All data were entered into a database and verified by a second independent person. The variables were examined using visual (histograms and

probability plots) and analytical methods to determine whether or they were normally distributed. Data are presented as mean ± SD for normally distributed variables and as median (minimum-maximum) ± IQR for skew-distributed continuous variables. Categorical variables are displayed as frequencies. The Pearson's Chi-square method for categorical parameters and the Mann–Whitney U Test for skew-distributed parameters were conducted for univariate analysis. Moreover, correlation analyses were performed via the Spearman's Rank Correlation Analysis for Non-Normal Data, and two-sided values of p< 0.05 were considered as statistically significant. A One-way ANOVA was used to compare normally distributed variables, and the Levene Test was employed to assess the homogeneity of variances. Post-hoc Tukey or Tamhane T2 tests were performed according to the homogeneity of variances.

Results

Patient ages ranged from 65 to 90 years, and the median age was 72.48 ± 5.98 years. A total of 128 patients (59%) were female and 89 (41%) were male. According to MNA-SF, 41 (18.9%) patients were malnourished, 82 (37.8%) at a risk of malnutrition, and 94 (43.3%) possessed normal nutrition. The current study observed that malnutrition and/or malnutrition risk increased in elderly patients who were living alone and unmarried (p> 0.005). In terms of laboratory values, Hb decreased while PLT, CRP, and ESR increased in elderly patients with malnutrition/malnutrition risk compared to elderly patients with normal nutrition (p <0,05). The amount of medication used regularly by patients ranged from 0 to 20 units, and the mean amount was 4.67 ± 2.98. The most common diseases were diabetes mellitus, cardiovascular disease, neuropsychiatric disease, musculoskeletal disease, and respiratory system disease, respectively. Patients' social and demographic information is displayed in Table 1. There was a statistically significant difference between the groups according to the MNA-SF score in terms of YGDS, Bartel ADL, Lawton-Brody IADL, loneliness frequency, marital status, walking speed, hand strength, CRP, ESR, and PLT (p<0005) (Table 1). Among the malnourished patients, 51.2% experienced CRP elevation and 70.7% displayed symptoms of depression. Patients at risk of malnutrition experienced 39.0% CRP elevation, and 46.3% displayed depression symptoms. There was a statistically significant negative correlation between MNA-SF scores and YGDS and CRP (r: -0,201, p: 0,003, r: -0,495, p: 0,000, respectively) (Table 2). The incidence of inflammation-depression association in malnourished patients was 36.6%, 12.2% in those at risk for malnutrition, and 10.6% in those with normal nutrition.

Discussion

Over the past century, the improvement of living conditions, technology, and science as well an increase in the elderly population has continued. With this increase, the frequency of GS in malnutrition-depression patients has increased, as well. This study is the first study that demonstrates the relationship among malnutrition, depression, and inflammation in elderly patients. Besides this is the first usage of the term of MID (Malnutrition, Inflammation, Depression) complex.

Malnutrition among the elderly is a public health problem that is important and often neglected. Moreover, it has been shown that more than one-third of the elderly (37-40%) are unable to meet their daily energy needs from food on a daily basis and that two out of three elderly individuals skip at least one meal a day (16). Studies have demonstrated that deteriorating nutritional health among the elderly decreases their quality of life, increases their hospital visits and lengths of stay, increases their frequency of infection, delays wound healing, disturbs their gait, increases their fall-fracture risk, and increses the likelihood of sudden death (17). The present study observed that the Bartel GYA, Lawton-Brody EGYA, YSGD, and hand - muscle strength values of elderly patients malnourished or at risk of malnutrition were negatively affected (p <0,05) compared to elderly patients with normal nutrition.

The second factor examined in this study, inflammation, plays a protective role in the body. Acute phase response is a major pathophysiologic event that accompanies inflammation and is associated with the increased activity of proinflammatory cytokines. If increased inflammation becomes permanent, a decrease

Table 1. The social and demographic distribution of the patients. Various letters describe statistically significant difference.

