

Effect of N3-Poliunsaturated Fatty Acids as Coadjuvant in the Antihypertensive Treatment in Spanish Postmenopausal Women

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Abstract

Objective: The purpose of this study is to evaluate the effects of taking low doses of omega-3 (1.5 g/day) in hypertensive women.

Method: Longitudinal clinical trial Health Center of San Fernando de Badajoz. Primary care. 55 postmenopausal hypertensive women. For the study, participants were divided into two groups, group supplementation (GS) (n=28) and one control group (CG) (n=27). Supplementation with n-3 PUFA to the experimental group for 6 months (1.5 g/day). The control group was given nothing. The variables of the study have been blood pressure, n-3 fatty acid supplementation and it was tried to control nutritional intake.

Results: Q 6 * V \ V W R O L F E O R R G S U H V V X U H G H F U H D V H G V L J Q L \ F D Q W O \ D W W K H V D I W H U V W D U W L Q J W K H V W X G \ D Q G W K U H H P R Q W K V S V L Q F H W K H H Q G R I V S U H V V X U H O H Y H O V L Q W K H V D P H J U R X S € • € P € X F K K K Å ° ° L K K r \ € ' b k H € € 0 • V L J V W D W L V W L F D O O \ V L J Q L \ F D W L R Q : H K D Y H V K R Z Q L Q F U H D V H V L Q W K H S O D V P D S D I W H U W K U H H P R Q W K V R I L Q L W L D W L Q J V X S S O H P H Q W D W L R Q S D I W H U P O H D Y L Q J V X S S O H P H Q W D W L R Q S \$ U D F K L G R Q L F D F L G G H F U H D V H V W K U R X J U H D F K H G D V W D W L V W L F D O O \ V L J Q L \ F D Q W G L I I H U H Q F H D I W H U P R Q W K V Z L W K L Q

Conclusions: 7 K H L Q W D N H R I J G D \ R I \ V K R L O D V F R D G M X Y D Q W L Q W K H W U H D W I improves blood pressure and other cardiovascular diseases.

Keywords: Postmenopausal women; Hypertension; Lipids; n-3-fatty acid

Introduction

Cardiovascular diseases (CD) are the main cause of death in Spain [1]. A wide number of surveys have shown an inverse relationship among CD and the n-3 polyunsaturated fatty acids (n-3 PUFAs) intake [2-5]. In this sense, it has been research in surveys of nutritional intervention, among humans and animals, the kinetics of n-3 PUFAs, their incorporation to cellular structures and their link to eicosanoids metabolism, in comparison with n-6 PUFAs [6-8]. Furthermore, the efficacy of several fatty acids derived from fish oil, like the eicosapentaenoic acid (20:5n-3 or EPA) and the docosahexaenoic acid (22:6n-3 or DHA) as well as other minor important PUFAs, in the treatment of cardiovascular diseases with minimum daily intakes of 0.5 g/day in healthy individuals and 1 g/day in patients diagnosed with CD [9]. Several surveys have demonstrated anticarcinogenic, antitrombotic and anti-inflammatory effects

[16,17] although the results are contradictory [5]. Some meta-analysis and reviews have attributed this discrepancy to the variability of several critical factors, like dosage, sample size, timing and duration of the treatment and the patient's selection criteria [18-20]. Although some data have demonstrated the diminution of arterial tension (AT) with n-3 PUFAs in the essential hypertension [18,21,22], it was suggested that the supplementation with diet could be more appropriate in the prevention strategies than in the AHT treatment [18]. Nutritional supplements rich in n-3 PUFAs can decrease the AT. However, their use has been reduced due to the high dosage needed as well as to the side concomitant effects. Several meta-analysis and intervention surveys [20,23] have suggested that high dosage supplementation with n-3 PUFAs (typically 3 g/day) can reduce significantly the AT in arterial hypertensive patients [22,24], but with side effects. So, the aim of the present survey was to evaluate the effect of low-medium dosage n-3

