



Original/Alimentos funcionales

# The Mediterranean Diet and micronutrient levels in depressive patients

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Abstract

**Introduction:** An inverse association between depression and some serum micronutrient levels (selenium, zinc, iron, magnesium, vitamin B and folic acid) has been reported. In addition, other studies reported that this micronutrient supplementation may improve depressed mood. The Mediterranean diet contains a sufficient amount of the micronutrients mentioned, although no study has reported an association between diet prescription and increased levels of them in depressive patients.

**Objective:** To examine the impact of dietary patterns recommendations on micronutrient levels in depressive patients.

**Methods:** 77 outpatients were randomly assigned either to the active (hygienic-dietary recommendations on diet, exercise, sleep, and sun exposure) or control group. Outcome measures were assessed before and after the six month intervention period.

**Results:** Serum selenium and zinc levels were slightly low at basal point and serum selenium was inversely correlated with severity of depression ( $r=-0.233$ ;  $p=0.041$ ). A better outcome of depressive symptoms was found in the active group. Nevertheless, no significant differences in micronutrient levels were observed after the Mediterranean diet pattern prescription, probably due to an insufficient adherence.

**Conclusion:** Selenium, zinc, iron, magnesium, vitamin B<sub>12</sub> and folic acid serum levels didn't increase in depressed patients after six months of the Mediterranean diet pattern prescription.

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Key words: *Depressive disorder. Lifestyle. Diet. Selenium. Zinc.*

## DIETA MEDITERRÁNEA Y NIVELES DE MICRONUTRIENTES EN PACIENTES DEPRESIVOS

Resumen

**Introducción:** Se ha comunicado una correlación inversa entre depresión y el nivel sérico de algunos micronutrientes (selenio, zinc, hierro, magnesio, vitamina B y ácido fólico). Además, otros estudios han señalado que la suplementar de estos micronutrientes puede mejorar la depresión. La dieta mediterránea proporciona una suficiente cantidad de los micronutrientes mencionados, aunque ningún estudio ha probado si la prescripción de dicha dieta puede incrementar los niveles de micronutrientes en pacientes depresivos.

**Objetivo:** Examinar el impacto de recomendar un patrón dietético mediterráneo en los niveles de micronutrientes de pacientes deprimidos.

**Material y Métodos:** 77 pacientes ambulatorios se aleatorizaron entre un grupo de intervención (recomendaciones higiénico-dietéticas sobre dieta, ejercicio, sueño y exposición solar) y un grupo control. La evolución fue evaluada antes y después de los seis meses del periodo de intervención.

**Resultados:** Los niveles de selenio y de zinc fueron ligeramente bajos en la determinación basal y el nivel de selenio correlacionaba inversamente con la severidad de la depresión ( $r=-0.233$ ;  $p=0.041$ ). El grupo activo evolucionó mejor de la clínica depresiva. Sin embargo, no se observaron diferencias significativas en los niveles de micronutrientes después de la prescripción del patrón de dieta mediterránea probablemente a causa de una insuficiente adherencia.

**Conclusión:** Los niveles séricos de selenio, zinc, hierro, magnesio vitamina B<sub>12</sub> y ácido fólico no aumentaron en pacientes depresivos seis meses después de prescribir un patrón de dieta mediterránea.

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Palabras clave: *Depresión. Estilo de vida. Dieta. Selenio. Zinc.*

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## Abbreviations

MDD: Major depressive disorder.

GP: General Practitioner.

ET: Trace elements.

## Introduction

Major depressive disorder (MDD) is a prevalent disorder with high personal and social cost<sup>1-3</sup>. Recent evidence suggests that there have been substantial increases in depression rates in developed societies and suicide is the most dramatic manifestation<sup>4,5</sup>. MDD is a complex and multifactorial condition; different biological and psychosocial factors interact in a particular and a dynamic form in each patient<sup>2,3,6</sup>.

The increased incidence of depression can be at least partially explained by changes in lifestyle factors<sup>2,4</sup>. Decreased social support, increased chronic stress, sedentarism, decrease in hours of sleep, reduced exposure to sunlight and dietary changes are some of the factors playing a significant role in current lifestyle of developed countries<sup>5</sup>. There is some evidence to suggest that diet consumed in these countries fails to supply the needed amount of vitamins, minerals and others micronutrients for optimal brain function<sup>1,4,6,8</sup>. Traditional diets such as Mediterranean and Asiatic diet contain a sufficient amount of micronutrients<sup>9</sup>.