	Malnutrition	With Malnutrition Risk	Normal Nutrition	P
N:217	41	82	94	
Age	74.1±7.5	72,8±6,1	71,5±4,9	0,054
Gender				
· Male	31.7%	43.9%	42.6%	0,398
· Femal	68.3%	56.1%	57.4%	
Smoking (+)	%24.4(10)	24,4%(20)	20,2%(19)	0,765
Alcohol (+)	2,4%(1)	9,8%(8)	5,3%(5)	0,232
Exercise (+)	14,6%(6)	30,5%(25)	19,1%(18)	0,080
Living Alone	31,7%(13)[a]	20,7%(17)[b]	12,8%(12)[c]	0,003
Education Status				
· Unaeducated	51,2%(21)	50%(41)	59,6%(56)	0,103
· Elementary	46,3%(19)	34,1%(28)	24,5%(23)	
· High School	2,4%(1)	7,3%(6)	9,6%(9)	
· College	0%	8,5%(7)	6,4%(6)	
Diagnosis				
· Diabetes mellitus	46.3%(19)	39,0%(32)	29,8%(28)	
· CVD	29,3%(12)	39,0%(32)	35,1%(33)	0,187
· SVD	14,6%(6)	9,8%(8)	9,6%(9)	
· Respiratory Diseases	4.9%(2)	3,7%(3)	12,8%(12)	
· Musculoskeletal Diseases	4.9%(2)	8,5%(7)	12,8%(12)	
Marital Status				
· Married	53,7%(22)a	75,6%(62)[b]	76,6%(76)[b]	0,015
Barthel ADL	3,68±7,02/±1,10[a]	2,42±6,19/±0,68[b]	0,87±3,58/±0,37[c]	0,015
Number of daily drugs	5,39±2,75	4,70±3,45	4,32±2,63	0,188
Lawton Brody IADL	9,44±6,20[a]	12,03±5,42[b]	13,11±4,01[b]	0,001
MMSE	25,95±4,09	25,81±4,18	26,00±3,18	0,971
MNA-SF	6.78±1,84[a]	9,46±1,60[b]	12,44±1,77[c]	0,000
YGDS	6.42±3.96[a]	5.87±3.98[a]	4.41±3.39[b]	0,011
CRP	10.7±8.7[a]	7.2±6.6[b]	3.6±3.4[c]	0,001
ESR	42,14±25,80[a]	23,62±17,90[b]	17,79±12,80[c]	0,000
Hemoglobin	11,79±1,54[a]	13,38±1,60[b]	13,66±1,49[b]	0,000
White blood cell	8243±2463	8074±2460	7736±2368	0,466
Platelets	324.550±122.362[a]	262.797±65.383[b]	253.963±69.171[b]	0,000
CRP>5	51.2%(21)[a]	39,0%(32)[b]	14.6%(20)[c]	0,039
YGDS>5	70,7%(29)[a]	46,3%(38)[b]	21,3%(20)[c]	0,012
CRP>5+YGDS>5	36.6%(15)[a]	12.2%(10)[b]	10.6%(10)[b]	0,002

CVD: cardiovascular diseases, SVD: Serebrobascular diseases, ADL: activities of daily living, IADL: Instrumental activities of daily living, MMSE: mini-mental state examination, MNA-SF: mini-nutritional assessment, YGDS: Yesavage Geriatric Depression Scale, ESR: erythrocyte sedimentation rates, CRP: C-reactive protein

