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## RESEARCH ARTICLE

### A Randomized Clinical Trial of the Effect of Zinc Supplement on Depression and Anxiety in the Elderly

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#### Abstract:

#### Background:

Anxiety and depression in the elderly are considered important mental disorders.

#### Objective:

This study was designed to determine the effect of zinc supplementation on depression and anxiety in the elderly.

#### Methods:

This study was a parallel randomized clinical trial. A total of 150 elderly aged 60 years and older were allocated into intervention and control groups by using the quadruple blocking method. The elderly in the intervention group received a daily dose of 30 mg zinc supplementation pill for 70 days and the elderly in the control group did not receive this supplement. Depression and anxiety in the elderly were measured using the Geriatric Depression Scale and the Beck Anxiety Inventory, respectively. A significance level of 0.05 was considered for all statistical tests.

#### Results:

After the intervention, the mean scores of depression and anxiety in the elderly were significantly decreased in the intervention group, as compared with the control group. Moreover, after the intervention, the serum zinc level in the elderly was significantly increased in the intervention group, as compared with the control group ( $P < 0.05$ ).

#### Conclusion:

The use of zinc supplements improved depression and anxiety in the elderly. Therefore, it is recommended to use zinc supplements as a new therapeutic strategy for the prevention and treatment of depression and anxiety in the elderly.

Registration No: This research was registered in the Iranian clinical trial system with code IRCT2017071635110N1.

**Keywords:** Anxiety, Depression, Elder, Geriatric nursing, Mood disorders, Zinc.

#### Article History

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## 1. INTRODUCTION

Aging has increased in the last decade worldwide [1]. Because of aging and related problems, the elderly would

suffer from at least a physical or mental illness with complicated conditions [2]. Paying attention to the mental health of the elderly is an important issue. One of the most important issues in mental health is depression and anxiety disorders, and the elderly are vulnerable in this area for many reasons [3]. Depression identifies as one of the main causes of disability which is one of the most common psychiatric

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disorders and a common risk factor for suicide in the elderly [4]. In a review and meta-analysis study, the prevalence of depression in the Iranian elderly was reported to be 43% [5]. Depression can lead to many problems and complications such as impaired individual function, reduction and withdrawal from treatment, reduced quality of life and increased risk of suicide [6].

One of the most common psychiatric disorders in years of aging is anxiety [7], which often occur concurrently with depression [8]. Depression and anxiety disorders as mood disorders are prevalent among elderly people [9] and associated with an increased risk of aging-related diseases, which almost contribute to morbidity and mortality in afflicted people [10]. Many physical illnesses are associated with mood disorders in the elderly [11]. Benzodiazepines and tricyclic antidepressants are among the most important medications for the treatment of mood disorders. Despite their benefits, anxiolytics such as benzodiazepines have side effects such as dependence; though less severe, these types of complications are also observed in tricyclic antidepressants [12, 13]. Some non-pharmaceutical interventions are also recommended for the treatment of depression and anxiety. These interventions include group recitation of memories, group therapy, social support, group counseling, music therapy, and life review, which in all cases have reduced the amount of depression in the elderly [14 - 17]. Also, the use of nutritional strategies is effective in improving the symptoms of mood disorders [18]. For example, the use of zinc supplements [19].

Moreover, the study of nutritional status in the elderly indicates that there are many shortcomings and problems, and many diseases are associated with nutritional problems [20]. Estimates have shown that about two billion people in developing countries are suffering from zinc deficiency [21]. Studies have shown that zinc is effective in regulating mood, and there is a relationship between zinc and psychiatric disorders such as depression and anxiety [22, 23]. Mental disorders, especially depression and anxiety, are a major problem in the elderly, which in addition to their psychological impact, can affect the physical status of the elderly. Prevention and treatment of depression and anxiety in the elderly is a critical issue; zinc supplements may have a potent effect on the mentioned problems. There is a controversy in recent studies that have investigated the effects of zinc supplements on depression and anxiety. For example, in a study by A.J. Russo (2011), zinc supplementation improved the anxiety symptoms, while in a study by Stewart-Knox *et al.* (2010), zinc supplements did not affect the participants' mood [24, 25]. In addition, we did not find any appropriate study investigating the effect of zinc supplements on depression and anxiety in the elderly. This study examines the effect of zinc supplements on depression and anxiety in the elderly.

