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Supplementations of Low Doses of Fish Oil Effects on Clinic and Ambulatory Blood Pressure Levels in Treated Hypertensive Postmenopausal Women Sex Hormones Influence

Muñoz D[1]*, Maynar I[2], Robles MC[1], Figuero MJ[3], Grijota F[1] and Maynar M[1]

[1]Sport Sciences Faculty, University of Extremadura, Spain
[2]San Fernando Health Centre, Badajoz, Spain
[3]Infanta Cristina Hospital, Badajoz, Spain

Abstract

In the present study, we evaluate the changes that fish oil intake has (as a treatment's coadjutant) over women's blood pressure (BP) levels and the possible changes in their sexual hormones. For this reason, two groups were constituted: one group took fish oil during 6 months (SG), and the other group did not (CG). Anthropometric, dietetic, blood pressure and sex hormones controls, including β-estradiol, total testosterone, free testosterone and dehydroepiandrosterone (DHEA), were carried out by RIA techniques at the third and sixth month of starting or not the intake of fish oil, and 3 months after the end of the supplementation.

Our study shows improvements in blood pressure only in the group that effectuated the supplementation. In these women, an increase of the total weight was noticed, accompanied by a decrease in the skinfolds. In regard to the hormones, it calls our attention the high DHEA levels in both groups. But the fish oil intake generated a very significant fall in it. Total testosterone also decreased significantly its concentrations.

Therefore, we can conclude that the intake of low doses of fish oil produces a decrease in BP, and that the decline in androgenic hormones (DHEA and total testosterone) can play an important role in this decrease.

Keywords: Hypertension; DHEA; Testosterone; Estradiol; N3-fatty acids

Introduction

More than 25% of the female adult population worldwide is hypertensive [1]. Elevations in blood pressure (BP) in women are related to cardiovascular risk with the prevalence of hypertension [2,3], being particularly high among women aged ≥ 60 years. In United States, approximately 75% of postmenopausal women are hypertensive [4]. Hypertension is often accompanied by other cardiovascular risk factors, e.g., obesity, dyslipidemia, and diabetes mellitus [5]. It is noteworthy that the prevalence of hypertension-related cardiovascular complications is higher in postmenopausal women than in age-matched men. Indeed, these complications represent the leading cause of death in women [6].

In premenopausal women, endogenous estrogens maintain vasodilatation and thus, contribute to the BP control. Aging and the loss of endogenous estrogen production after menopause are accompanied by increases in BP, contributing to the high prevalence of hypertension in older women [7]. Cross sectional [8,9] but not longitudinal [10] studies showed a significant increase in systolic (SBP) and diastolic blood pressure (DBP), following the onset of menopause. Staessen et al. [8] reported a four-fold increase in the incidence of hypertension in postmenopausal women (40% in postmenopausal women vs. 10% in premenopausal women).

However, relatively little is known regarding the influence of androgens on BP and cardiovascular disease. There are reports of lower circulating testosterone and androstenedione levels in hypertensive men [11,12] and circulating testosterone levels in men with coronary artery disease [13] or myocardial infarction [14] are either unchanged or decreased.

Furthermore, women suffering from chronic anovulation and displaying hypertestosteronemia have an increased risk of coronary artery disease and myocardial infarction. Moreover, men with testosterone deficiency following orchiectomy present a slightly lower mortality from heart disease, suggesting that lower testosterone may protect against cardiovascular disease [14]. In female SH rats testosterone increases BP when they are ovariectomized [15,16].

N-3 PUFAs supplements may effectively reduce BP, but their use has been limited due to a requirement for high doses with its attendant side effects. It is not clear neither n-3 fatty acids would significantly lower BP in patients with high to normal BP nor lower doses would be effective and free of side effects [17,18]. Few studies have looked at the effects that these fatty acids supplementation may have on some hormones which in turn can have effects on BP.

The aim of our study is to evaluate the effects of having low doses of n-3 fatty acids (1.5 g/day) in hypertensive women who followed different antihypertensive therapies, with special focus on the effect that n-3 fatty acids has on sex hormones that may be linked to the pathogenesis of hypertension.

***Corresponding author:** Diego Muñoz, Sport Sciences Faculty, Avda de la Uniersidad, Cáceres, Spain, Tel: 927257460 (57833); E-mail: diegomun@unex.es

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Material and Methods

Study population

Fifty-five hypertensive postmenopausal women were voluntarily recruited from San Fernando Health Centre in Badajoz. All participants were informed and signed in a written informed consent. This study was conducted in accordance with the guidelines proposed in The Declaration of Helsinki and the study protocol was reviewed and approved by the Ethics Committee, University of Extremadura, Spain.

For the study, all members were divided into two groups, the supplementation group (SG) (n=28) which received supplementation with fish oil fatty acids, and a control group (CG) (n=27) which received no supplementation. As inclusion criteria**,** they were asked to present at least 12 months of amenorrhea, to be considered postmenopausal. The general features of the selected groups are shown in Table 1. The Supplementation Group was given a dietary supplement of fish oil capsules as co-adjuvant treatment containing the ingredients: oil of salmon, trout, mackerel, herring, sardine (Equivalent to a 21% EPA and 11% DHA) during six months.

Both groups were controlled at the 3rd and 6th month of beginning the period of supplementation or no supplementation, and 3 months once finished the study. Dietary and anthropometric control, blood pressure and blood extraction was made.

All hypertensive patients were diagnosed according to the criteria of fifth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure of 1993 (JNC-V) (SBP>140; DBP>90 mm Hg) , and included in the Hypertension agenda of the Health Centre. Antihypertensive farmacological 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 fixed as exclusion criteria.

