nutrición clínica y Dietética Hospitalaria

Artículo Original

Nutr Clín Diet Hosp. 2024; 44(1):303-309
DOI: 10.12873/441castano

Association of major depressive disorder (MDD) with zinc levels and handgrip muscle strength in a sample of Colombian adults

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Recibido: 6/octubre/2023. Aceptado: 25/enero/2024.

ABSTRACT

Introduction: Depression is related with poor muscle strength, and deficiencies of microelements such as Zinc (Zn). Otherwise, Zn is related with muscle strength, but there is no evidence of the relations between muscle strength and Zn levels in depression.

Objective: To determine the association between serum Zn levels, handgrip muscle strength, and depression.

Methods: An observational, analytical case-control study. 102 depressive patients hospitalized at the San Juan de Dios Clinic in Manizales, and 36 controls with no personal history of mental illness were evaluated for depression severity, serum Zn levels, and handgrip muscle strength. The groups were matched by sex, age, educational level, and socioeconomic stratum. The severity of depression was assessed using the Montgomery–Asberg Rating Scale (MADRS). Serum Zn levels were determined, and handgrip muscle strength was assessed using dynamometer. Descriptive analysis, logistic regression and linear models were performed with depression and severity of depression as dependent variables.

Results: Lower Zn levels and reduced handgrip muscle strength were related to the presence of depression with the logistic model. Lower handgrip muscle strength and severity of depression were associated with the linear model.

Conclusion: An association was found between depression and low Zn levels, and an inverse association between severity of depression and handgrip muscle strength. Future studies should investigate causality, and to evaluate the relationship between depression, muscle strength and nutritional status.

KEY WORDS

Micronutrient, handgrip strength, major depressive disorder, mental health, minerals.

INTRODUCTION

Major Depressive Disorder (MDD) is a chronic, relapsing condition, with a lifetime prevalence of approximately 20%, that causes severe disruptions in social, family, and occupational functioning of the affected person, as well as increasing the suicide risk[1]. Its etiology is multifactorial and complex, involving genetic factors, traumatic life events and environmental stressors[2].

Nutritional psychiatry studies have shown that trace elements such as copper, selenium, magnesium, and Zn play important roles in multiple physiological processes and their deficiency has been associated with depression[3]. Zn is the second most abundant metal in humans and is widely distributed in different organs and tissues[4]. It is an essential element in neuronal metabolism, transcription of brain neurotrophic factor-related products and synaptic transmission in the hippocampus, amygdala, and cerebral cortex[3]. In addition, it plays a role in the inflammatory response, maintenance and development of immune system cells and the response to oxidative stress, all of which are part of the biological mechanisms in the pathophysiology of depression[4].

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Following the discovery of the importance of Zn in human health, its deficiency has been linked to psychiatric conditions such as impaired cognitive function, learning and depression[3,5]. The use of Zn supplementation appears to enhance the effect of antidepressants. One pathway by which Zn is thought to have antidepressant characteristics is its role as an antagonist of the N Methyl D Aspartate receptor, mediating effects on synaptic plasticity and 5HT1A receptor expression[3,6-8].

On the other hand, low Zn levels have deleterious consequences in tissues with high energy demand such as the skeletal muscle, where it has been found that myogenesis and muscle regeneration can be affected and decrease muscle strength[9]. There is evidence in favor of a relationship between reduced muscle strength and the intensity of depressive symptoms in adult populations, especially those middle-aged and over 60 years of age[10]. Cross-sectional and longitudinal studies have reported that muscle strength is independently associated with an increased risk of developing depression, but this mechanism requires further confirmation[11-13]. handgrip strength is a valid and simple technique for determining muscle strength with satisfactory inter-individual and inter-evaluation reliability[14].

In Latin American, Zn deficiency has been catalogued as a public health problem and is one of the causes for loss of healthy life years[2]. Indicators of low socioeconomic status (educational level, income, and employment) limit access to varied, nutritious, and safe foods, favoring diets consisting of vegetables, unrefined cereals, legumes, and giant seeds as energy sources, foods rich in phytic acids that decrease Zn bioavailability[7,15].

The purpose of the present study was to determine the association between the serum Zn levels, handgrip muscle strength and depression among hospitalized patients with severe MDD in San Juan de Dios Clinic in Colombia.

METHODS

Study Design: The present study was an observational, analytical, case-control study.