## MATERIALS AND METHODS

### 2.1. Study Design

This parallel randomized clinical trial was registered in Iran's clinical trial system (Registration Code: IRCT2017071635110N1). In this study, the questioners and the analyzer were blinded to the allocation of the participants in

two groups.

### 2.2. Inclusion Criteria

Being 60 years or older, the ability to speak Persian and answer questions, Iranian citizenship, not taking zinc supplements, lack of renal and intestinal diseases as diagnosed by a physician, and lack of cognitive impairment (in the illiterate group it was determined based on the Abbreviated Mental Test Score (AMTS) score of 7 or higher [26], and in the literate group, which was determined based on the Mini-Mental State Examination (MMSE) score of 25 or higher [27], which indicates the non-existence of cognitive impairment.

### 2.3. Exclusion Criteria

Refusal to continue the use of zinc supplements, taking zinc supplements by the subjects in the control group during the 70 days of intervention, known cases of depression and anxiety who had been diagnosed by a physician before the start of the study, the occurrence of any severe stress such as hospitalization or death of a close relative in the two groups during the research.

#### 2.3.1. Sample Size and Sampling Method

Consistent with a study by M.A. Gosney *et al.* (2008) [28], we set a confidence interval of 95% and a strength of 80% and the total sample size was determined to include 104 people, with 52 samples in each group. In order to increase the effectiveness of the study and generalize the results of the study more comprehensively, and considering a drop in the subjects, the total sample size was set as 150 subjects, with 75 members in each group.

To conduct sampling at the city level, firstly, the health centers covering the desired population groups were clustered. Then, four health centers were selected based on socio-economic conditions of people and consistent with the statistical data of the health deputy of Kashan. In the next stage, taking into account the ratio of the elderly in each cluster, stratified sampling was performed. The random allocation and quadruple blocks were done by a statistician using software and the participants were divided into two groups: A (intervention) and B (control). The randomization sequence was carried out secretly. Accordingly, 38 envelopes containing quadruple codes were prepared. After ensuring the eligibility of each subject, the researcher selected an envelope and allocated the member as specified in the envelope.

### 2.4. Measuring Tools

Data collection tool and method of implementation: Data collection tools used in this study included a demographic questionnaire, Geriatric Depression Scale (GDS), Beck Anxiety Inventory (BAI), interviews for the evaluation of cognitive status, and serum zinc level measurement (through sampling blood and sending to a library).

The individual demographic questionnaire collected data on age, gender, marital status, education level, and income level.

15-item Geriatric Depression Scale (GDS) was used in

order to assess depression in the elderly; it was designed and validated by Yesavage *et al.* (1983) to estimate depression in the elderly [29]. This tool was evaluated and validated in Iran by Malakoti *et al.* (2006) and its Cronbach's alpha and validity were 0.9 and 0.89, respectively. The classification of depression in this scale is as follows: the scoring system of the questionnaire has a total of 15 points that are determined via yes or no answers. A score of 0-4 is normal, a score of 5-8 indicates mild depression, a score of 9-11 indicates moderate depression, and a score of 12-15 shows a severe depressive disorder [30].

Beck Anxiety Inventory, designed by Beck *et al.* (1990), was used to assess anxiety in the elderly [31]. This questionnaire was validated in Iran by Kaviani *et al.* and it has appropriate validity ( $r=0.72$ ,  $p<0.001$ ), reliability ( $r=0.83$ ,  $p<0.001$ ), and internal consistency ( $\text{Alpha}=0.92$ ). This test, in addition to diagnostic capabilities, can also be used for treatment. The questionnaire has 21 questions, each scored from 0 to 3 points. Based on the scores obtained in this questionnaire, anxiety is classified as follows: a score of 0-7 indicates no or minimum anxiety, a score of 8-15 indicates mild anxiety, a score of 16-25 indicates moderate anxiety, and a score of 26-63 indicates severe anxiety [32].

In order to evaluate the cognitive status in the illiterate elderly, the Abbreviated Mental Test (AMTS) questionnaire was used. The questionnaire, with 10 questions, was first used by Hutchinson in 1972. The overall score is calculated based on the number of correct answers [33]. In addition, Mini-Mental State Examination (MMSE) was used to assess the cognitive status of the literate elderly. This questionnaire was introduced in 1975 by Folstein, and it has a score of 30 points [34]. This questionnaire was validated in Iran by Seyedian *et al.*; based on the results of the mentioned study, a sensitivity of 90% and a specificity of 93.5% were reported. Moreover, considering the Cronbach's alpha coefficient for the whole questionnaire, its reliability was 0.81 [35].