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Received August 23, 2017; Accepted September 04, 2017; Published September 11, 2017

Citation: Muñoz D, Maynar I, Maynar MA, Bartolomé I, Maynar IS, et al. (2017) Effect of N3-Poliunsaturated Fatty Acids as Coadjuvant in the Antihypertensive Treatment in Spanish Postmenopausal Women. Sports Nutr Ther 2: 127. doi: [10.4172/2473-6449.1000127](https://doi.org/10.4172/2473-6449.1000127)

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PUFAs (1,5 g/day) as coadjuvant treatment, in combination with other antihypertensives, in the AT of Spanish postmenopausal women.

Material and Methods

Participants

55 hypertensive postmenopausal women participated in this survey. All of them were recruited from the San Fernando Clinic of Badajoz (Spain). The participants were randomly divided in two groups: the supplementation group (SG; n=28) who were supplemented with n-3 PUFAs, and the control group (CG; n=27) who were not supplemented. As inclusion criteria, it was established by the physician that all participants should present at least 12 months of amenorrhea and to should be diagnosed as hypertensive at least 3 months before the beginning of the survey. General characteristics of both groups are presented in Table 1. All hypertensive participants were diagnosed in accordance with the criteria of the 5th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure of 1993 (JNC-V) (SBP> 140; DBP> 90 mmHg). Antihypertensive pharmacological treatment were followed homogeneously between groups, and consisted in: diet (n=8), diuretics (n=16), calcium antagonists (n=10), Inhibitors of the angiotensin-converting enzyme (n=6), calcium antagonists plus diuretics (n=10). Inhibitors of the angiotensin-converting enzyme plus calcium antagonists plus diuretics (n=5). The change of pharmacological treatment during the experimental period was considered as exclusion criteria.

The supplementation of the SG consisted in fish oil capsules composed of fish from salmon, trout, mackerel, herring and sardine, with a nutritional composition equivalent to 21% of EPA and 11% of DHA. Both groups were controlled in the third and sixth months of the survey and three months after the supplementation period (6 months). All participants were previously informed about the survey, participated voluntarily and all of them gave their signed informed consent. This research was carried out under the Helsinki Declaration, ethical guidelines, updated at the World Medical Assembly in Seoul in 2008, for research with human subjects.

Dietetic control

All participants followed a similar 1500 Kcal, low in sodium, diet. Before the start of the survey a nutritional questionnaire was applied to each participant in order to ensure no differences between groups in the intake of macronutrients and n-3 and n-6 PUFAs. The nutritional control was carried out by the same physician during the whole experimental period. The questionnaire consisted of 3 consecutive days (2 weekdays and 1 weekend day) registry. The same registry was applied to all participants at the beginning, at the third and sixth months of the supplementation period and three months after this period. In order to determine macro and micronutrients of their diets, different tables of nutritional composition were used [25]. It was previously established and protocolized the different quantities of food ingested by participants, establishing a standardization in order to diminish the error in the nutritional records introduced in the databases.

Anthropometric measurements

Anthropometric characteristics of all participants were evaluated always at the same time. To determine the body weight, a Seca weighing machine (Hamburg, Germany) with a precision of ± 100 g was used; to determine the height, a Seca tallimeter (Hamburg, Germany) with a precision of ± 1 mm was used; body fat percentages were measured with a Holtain plicometer (Crymch, United Kingdom) with a precision of ± 0.2 mm. The equations used to calculate the body fat mass were determined by Porta et al., (1993) [26] of the Spanish Group of Cineanthropometry. Body mass index (BMI) was calculated dividing body weight (kg) by squared height (m).

Blood arterial pressure measurement

Blood arterial pressure was measured in sitting position in the left forearm, leaning it in a soft surface, at the heart high. Each measurement was repeated three times in similar conditions, waiting three minutes between measurements. All measurements were performed by the same skilled physician with an esgmonometer of mercury (Riester, 660-2-306). The measurements were made at the beginning of the survey and each 15 days of the experimental period. All evaluations were performed in the same clinic, in similar conditions.