Ethical aspects: This study was conducted according to the guidelines in the Declaration of Helsinki[16]. It was approved by the research bioethics committee of the University of Caldas and San Juan de Dios Clinic of Manizales (CSJDM). All participants received detailed information about the study and signed informed consent prior to participation.

Participants:

The cases group (n=102) consisted of patients who were hospitalized at CSJDM. Patients over 18 years of age, who had required at least one hospitalization for a depressive episode, and with a current episode that met the criteria for severe MDD (Diagnostic Statistical Manual 5th edition (DSM 5), and at least 1 week of hospitalization were invited to participate in the study. Diagnosis was established through medical history review and the semi-structured MINI interview carried out by a psychiatrist and a resident of psychiatry. The comorbidities were established through medical history, and laboratory tests. Patients with intellectual disability, severe chronic neurological disease, substance use disorder, cancer, HIV, intestinal malabsorption syndromes, rheumatologic diseases, liver cirrhosis, chronic renal failure, history of gastric surgery, pregnancy, lactation, and people taking vitamin supplements or on antibiotic or anti-inflammatory treatments at the time of assessment were excluded.

The control group (n=36) was matched by age, sex, level of education and socioeconomic stratum. People with no history of mental illness and who did not have mental illness in the first degree of consanguinity were included, with the same exclusion criteria as in the group of patients with MDD.

Instruments applied

The sociodemographic data from the study participants was obtained using a questioner that was competed by a face-to-face interview.

To obtain the body mass index, height and weight were measured (BMI= weight (kg)/ height (m) 2. A wall-mounted measuring rod and a calibrated digital scale were used. Both measures were taken with minimal clothing and bare feet.

A validated depression rating scale for the Colombian population (Montgomery - Asberg Depression Rating Scale (MADRS)) was used to measure the severity of depressive symptoms[17].

Collection and processing of blood samples

Ten ml of blood were obtained from each participant between 7 and 9 am. The blood was centrifuged at 1800 g for 30 minutes. The serum was stored at - 80 Celsius degrees for a maximum period of one month. Measurement of Zn was done by flame atomic absorption spectrophotometry in serum using the AAcle 900F pin (Perkin Elmer Inc). Samples were prepared as water solutions. The Zn was measured in microgram/dL and the minimum detectable Zn concentration was 0.05 microgram/dL.

The evaluation of handgrip muscle strength was performed with a JAMAR hydraulic dynamometer in position II. The following procedure was adopted according to the guidelines of the American Society of Hand Therapists (ASHT): The patient was seated in a chair without armrests, with feet fully supported on the floor, hips and back resting on the back of the chair as much as possible, hips and knees forming a 90-degree angle. The position of the arm performing the test was as follows: the shoulder in adduction to the side of the thorax with 90 degrees of elbow flexion,

with the forearm and wrist in a neutral position; that is, in dorsiflexion between 0 - 30 degrees, with an ulnar deviation of 0 - 15 degrees. It was determined to use this range of angles because of the controversy in the literature regarding forearm posture. During the examination, the patient was not allowed to rest the assessed upper limb on his body or any part of the chair, and the position was corrected if necessary. The examiner explained to the participant the technique for holding and using the dynamometer; after verifying full understanding of the commands, and once the participant was ready, the participant was asked to perform the maximum grip for 5 seconds counted with a stopwatch for each of three attempts with the dominant hand. A rest of one minute was allowed between the grasps to avoid fatigue. The data taken was the result of the average of the three measurements taken for each participant and handgrip muscle strength was measured in kilopond[18].

Statistical analysis

Sociodemographic and clinical variables were evaluated using frequencies, percentages, means and standard deviation. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of quantitative variables. As age, age at onset of depression, and MADRS scale did not show normal distributions, these variables were transformed using the two-step transformation method. The analysis between the two groups was performed using Student's t-test for quantitative variables and the X^2 for qualitative variables. The association between handgrip muscle strength and Zn levels was analyzed using binary logistic regression models by the stepwise method, adjusting for confounding variables and the presence of depression as dependent variable. In the group of patients with depression, a linear regression analysis was performed with the MADRS scale as the dependent variable. The goodness of fit of the logistic regression model was examined with the Hosmer-Lemeshow test. All the statistical analyses were evaluated using a 2-tailed test, and a value of $p < 0.05$ was considered statistically significant. The analysis was performed using SPSS version 23 statistical software.