Normal serum zinc level level was set at 72.6-127  $\mu\text{g}/\text{dL}$  for males and 70-114  $\mu\text{g}/\text{dL}$  for females [36]. Serum zinc level was measured by OLYMPUS AU400 auto-analyzer, made in Japan, and using the Audit Diagnostics laboratory kit manufactured in Ireland.

## 2.5. Intervention Procedures

The research team first reviewed the profiles of the elderly cases registered in the health centers under the study and extracted the names of the elderly eligible to be enrolled in the study and determined the cognitive status of the elderly; then they were invited to participate in the study. Prior to the initiation of the study, verbal and written informed consent was received from all the selected elderly. The elderly were divided into two groups of intervention and control groups by the first author; accordingly, one of the 38 envelopes in the specified order was picked up, and given the written group specified in the envelope, the subject was enrolled into one of the two groups of intervention and control. Individual demographic questionnaires, GDS and BAI were completed by interviewers as specified in the interview manual. Then, 5 ml of venous blood samples were taken from the elderly in both groups and

the clot samples were sent to the laboratory to separate blood serum and measure zinc serum level. Zinc measurements were performed via the auto-analysis method. After these steps, zinc supplements containing 30 mg of zinc [24] were administered to the elderly in the intervention group for 10 weeks [37]. In order to evaluate the status of the older adults in the intervention group, after seven days and taking seven tablets, the elderly in the intervention group were contacted to ensure they had an optimal status. It was also explained to the elderly in the intervention group that if at any stage of the study and during the 70 days of drug administration, if encountered with problems or complications, they should contact the first author who was the head of the project. Furthermore, in order to ensure the use of supplementation pills, the subjects in the intervention group were contacted every ten days and the use of supplementation pills was emphasized. The supplement used in this study was a Nature-made Zinc tablet, manufactured in the United States, which contained 30 milligrams of zinc in the form of zinc gluconate. The elderly in the intervention group received one 30-mg zinc pill and a glass of water 30 minutes after eating lunch. After the end of the 10-week period of the intervention, serum zinc level was re-measured using the above-mentioned method and the GDS and BAI questionnaires were completed and controlled for both groups of intervention and control (Fig. 1). In order to comply with ethical principles, if after 70 days of intervention, the serum zinc level was aged below the normal range in the members in the intervention or control group, they were referred to a dietician to initiate treatment interventions to raise the serum level of zinc for the elderly. If, after 70 days of intervention, the scores of depression or anxiety of each elderly, measured by the questionnaires, were outside the normal range, the elderly with the problem were referred to a psychiatrist.

## 2.6. Data analysis

In order to categorize and summarize the findings, the data were analyzed using descriptive statistics including mean, standard deviation, absolute frequency, and relative frequency. Then, in order to achieve the main goals of the research, the data collected from the control and intervention groups were analyzed by inferential statistics, chi-square test, and through the comparison of the mean differences using an independent t-test.

## 3. RESULTS

In this study, 150 eligible elderly were selected and randomly divided into intervention and control groups. Five people in the intervention group and five people in the control group were excluded since they met the exclusion criteria (Fig. 1).

The findings of this study were extracted from 140 elderly who were present at the end of the study. The mean and standard deviation of the age of the subjects in the intervention and control groups were  $66.5\pm 6.9$  and  $66.1\pm 5.8$  years, respectively. Most of the elderly in both the intervention group (61.4%) and the control group (75.7%) were female. The mean and standard deviation of the number of years of study in the intervention and control groups were  $3.6\pm 3.1$  and  $2.9\pm 3.5$ . The majority of the elderly in both the intervention group (81.4%)

and the control group (87.1%) were married. Most of the elderly in both the intervention group (38.6%) and control group (50%) were dependent on the spouse's income source, which might be due to the fact that the number of older women was more than the number of older men. The mean serum zinc level before and after the intervention were  $66.8 \pm 16.3$  and

$68.3 \pm 10.3$  in the intervention and control groups, respectively, lower than the normal range based on the laboratory references. Based on the results of the t-test and chi-square test, there was no significant difference between the two groups in terms of the demographic variables before the intervention and the two groups were homogeneous (Table 1).