Table 2. The correlation between MNA(SF), YGDS, and CRP

	MNA(SF)		YGDS		CRP	
	r	p	r	p	r	p
MNA(SF)	1		-0.201	0.003	- 0.495	0.000
YGDS	-0.201	0.003	1		0.264	0.000
CRP	-0.495	0.000	0.264	0.000	1	

in appetite can lead to negative consequences such as skeletal muscle loss and protein loss in tissues. It is also believed that inflammation plays an important role in the prevalence of aging-related cardiovascular disease and mortality (18-20). In older people, increased IL-6 and CRP have been shown to increase mortality, cause functional regression, and reduce physical activity (21-23). Yukiko et al. have observed that higher levels of plasma tumor necrosis factor alpha (TNF-α) are associated with various parameters related to the nutritional status of the elderly (24). In the present study, the ESR and CRP values of patients with malnutrition and/or malnutrition risk were significantly higher than those with normal nutrition ($p < 0.005$). Moreover, there was a statistically significant negative correlation (r: -0.495, p: 0.000) between MNA-SF scores and CRP in all patients with CRP elevation in more than half of malnourished patients (51.2%).

In addition to inflammation and malnutrition, depression also significantly impacts much of the elderly population. Studies have demonstrated that inflammatory responses play an important role in the pathophysiology of depression. In patients with depression, higher proinflammatory cytokines, acute phase proteins, chemokines, and cellular adhesion molecules are higher (25,26). In a population study conducted among 2,861 individuals, a positive correlation was observed between depressive symptoms and IL-6, TNF-α and CRP (27). Moreover, a relationship between the somatic symptoms of both depression and anxiety and IL-6, TNF-α and CRP levels was observed. Thus, it has been suggested that the somatic symptoms of depression and anxiety may be related to inflammation (27). Psychological stress can also increase inflammatory response via sympathetic and parasympathetic pathways (28). The results of the present study have demonstrated a positive correlation between CRP elevation and YGDS as well as CRP levels in 34% of patients with depressive symptoms. Patients who were either malnourished or at risk for malnutrition also exhibited increased depressive symptom frequency (r: 0,264, p: 0,000). While 14.6% of patients with depressive symptoms also experienced malnutrition and inflammation, 24.3% experienced malnutrition risk and inflammation comorbidity.

Regarding the association among malnutrition, inflammation, and depression, Choi et al.'s recent study among chronic hemodialysis patients described these, along with atherosclerosis, as a MIDA complex proven to be an independent risk factor for cardiovascular disease as well as chronic hemodialysis for all causes of death (29).

Limitations

There are some limitations of the present study that should be considered when interpreting the findings. First, CRP in this study were only measured once, so it was not possible to determine whether an acute and brief episode of infection or chronic inflammation was responsible for the observed correlation. Moreover, as this study was cross-sectional in design, it was not possible to establish a causal relationship among malnutrition, inflammation, and depression. Further studies conducted among a larger number of participants over a longer period of time are warranted to confirm the cause-and-effect relationship among MID complex components.

Conclusion

Depression and inflammation may occur frequently as well as simultaneously in elderly malnutrition patients. Thus, physicians in outpatient clinics should be informed regarding the association among malnutrition, inflammation, and depression in these individuals. Finally, in the presence of one or two MID components, physicians should seek to identify the second or/and third components. But further comprehensive studies are needed to gain general acceptance of MID complex in the clinics.