RESULTS

Out of a total of 140 subjects invited to participate, 102 cases and 36 controls accepted (response rate: 97.8%). The depression group and the healthy control group were matched by age (t= 1.32, p= 0.18), sex (chi-square= 0.48, p=0.82), schooling (chi-square= 3.32, p=0.19) and socioeconomic stratum (chi-square= 2.25, p=0.32). No significant differences were found between cases and control groups regarding occupation and marital status (Table 1). In the group of patients with MDD, the mean age of presentation of the first depressive episode was 26.46 ± 15.04, presence of psychotic symptoms was found in 32.4%, comorbidity with other anxiety disorders in 35.3%, history of mental illness in first degree relatives of consanguinity in 49% and a MADRS scale score of 34.27 ± 12.98.

Comparison of clinical variables showed significant differences in the presence of metabolic disease (diabetes, dyslipidemia, obesity), Zn levels and handgrip muscle strength. Metabolic disease was more frequently present in patients with depression than in the control group. Zn levels and handgrip muscle strength were lower in patients with depression (Table 2).

The binary logistic regression model included the variables used to match the groups and the independent variables that showed statistical significance when comparing the two groups. In this model, female sex, metabolic disease, low Zn levels and lower handgrip muscle strength showed a positive association with the presence of depression (Table 3).

In the depression group, the linear regression model used the severity of depression measured by the MADRS scale as the dependent variable. In this model, handgrip muscle strength showed an inverse association with the MADRS scale, and there was no association was found with age, sex, socioeconomic stratum nor Zn levels (Table 4).

DISCUSSION

This study demonstrated an association between low serum Zn levels and decreased muscle strength with the presence of depression. Furthermore, the analysis showed an association between depression severity and muscle strength but no Zn levels. The current findings confirmed that serum Zn levels in depressive patients were lower when compared to non-depressed volunteers, as confirmed in previous studies[9,19]. Similarly, this study further corroborates previous studies that have shown an inversely proportional and significant relationship between muscle strength and depression[20,21].

Zn deficiency results from decreased Zn intake, inappropriate absorption or high Zn expenditure[22]. In congruence with the findings of the study, there is evidence that has demonstrated the development of depressive symptomatology in people with an inappropriate intake of Zn-rich foods[23,24]. One possible explanation is that Zn intake may be affected by decreased appetite, which is one of the most frequently occurring symptoms of depression (DSM-5)[25]. Likewise, Zn deficiency has been linked to metabolic syndrome, inflammation and oxidative stress, mechanisms involved in the physiopathology of depression and decreased muscle strength[26]. On the other hand, the use of antidepressants can increase Zn levels and attenuate the immune response. Moreover, Zn intake can improve muscle strength, which would support the use of Zn supplements as an adjuvant in the management of depression[27-29]. Symptoms like loss of energy and psychomotor retardation, or psychosocial

Table 1. Comparison between the depressed group and the control group: bio demographic and socioeconomic variables

Variable	Depressed (n= 102)	Control (n= 36)	Total (n= 138)	t / Chi^2	*p*
Age Mean (SD)	37.5 (15.2)	41.31 (13.8)	38. 49 (14.9)	1.3	0.18
Sex				0.48	0.83
Male N (%)	46 (45.1)	17 (47.2)	63		
Female N (%)	56 (54.9)	19 (52.8)	75		
Socio economic stratum				2.25	0.32
High N (%)	5 (4.9)	3 (8.3)	8		
Medium N (%)	51 (5..0)	13 (36.1)	64		
Low N (%)	46 (45.1)	20 (55.6)	66		
Schooling				3.32	0.19
Basic N (%)	14 (13.7)	9 (25.0)	23		
Superior N (%)	46 (45.1)	17 (47.2)	63		
Technical/ university N (%)	42 (41.2)	10 (27.8)	52		
Occupation				5.56	0.13
Employed N (%)	64 (62.7)	28 (77.8)	93		
Student N (%)	16 (15.7)	1 (2.8)	17		
Retired N (%)	3 (2.9)	0 (0.0)	3		
Unemployed N (%)	19 (18.6)	7 (19.4)	26		
Marital status				0.67	0.41
Married/Consensual union N (%)	32 (31.4)	14 (38.9)	46		
Single/divorced/ widowed N (%)	70 (68.6)	22 (61.1)	92		

factors that are often present in patients with depression such as low socioeconomic status and poor support network may influence both muscle strength and decreased Zn levels due to low Zn intake[7,16]. But is necessary research if there is a relation between Zn, muscle strength, nutritional status in depression. Although the groups were matched by socioeconomic stratum and the variable was included in the logistic regression model to minimize its effect on the results, longitudinal studies should be conducted to confirm the findings and evaluate the relationship between depressive symptoms, muscle strength, and Zn.