Blood samples determination

One blood extraction was taken of the antecubital vein to each participant. The extractions were performed in the morning after, at least, 8 hours of fasting. Blood samples were placed in glass tubes with lithium heparine. Once obtained, the samples were centrifuged at 2500 rpm during 10 minutes. After this process, erythrocytes were isolated, extracted from plasma and washed three times with a sodium chloride at 0.9%. Finally, they were frosted at -80°C until biochemical analysis. Total plasma cholesterol and triglycerides were determined by spectrophotometry, using a Hitachi 717 autoanalyzer and commercial kits for biochemical determination. To determine total fatty acids in plasma and erythrocyte, 0.5 mL were extracted of each sample, then, 2 mL of methanol/benzene (4:1) with an internal pattern (17:0) were added. Once mixed, the samples were slowly shaken in a magnetic stirrer while 200 μL of Acetyl chloride were progressively added. After that, the samples were stoppled and sealed with Teon in order to avoid evaporation losses. Once sealed, the samples were heated at 100°C for one hour and cooled in cold water. Then, 5 mL of CO_2 at 6% were slowly added to each sample to stop the reaction and neutralize the mixtures. After that the samples were centrifuged at 6000 rpm during 5 minutes. Then, the benzene extracts containing methylated fatty acids were taken for the tubes to be injected in the chromatographer.

For each sample, 3 μL of benzene extract were injected. A gas chromatographer HP-5890 Series II was used to determine the biochemical analysis. This chromatographer was equipped with a HP-5972 mass spectrometer detector. The column used to determine the samples was a capillary column SGE-BPX70 of 50 m. 0.33×0.25 . The fatty acids determined with this technique were: saturated fatty acids (SFAs): 14:0, 16:0, 18:0; Monounsaturated fatty acids (MUFAs) 16:1, 18:1 y 20:1; n-6 polyunsaturated fatty acids (n6-PUFAs): 18:2, 18:3, 20:3 y 20:4; and n-3 polyunsaturated fatty acids (n3-PUFAs): 18:3, 20:5, 22:5 y 22:6.

Statistical analysis

All data were analyzed with the software IBM SPSS Statistics in the version 22.0 for windows

significance was reached in 5% ($p < 0.05$). Wilcoxon test was used to compare differences between each group along the different moments of evaluation.

Results

Participants characteristics

All the 55 women completed the survey. Table 1 recopiates the characteristics of both groups at the beginning of the survey. This data manifest an accurate adaptation of the participants to the inclusion criteria.

Dietary intake of cholesterol and fatty acids during the survey

Table 2 reflects the weekly nutritional intake of SFAs, MUFAs, n3-PUFAs and n6-PUFAs of all participants of both groups.

Anthropometric evaluation

Table 3 shows the anthropometric characteristics of both groups during the survey.

As it can be observed in Table 3, no anthropometric changes are produced in the CG. However, the SG experienced a highly significant ($p < 0.001$) diminution in the triceps and subscapular folds

after 6 months of supplementation. Additionally, 3 months after the supplementation period, the diminution in body weight ($p < 0.01$) and in triceps ($p < 0.001$), subscapular ($p < 0.001$) and abdominal ($p < 0.001$) folds maintain significantly lower in comparison to the initial values.

Blood pressure and lipidic profile

Table 4 shows data about blood pressure and total plasma cholesterol and triglycerides concentrations during the research period.

Table 4 shows that no changes have been occurred in any parameter of the CG. In the SP, the SBP decreased significantly ($p < 0.01$) during the supplementation period, and it was maintained decreased ($p < 0.05$) three months after this period, in comparison to the initial values. However, the DBP only decreased significantly ($p < 0.05$) after 6 months of supplementation. Total cholesterol decreased ($p < 0.05$) after 3 months after supplementation and it was maintained ($p < 0.05$) 3 months after the supplementation period. Triglycerides only reaches statistical significance after 6 months of supplementations, being higher ($p < 0.05$) in comparison to the initial values.