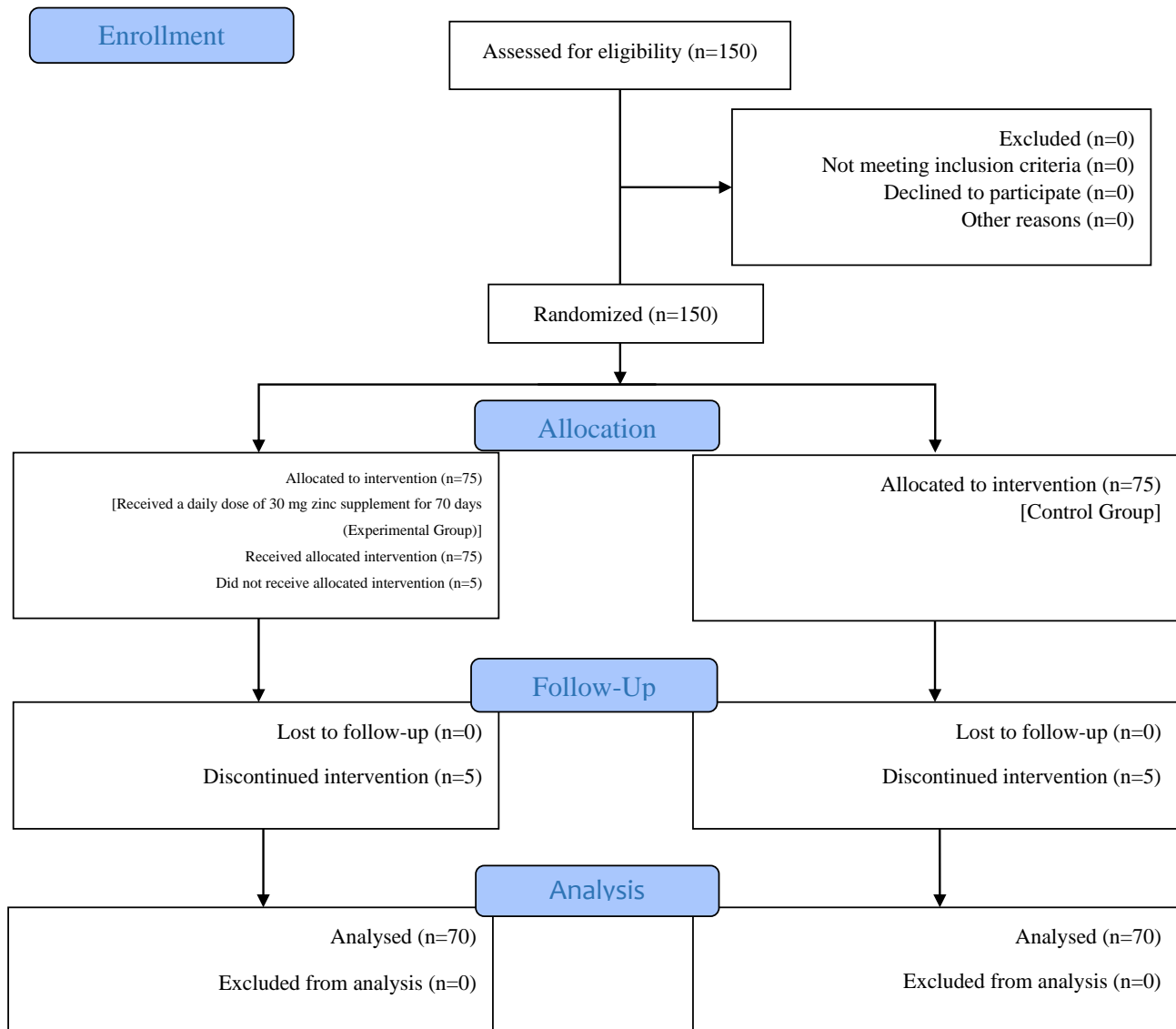


Figure (1). Flow Diagram of the study.

Table 1. Distribution of absolute and relative frequency of elderly people studied based on demographic variables.

Variable		Intervention	Control	P Value
		(Mean ± SD)	(Mean ± SD)	
Age (year)		66.5±6.9	66.1±5.8	0.75*
Education (year)		3.6±3.1	2.9±3.5	0.22*
Serum zinc level (µg/dL)		66.8±16.3	68.3±10.3	0.5*
		N (%)	N (%)	
Gender	Male	27(38/6)	17(24.3)	0.06**
	Female	43(61.4)	53(75.7)	

(Table 1) contd....