Regarding depression severity, this study found an inverse relationship between muscle strength and depression severity, but not with Zn levels. In agreement with the results, previous studies have also found no relationship between low Zn levels and severity of depression[10,30]. There are some possible mechanisms by which muscle strength is decreased in depressive patients. First, patients with severe depressive symptoms have more psychomotor retardation, marked decrease in interest in daily activities and greater loss of energy that may favor the decrease in muscle strength. Second poor intake of micronutrients, inflammation and oxidative stress are related with muscle strength[13,18] and depression[8]. To corroborate this possibility, studies comparing the evolution of depressive symptoms with variations in muscle strength and inflammatory biomarkers, nutritional status and oxidative stress biomarkers should be performed.

The study has limitations that should be taken into account. The design did not allow us to establish causality between decreased Zn levels and muscle strength with the severity of de-

Table 2. Comparison between the depressed group and the control group: comorbidities and clinical variables

Comorbidities	Cases N=102	Controls N=36	Chi^2	*p*
	N (%)	N (%)		
Cardiovascular disease	20 (19.6)	6 (17.6)	0.15	0.69
Metabolic disease (diabetes, dyslipidemia, obesity)	26 (25.5)	3 (83.3)	4.71	0.03
Hypothyroidism	14 (13.7)	2 (5.6)	1.73	0.19
Migraine	25 (24.5)	1 (2.8)	8.2	< 0.01
Nicotine dependency	23 (22.5)	4 (11.1)	2.2	0.14
Clinical variables	Mean (±SD)	Mean (±SD)	t Student	*p*
Body Mass Index (kg/m^2)	25.9 (4.8)	25.6 (4.4)	0.75	0.45
Zn level (ug/dL)	80.8 (13.8)	91.2 (16.4)	3.7	< 0.01
Handgrip Muscle Strength (kp)	20.1 (10.6)	27.2 (10.4)	3.4	< 0.01

SD= Standard Deviation

Table 3. Regression model to evaluate the likelihood of having depression (outcome)

Characteristic	B	z	p	OR	CI 95%
Female sex	1.67	6.09	0.014	5.30	1.4-19.3
Metabolic disease (diabetes, obesity, dyslipidemia)	1.82	5.41	0.02	6.18	1.33-28.65
Zn level (ug/dL)	-0.041	6.45	0.01	0.95	0.93-0.99
Handgrip Muscle strength (kp)	-0.121	10.96	< 0.01	0.88	0.82-0.95

Hosmer-Lemeshow goodness-of-fit test (chi-square= 8.26, p-value= 0.41) r-square Nagelkerke= 0.36. B: Beta value. z= z score.
Variables excluded from the model, social stratum, schooling, age, etc.
OR= Odds Ratio, CI= Confidence Interval.

Table 4. Regression model to evaluate the severity of depression using Montgomery Asberg Depression Rating Scale (outcome)

Characteristic	B	p value	CI 95%
Handgrip Muscle strength (kp)	-2.54	0.01	-0.53 -0.74

Predictor variables of the model: age, sex, Zn, socioeconomic stratum.
Adjusted R-square= 0.06. Durbin Watson= 2.14.

pressive symptoms. Another limitation is that people with depression may have little motivation to complete the muscle strength assessment, which may interfere with the validity of the findings. Another limitation is that there was no follow up of diet lifestyle and pharmacological treatment of patients, which can influence Zn metabolism and interactions with medications or certain types of foods.

The study has strengths such as the participant selection mechanism, which included patients with depression who required hospitalization. From a clinical point of view, it is important to consider muscle strength as a possible indicator of depressive symptomatology and to evaluate the effect of interventions aimed at improving muscle strength in the prevention and recovery of depression.

CONCLUSION

An association was found between depression and low Zn levels, and an inverse association between depression sever-

ity and muscle strength. The research suggest that low Zn levels and low muscle strength are potential risk factors for depression development. Therefore, cohort studies and clinical trials with a large sample size are necessary to find causal links between these factors and depression.

FUNDING

This study was supported by University of Caldas grant: 0745619.

ACKNOWLEDGMENT

We thank the CSJDM and all study participants for making this work possible.

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