Total plasma fatty acids concentrations

Table 5 presents the effects of MUFAs supplementations in the total plasma fatty acids profile.

As previously occurred, no changes were produced in the CG in any parameter. The n3-PUFAs supplementation affected the levels of DHA and EPA, which increased ($p < 0.05$) after 3 months of supplementation, after 6 months of supplementation ($p < 0.001$), and continued augmented ($p < 0.001$) after three months after the supplementation period. N3-PUFAs also showed a similar trend during the survey. N6/n3-PUFAs index decreased ($p < 0.05$) after 6 months of supplementation, and maintained these values three months after the end of the supplementation ($p < 0.05$). It is remarkable that after the survey the FA C24:1, C18:2-6, C20:3-6, C20:4-6, C20:5-3, C22:6-3 ($p < 0.001$); C18:3-6 ($p < 0.01$); C14:0 and C18:1E ($p < 0.05$) increased in comparison to the initial values.

Erythrocyte fatty acids profile

The results of the different percentages of fatty acids in the erythrocyte membrane are presented in Table 6.

Biochemistry	Quantity
Cholesterol	1285.40 ± 272.10
Saturated Fatty Acids (SFA)	106.45 ± 44.71
Monounsaturated Fatty Acids (MUFAs)	174.35 ± 82.08
Total Polyunsaturated Fatty Acids (PUFAs)	52.71 ± 28.55
C14:0	9.44 ± 5.85
C16:0	63.06 ± 25.74
C18:0	21.21 ± 9.52
C16:1	7.44 ± 3.19
C18:1	154 ± 74.93
C18:2-6	48.6 ± 29.25
C18:3-3	0.36 ± 0.27
C20:4-6	3.35 ± 1.41
C20:5-3 (EPA)	0.89 ± 0.90
C22:6-3 (DHA)	2.38 ± 2.13

Table 2: Weekly intake of Cholesterol (mg/week) and fatty acids (g/week).

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It can be observed in the Table 4 that no changes occurred in

Some previous surveys have demonstrated a diminution in the blood pressure as consequence of n3-PUFAs [22,28], but with dosages higher than 3 g/day. In this sense, surveys with animals and humans have demonstrated that EPA and DHA are incorporated in a different way in plasma [29], platelets, cellular membranes [6] and fatty tissue [30]. According to these reports, the diminution in the SBP experienced by the SG could be due to a progressive body accumulation of n3-PUFAs during the supplementation period. It is highly remarkable here that these participants had previously had a low nutritional intake of these nutrients. So, the administration of fish oils in this survey could effectively reduce their BP. In fact, this diminution is higher when the supplementation period is lengthened. Theoretically, this n3-PUFAs accumulation could maintain the BP diminution three months after the supplementation. However, the DBP diminutions were produced more slowly, reaching the statistical significance ($p < 0.05$) 6 months after the beginning of the supplementation period. After the treatment, the BP trends to return to the previous values, without statistical significance (Table 4). Additionally to these cardiovascular effects, anthropometric changes were produced in this survey. The SG experienced a diminution of subcutaneous body fat. This is a remarkable fact, because the subcutaneous fat induces a great tension on the cardiovascular system, increasing the cardiac output and finally reaching the BP. This peripheral subcutaneous fat reduction could reduce the BP by itself. It should be considered that in the previous surveys the skinfolds were not considered among hypertensive patients and this could taint the obtained results. Cholesterol concentrations were high (> 200 mg/dL) during all the survey and only decreased significantly at the third month of the supplementation. This fact reinforces the results previously obtained in similar populations with fish oils and vitamin E [31], as well as with an increment in the intake of PUFAs from extra virgin olive oil [32]. In relationship to total plasma FA (Table 5), the increment of FA 16:0 and C18:0 experienced in the SG at 3 and 6 months of supplementation can be due to a greater mobilization of peripheral fat mass as consequence of a higher n3-PUFAs intake. In the

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