Marital status	Married	57(81.4)	61(87.1)	0.35**
	Wife died	13(18.6)	9(12.9)	
Source of income	Subsidy	10(14.3)	11(15.7)	0.39**
	Spouse	27(38.6)	35(50)	
	Self-employed	11(15.7)	6(8.6)	
	Retirement	22(31.4)	18(25.7)	

\*: independent t-test; \*\*: Chi-square; SD: Standard Deviation; N: Number; %: Percent;

Of all, 52.9% of the elderly in the intervention group and 58.5% of the elderly in the control group had a degree of depression; moreover, mild depression was the most prevalent one, so that before the intervention, 32.9% and 30% of the elderly in the intervention group and control group, respectively, had mild depression. In addition, 62.9% of the elderly in the intervention group and 70% of the elderly in the control group had some degree of anxiety. The most prevalent level of anxiety was mild anxiety, which was observed in 31.4% of the elderly in the two groups before the intervention. In addition, the serum zinc level in 60% of the elderly in the intervention group and 47.1% of the elderly in the control group before the intervention was lower than the normal range.

Tables 2 and 3 present the factors affecting scores of depression and anxiety after the intervention; these results were obtained from two-way ANOVA analysis.

**Table 2. The relationship between zinc consumption and GDS scores after intervention by analysis of two-way ANOVA.**

Variables		β	SE	t	P Value
Constant value		1.612	0.305	5.280	<0.001
Mean difference of level zinc serum before and after intervention		-0.032	0.014	-2.218	0.023
Mean score of GDS before intervention		0.823	0.037	22.307	<0.001
Group	Control	ref			
	Intervention	-2.436	0.350	-6.964	<0.001

SE: Standard error; GDS: Geriatric Depression Scale;

**Table 3. The relationship between zinc consumption and BAI scores after intervention by analysis of two-way ANOVA.**

Variables		β	SE	t	P Value
Constant value		3.260	0.653	4.990	<0.001
Mean difference of level zinc serum before and after intervention		-0.133	0.032	-4.099	<0.001
Mean score of BAI before intervention		0.905	0.032	28.545	<0.001
Group	Control	ref			
	Intervention	-5.378	0.779	-6.903	<0.001

SE: Standard error; BAI: Beck Anxiety Inventory;

The results showed that factors such as differences in serum zinc levels before and after the intervention, pre-intervention mean score of depression and group variables were effective on the post-intervention mean score of depression. As for each unit increase in post-intervention serum zinc level, 0.032 unit post-intervention depression score decreased. Also, the participants in the intervention group had a lower depression score of 2.436 units than the control group (Table 2).

Moreover, the factors affecting the post-intervention anxiety included the mean difference in serum zinc levels before and after the intervention, the pre-intervention anxiety score and group variables. For each unit increase in serum zinc levels, 0.133 units post-intervention anxiety decreased. Also, the intervention group had a lower anxiety score of 5.378 units than the control group. Additional results are available in Table 3.

**4. DISCUSSION**

According to the results of this study (55.7%) of the elderly had a degree of depression. Ezgi Demirteurk *et al.* (2018) conducted a study to determine the effects of depression on the adherence to the use of antihypertensive drugs in the elderly with high blood pressure, and it was found that 57.1% of the elderly had depression that is consistent with the results of the present study [38]. In a study by Yongchuan Liu *et al.* (2018), which aimed at determining poor sleep quality and depression in the urban elderly in China, 35.2% of the elderly had depression that is not in line with the results of the present study [39]. The lower prevalence of depression in the Chinese elderly can be due to the healthy lifestyle of the elderly in that country. Hanan Y. Aly (2018) conducted a study aimed at determining depression among the elderly population in one of the Egyptian provinces, and it was found that 62.7% of the elderly were suffering from depression [40]. The higher prevalence of depression in the Egyptian elderly may be due to social problems and wars that occurred over the past few years in this country.

In the present study, 66.4% of the elderly had a degree of anxiety. In a systematic study by Christina Bryant (2007), which examined about 2500 articles to determine the prevalence of anxiety in the elderly between 1980 and 2007, it was found that the prevalence of anxiety symptoms was between 15% and 52.3% [41]. In a study by Hee-Ju Kang (2016), which aimed at investigating anxiety symptoms in the elderly in Korea, the prevalence of anxiety symptoms was reported to be 38.1% [42]. The lower prevalence of anxiety reported by other studies, as compared with the present study, may indicate a lower risk of anxiety in other countries, especially in European countries, and the availability of better living conditions and welfare.