Selenium, zinc, magnesium, vitamin B<sub>12</sub> and folic acid have been found inversely associated with increased risk of depression<sup>7-9,11</sup>. Therefore, the study of these micronutrients in depressive patients is important, especially in countries where traditional diets are being abandoned<sup>1,4</sup>. The availability of micronutrients depends not only on diet quality, but on soil and water characteristics and genetic factors as well<sup>6-12</sup>. Selenium, zinc, magnesium, vitamin B and folic acid are vital to the proper functioning of the nervous, immune, endocrine and reproductive systems, as well as in the prevention of cancer and cardiovascular diseases<sup>13-18</sup>. Several hypothesis link selenium, zinc, iron, magnesium, vitamin B<sub>12</sub> and folic acid with the physiopathology of depression, being the oxidative stress one of the main mechanisms implicated<sup>13,14</sup>. It has been proposed that the Mediterranean diet reduces the oxidative stress and help to prevent many illnesses, including depression<sup>15,16</sup>. It has also been shown that the Mediterranean diet ensures the entire micronutrients intake and that micronutrients deficit can increase the risk to develop depression<sup>16-18</sup>. Consistent with this, longitudinal studies have shown the preventive role of the Mediterranean diet in depression<sup>14-16</sup>. For these reasons, it has been proposed to promote the Mediterranean diet in people at risk of suffering micronutrients deficiencies with a wide range of health problems, depression included<sup>18</sup>.

Although it might be less effective, it has been suggested that dietary changes are safer than micronu-

trient supplementation<sup>19</sup>. However, as far as we know, it still has not been proved the efficacy of this dietary strategy in depressive patients. The hypotheses of this study is that giving a simple pattern of the Mediterranean diet, low micronutrient levels in depressive patients can improve after six months.

## Methods

### *Participant Characteristics*

We screened 77 patients that were recruited for a study already published about the effectiveness of prescribing hygienic-dietary recommendations for depression<sup>20</sup>. Eligibility criteria included age over 18 years, meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depressive disorder, dysthymic disorder or bipolar disorder, receiving current antidepressant treatment and having a determination of plasma micronutrient levels during the previous month. The exclusion criteria were having any other mental or severe neurological disorder, uncontrolled medical comorbidity or medical issues that would preclude participation in the trial; suffer from delusions or hallucinations; active suicidal risk and being pregnant or lactating.

Fifty-one patients completed the study after the six months period and obtained the final analytical determinations. Reasons for drop out were: patient decision, protocol violations (current active alcohol or drug abuse or dependence) or any medical illness not previously diagnosed. The study protocol was approved by the local ethical committee (CEIC: Comité Ético y de Investigación Clínica de las Islas Baleares) and was registered (Trial registration: Current Controlled Trials ISRCTN59506583) and published<sup>21</sup>.

### *Dietary Patterns*

After signing informed consent outpatients were randomly assigned either to the active treatment or the control group. Patients assigned to the active treatment group received an envelope containing a sheet of paper with the four hygienic-dietary recommendations under consideration, the last one related to the Mediterranean diet guidelines:

1. Go to bed when sleepy and not before 11 p.m. Use your bed and bedroom only for sleep and sex (do not read, watch TV or lie on the bed during the day). If you do not fall asleep after 15 or 20 minutes, get up and start an activity until you feel sleepy enough to go back to bed. Get up early, never later than 9 a.m., no matter how well you have slept the night before. Do not lie down or take a nap during the day.
2. Walk at least 1 hour a day, at a good pace but without becoming short of breath or being una-

ble to talk while walking. If you think you have a medical problem which makes walking difficult or uncomfortable consult your doctor. Use appropriate footwear for walking and have a shower or a bath afterwards.

3. Expose yourself to sunlight at least 2 hours per day, taking precautions to avoid sunburn or sunstroke (sunscreen, hat, etc.).
4. Try to eat a healthy and balanced diet. Eat at regular hours without snacking between meals. Avoid especially sweet or sugary drinks. Eat fish at least three times per week, plus fruit, cereals, nuts and vegetables daily.

The control group received an identical envelope, but in this case the recommendation was to perform the pattern of eating and exercise according to what they thought might make them feel better:

1. Sleep the hours that you feel your body needs.
2. Adapt the pace of daily physical activity that meets your needs.
3. If exposed to sunlight take precautions to avoid sunburn or sunstroke (sunscreen, hat, etc.).
4. Try to eat a healthy and balanced diet.

### Outcome

The Mini International Neuropsychiatric Interview (MINI), the Hamilton rating scale for depression (HAM-D) 17-item version, the 21-item Beck Depression Inventory, and the Clinical Global Impression scale (CGI) were administered. After the sixth month intervention tests were again administered by blind raters. During this time the patients were taking antidepressants, and continued to be treated by their General Practitioner (GP) or psychiatrist without any interference from the research team. Analytical determinations were measured again after six months. The samples were taken between 8am and 10am in BD Vacutainer tubes for trace elements (ET). The laboratory that made the study considered optimal selenium levels from 90 ug/L; zinc levels from 80 ug/dl, magnesium levels from 1.80 mg/dl; vitamin B12 from 200 pg/ml and folic acid from 3.37 ug/mL.

### Statistical Analysis

Categorical variables were described using percentages. Continuous variables were expressed by mean and the standard deviation or the median and the interquartile range were used depending on a normal distribution (Kolmogorov-Smirnov test). To detect significant differences between groups Fisher's exact test was used for categorical variables and Student t test and Mann-Whitney test for continuous variables according to follow a normal distribution or not. Subsequently, the strength of the linear correlation between variables was calculated using the Pearson

correlation coefficient, setting the significance level at  $p < 0.05$ .