References

1. TUIK, 2016, TC. Turkish Statistical Institute The Results of Address Based Population Available from: http://www.tuik.gov.tr/ doid=246382016. Number: 21507, 26 January 2017.
2. Situation of Elderly People in Turkey and National Action Plan on Ageing. General Directorate of Social Sectors and Coordination; The Repuclic of Turkey: 2007.
3. Kane RL, Shamliyan T, Talley K, Pacala J. The association between geriatric syndromes and survival. J Am Geriatr Soc 2012; 60(5): 896-904.
4. Harith S, Shahar S, Yusoff M, Kamaruzzaman B, Hua P. The magnitude of malnutrition among hospitalized elderly patients in university Malaya medical centre. Health Environ J. 2010;1:64-72.
5. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Frequency of malnutrition in older adults: a multinational perspective using the mini nutritional assessment. Journal of the American Geriatrics Society. 2010;58(9):1734-8.
6. Shingh T, Newman AB. Inflammatory markers in population studies of aging. Aging Res Rev 2011;10: 319-329.
7. Taylor WD. Clinical practice. depression in the elderly. N Engl J Med 2014;371:1228.
8. Luppa M, Luck T, König HH, Angermeyer MC, Riedel-Heller SG. Natural course of depressive symptoms in late life. An 8-year population based prospective study. Journal of Affective Disorders 2012;142 (1-3):166-71.
9. Krishnadas R, Cavanagh J. Depression: an inflammatory illness? J Neurol Neurosurg Psychiatry 2012; 83:495-502
10. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982–1983; 17: 37–49.
11. Folstein MF, Folstein SE, McHugh PR Mini-Mental State: A practical method for grading the cognitive state of patients for clinician. J Psychiatr Res, 1975;12: 189-98.
12. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. Md State Med J. 1965;14:61-65.
13. Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist 1969;9(3):179-86.
14. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. The journal of nutrition, health & aging. 2009;13(9):782-8.
15. Bahat G, Tufan A, Tufan F, Kilic C, Akpinar TS, Kose M, Erten N, Karan MA, Cruz-Jentoft AJ. Cut-off points to identify sarcopenia according to European Working Group on Sarcopenia in Older People (EWGSOP) definition. Clin Nutr. 2016 Dec;35(6):1557-1563. doi: 10.1016/j.clnu.2016.02.002.
16. Morley JE. Anorexia of aging: physiologic and pathologic. Am J Clin Nutr 1997;66:760-73.
17. Agathe Raymond-Simon. Virtual Clinical Nutrition University: Malnutrition in The Elderly, Epidemiology and Consequences. E-SPEN. 2009;4(2):86-89.
18. Newman Dorland W, Anderson D. Dorland's Illustrated Medical Dictionary. Philadelphia, PA: Saunders; 2000.
19. Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340:448-54.
20. Suffredini AF, Fantuzzi G, Badolato R, Oppenheim JJ, O Grady NP. New insights into the biology of the acute phase response. J Clin Immunol. 1999;19:203–14.
21. Maggio M, Guralnik JM, Longo DL, Ferrucci L. Interleukin 6 in aging and chronic diseases: a magnificient pathwaty. J Gerontol A Biol Sci Med Sci 2006;61:575-584.
22. Trayhurn P, Wood IS. Signalling role of adipose tissue. Adipokines and inflammation in obesity. Biochem Soc Trans 2005;33:1078-1081.
23. Reuben DB, Cheh AI, Harris TB, Ferruci L, Rowe JW, Tracy RP et al. Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons. J Am Geriatr Soc. 2002 Apr;50(4):638-44.
24. Oe Y, Mochizuki K, Miyauchi R, Misaki Y, Kasezawa N, Tohyama K et al. Plasma TNF-α Is Associated with Inflammation and Nutrition Status in Community-Dwelling Japanese Elderly. J Nutr Sci Vitaminol (Tokyo). 2015;61(3):263-9. doi: 10.3177/jnsv.61.263.
25. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 2009; 71:171-186.
26. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK et al. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010; 67:446-457.
27. Duivis HE, Vogelzangs N, Kupper N, de Jonge P, Penninx BW. Differential association of somatic and cognitive symptoms of depression and anxiety with inflammation: findings from the Netherlands Study of Depression and Anxiety (NESDA). Psychoneuroendocrinology 2013; 38:1573-1585.
28. Raison CL, Capuron L, Miller AH.Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006 Jan;27(1):24-31.
29. Choi MJ, Seo JW, Yoon JW, Lee SK, Kim SJ, Lee YK, et al. The malnutrition-inflammation-depression-arteriosclerosis complex is associated with an increased risk of cardiovascular disease and all-cause death in chronic hemodialysis patients. Nephron Clin Pract. 2012;122(1-2):44-52.

Correspondence:
Asoc. Prof.Ibrahim Halil Turkbeyler,
Dr. Ersin Arslan Education and Research Hospital, Department of Internal Medicine, Division of Geriatric Medicine, 27100 Sahinbey, Gaziantep, Turkey.
E-mail: turkbeyler@mynet.com