In the present study, serum zinc level in 53.5% of the elderly was lower than the normal range. In a study by Markiewicz-Żukowska, Renata *et al.* (2015), which aimed at determining the relationship between serum zinc concentrations and the physical and mental status of the elderly living in nursing homes, 28% of the elderly were suffering from zinc deficiency. Moreover, in Magnus Kvamme *et al.*'s study (2014), which aimed at investigating the risk of

malnutrition and zinc deficiency in the elderly men and women, about 10% of the elderly were suffering from zinc deficiency that is not consistent with the results of the current study [43, 44].

In the present study, the use of zinc supplements significantly improved depression scores in the intervention group. In addition, there was a significant difference between the mean depression scores before and after the intervention in the two groups. In this regard, the results of the study by Yosae *et al.* (2020) showed that zinc supplementation, vitamin D, or in combination for 12 weeks has a significant effect on alleviating depressive symptoms [19]. Studies have shown that there is an inverse relationship between zinc and depression in humans [45, 46]. It has also been shown that older people with a low serum zinc level and less zinc intake through the diet have symptoms of depression [22]. The results of a study by T Sawada *et al.* (2010), which aimed at examining the effect of zinc supplementation on the mood of young women, showed that zinc supplements significantly increased serum zinc concentrations and had decreased anger and depression; however, it did not have any effect on anxiety [37]. Nevertheless, a study by Stewart-Knox *et al.* (2010), which aimed at examining the effect of Zinc gluconate supplementation on the mood of European elderly, showed that zinc supplement did not change the mood in healthy European elderly [24]. The possible reason for this discrepancy is the difference in the amount and duration of taking zinc supplements in this study. Zinc has been shown to be an N-methyl-D-aspartate (NMDA) antagonist receptor in the glutaminergic system, which plays an important role in the treatment of depression [47].

In the present study, the use of zinc supplements significantly improved anxiety scores in the intervention group. Moreover, there was a significant difference between mean anxiety scores before and after intervention in both groups. In a study by A.J. Russo (2011), it was found that serum zinc level in people with anxiety was lower than that in other people, and zinc supplementation significantly increased serum zinc levels and improved anxiety symptoms [25]. It seems that the effect of zinc on depression and anxiety is due to its impact on GABA function, as zinc deficiency seems to be associated with GABA functional impairment; moreover, GABA and glutamate play an important role in depression and anxiety [48, 49]. The results of the study by Edalatfard *et al.* (2016), which aimed at investigating the effect of zinc supplementation and magnesium supplementation on depression and postpartum anxiety, showed that supplementation of zinc and magnesium after delivery did not prevent the symptoms of depression and anxiety in non-depressed people [50]. The results of Edalatfard *et al.*'s study are not consistent with the results of the present study, which can be due to differences in age and demographic features of the subjects in the two studies.

## 5. STUDY LIMITATIONS

Since the intervention was performed over 70 days and the study showed that 70-day consumption of zinc supplement improved serum zinc levels and reduced anxiety and depression scores, the study on the type of improvement of

these variables (permanent or temporary improvement) was not one of the objectives of this study, more research is needed in the future. Although the side effects of zinc supplements include copper deficiency and gastrointestinal disorders, they were not controlled in the present study, and only its benefits in terms of effectiveness on the psychological aspects of the elderly were investigated.

## CONCLUSION

The results of this study showed that the use of zinc supplements improved depression and anxiety in the elderly. Therefore, considering the role of nurse in the prevention and treatment of diseases, it is recommended to use zinc supplements as a new therapeutic strategy for the treatment of depression and anxiety in the elderly.

## LIST OF ABBREVIATIONS

<b>GDS</b>	=	Geriatric Depression Scale
<b>BAI</b>	=	Beck Anxiety Inventory
<b>AMTS</b>	=	Abbreviated Mental Test Score
<b>MMSE</b>	=	Mini-Mental State Examination

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Shahrood University of Medical Sciences, Iran (Registration Code: IR.SHMU.REC.1396.42).

## HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All human research procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

## CONSENT FOR PUBLICATION

Informed consent was obtained from participants.

## AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available from corresponding author [H.E] upon reasonable request.

## STANDARDS OF REPORTING

CONSORT guidelines and methodologies were followed in this study.

## FUNDING

None.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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