### Results

The main sociodemographic and clinical data of the study sample are shown in table I. At baseline, we observed a slight negative correlation between selenium levels and Hamilton Depression Rating Scale (HAM-D) ( $r = -0.233$ ;  $p = 0.041$ ). Groups were unbalanced according to the sex percentages and the diagnosis of major depressive disorder. After six months, the rating scales for depression pointed to a trend of improvement in the active group compared to the control group. Selenium plasma levels found in patients was lower than the limit considered as normal in laboratory (86.06 ug/L  $\pm$  17.3). Up to 31 of the 77 patients (40.3%) had selenium levels in plasma lower than 89 ug/L, but anyone had lower levels than 40 ug/L.

Zinc, iron, magnesium, vitamin B12 and folic acid levels are also shown in table I. Forty-one of the 77 patients (51.3%) had zinc levels in plasma lower than 80 ug/L. There were not significant differences related to the micronutrient levels analyzed after the six months period in both groups.

### Discussion

Selenium levels in this sample at baseline were moderately low and slightly correlated to depression severity. However, these levels were still low six months after in both control and active group despite the fact that the active group received a prescription of the Mediterranean diet pattern. The rest of micronutrients analyzed (zinc, iron, magnesium, folic acid and vitamin B12) neither changed. Low serum levels of all these micronutrients can be related to depression, so the low serum levels of zinc found in the present study may suggest that there could be an etiopathogenic role of this element in the patients depression symptoms as well<sup>22,23</sup>.

The correlation with selenium and depression could be also explained according to an inverse interaction. Therefore, depressed patients tend to worsen the quality of their diet toward processed foods, easy to prepare and hypercaloric, with few vegetables, cereals and fish<sup>24,25</sup>. These diets do not ensure an adequate intake of micronutrients and it has been suggested that they might be also induced by taking some kind of psychotropics drugs<sup>26</sup>. An important consideration when interpreting our results is the possibility that patients may not adequately met dietary recommendations; therefore their nutritional status has not changed. In medical literature it is already pointed that modifying dietetic habits in population to improve the micronutrients intake is a complex and difficult problem<sup>27</sup>. Adherence to dietary recommendations could be even lower in patients with depression<sup>5,27,28</sup>. It is possible

**Table I**  
*Demographic and Clinical Characteristics*

	Active n=38	Control n=39	P value
Female sex, N°	33	26	0.03
Age y, Mean (SD)	49.1 (12.5)	51.8 (10.8)	NS
Major Depression, N°	23	13	0.01
HAM-D increment	- 8.14 (8.8)	- 4.72 (5.6)	0.08
BDI increment	- 8.75 (8.8)	- 4.51 (6.6)	0.05
GCI increment	- 1.64 (1.3)	- 0.62 (1.0)	0.03
Selenium basal (ug/L)	85.89 (18.9)	86.23 (15.8)	NS
Selenium increment (ug/L)	4.61 (18.7)	2.52 (18.7)	NS
Zinc basal (ug/dl)	79.51 (16.2)	81.31 (17.1)	NS
Zinc increment (ug/dl)	0.88 (20.2)	-1.20 (22.6)	NS
Iron basal (ug/dl)	76.05 (16.2)	89.74 (17.1)	NS
Iron increment (ug/dl)	6.79 (17.3)	0.41 (2.6)	NS
Magnesium basal (mg/dl)	2.16 (0.24)	2.07 (0.16)	NS
Magnesium increment (mg/dl)	4.16 (6.9)	1.83 (3.3)	NS
Folic acid basal (ng/mL)	8.20 (4.2)	7.34 (3.3)	NS
Folic acid increment (ng/mL)	0.03 (3.1)	- 0.48 (3.1)	NS
Vitamin B12basal (pg/mL)	421.97 (151.3)	414.02 (200.0)	NS
Vitamin B12 increment (pg/mL)	16.33 (81.9)	- 20.57 (92.2)	NS

Hamilton 17-item scale (HAM-D), Beck Depression Inventory 21-item (BDI), Global Clinical Impression scale (GCI).

that the differential mood enhancement founded could be related to other lifestyle suggestions that were recommended to patients such as physical exercise<sup>29</sup>. In fact, we objectively confirmed, with a group of these patients by using actigraphs, that they changed their activity level<sup>5</sup>. It would have been interesting to use objective diet adherence measures from all the patients during the follow-up. Unfortunately, it could not be put into practice due to logistical limitations. However, the aim of the study was to assess the effectiveness of these recommendations, not assess the compliance.

Our study has some other weaknesses that need to be acknowledged for proper interpretation, such as small sample size and the short follow-up period. The reduced size of the sample may explain the imbalance between groups in terms of sex and diagnosis, something we think did not have any influence on the results. Finally, a validated dietary questionnaire was not performed at baseline and the dietary prescription does not completely describe the Mediterranean diet<sup>17</sup>.

In summary, to our knowledge this is the first attempt to explore the impact of dietary recommendations in serum micronutrient level of depressed patients. However, it could not be demonstrated that the provision of an informational sheet with simple recommendations concerning the Mediterranean diet exert changes in micronutrient levels six months later.

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## Conflict of interest

Authors declare that they have no conflict of interest.

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