Dietary control

All women followed a similar diet of 1500 kcal with a low sodium concentration. Prior to the start of the seizure of a dietary supplement, a dietary study was performed for all women in the studied population to assess about the intake of n-3 fatty acids and lipids. Dietary intake was monitored by the same dietitian throughout the study, with fulfillment of a 3-day diet record (2 weekdays and one weekend day) at baseline and repeated at the end of the 3rd and 6th month of the study, and at the 3rd month post intervention period. The dietitian determined if their usual eating habits were maintained and reminded them to make no changes. For its evaluation we use food tables prepared by Moreiras et al. [19].

Anthropometric measurements

The morphological characteristics of the participants were measured in the afternoon and always at the same time. Body height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca 220), and body weight was measured to the nearest 0.01 kg using calibrated electronic digital scales (Seca 769) with subjects barefoot. Body Mass Index was calculated by dividing the weight (in kg) by the height squared (in m^2). Body fat composition was evaluated using a skinfold thickness (Harpender calliper) by the same operator.

Blood pressure measurements

Hypertension was defined as blood pressure ≥ 140 mmHg and/or ≥ 90 mmHg, and/or use of antihypertensive medication. Blood pressure was measured in the sitting position on the right arm, and the mean of tree recordings, at least 3 min apart, was registered. This determination was made with a Mercury Sphygmomanometer (Riester, 660-2-306). The Blood Pressure was determined at baseline and every 15 days in the nursing office at the Health Centre, provided by the same person.

Blood sample measurements

All women were taken a sample of blood from the antecubital vein after overnight fasting, deposited in glass tubes containing lithium heparin and immediately centrifuged (2500 rpm for 10 min.). The separated plasma was stored at -70°C until analysis.

Total testosterone (TT), Free Testosterone (FT), Dehydroepiandrosterone (DHEA) and β-estradiol (E2) were determined with commercial kits by RIA. Aromatase activity was evaluated by the rate between β-estradiol/total testosterone.

Statistical procedures

All data were analysed using the analysis program SPSS version 17.0. The results are expressed as mean ± standard deviation and comparison of samples required a minimum of 5% significance ($p<0.05$). The normality of the variables' distribution was assessed using the Shapiro-Wilks test and Levene´s Test. We applied the Wilcoxon test to compare the changes throughout the studio between the two groups and the t-test for comparison of both groups.

Results

Study population

All the fifty-five randomized subjects completed the study. Baseline characteristics about blood pressure of the two groups are shown in Table 2, and confirmed that they were well matched for the entry criteria.

Cholesterol and Fatty acid ingested

The nutritional study for cholesterol and saturated, monounsaturated and polyunsaturated fatty acids in the diet followed by women is reflected in the Table 3.

Low levels of cholesterol were observed in the diet of participants. Monounsaturated and saturated fatty acids were consumed on high levels. Likewise, within the saturated fatty acids, highlights the high consumption of palmitic acid (C16:0), together with stearic acids (C18:0) (Table 4). However PUFAs were consumed on low levels,

	Initial		3 Months		6 months		3 months post	
	Supplement	Control	Supplement	Control	Supplement	Control	Supplement	Control
SBP (mm Hg)	159.53 ± 19.58	157.56 ± 20.48	146.37 ± 13.90***	158.62 ± 20.23	144.44 ± 18.20***	160.18 ± 18.22	153.88 ± 18.04**	160.44 ± 16.12
DBP (mm Hg)	96.44 ± 11.61	97.01 ± 10.24	93.80 ± 6.04	95.22 ± 10.42	90.06 ± 7.96**	96.01 ± 12.32	93.77 ± 9.06	97.12 ± 9.18

*p<0.05; **p<0.01; ***p<0.001.

Table 1: Effect of supplementation whit n-3 fatty acids on Blood Pressure.

Biochemistry	Quantity
Cholesterol	1285.40 ± 272.10
Saturated Fatty Acids (SFA)	106.45 ± 44.71
Monounsaturated Fatty Acids (MUFAs)	174.35 ± 82.08
Total Poliunsaturated Fatty Acids (PUFAs)	52.71 ± 28.55

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

	Initial		3 Months		6 months		3 months post	
	SG	CG	SG	CG	SG	CG	SG	CG
Wheigh (kg)	75.16 ± 11.69	76.18 ± 11.44	75.96 ± 11.57**	75.33 ± 11.34	76.43 ± 11.75*	76.13 ± 11.43	76.39 ± 11.71**	75.99 ± 10.22
Triceps fold (mm)	38.52 ± 6.71	37.42 ± 5.2	36.21 ± 8.57	38.02 ± 6.92	33.48 ± 7.28***	37.62 ± 6.40	30.01 ± 6.87***	35.01 ± 4.61
Subescapular fold (mm)	31.17 ± 6.83	30.17 ± 5.31	29.28 ± 7.93	31.57 ± 5.43	28.37 ± 7.55***	30.97 ± 6.23	24.96 ± 5.64***	31.98 ± 2.25
Suprailiac fold (mm)	22.64 ± 5.24	23.04 ± 4.22	23.05 ± 5.39	22.98 ± 6.02	23.69 ± 6.16	23.95 ± 6.00	20.27 ± 4.80	23.52 ± 6.02
Abdominal fold (mm)	38.70 ± 6.61	39.42 ± 6.02	38.31 ± 6.03	38.90 ± 5.99	35.37 ± 5.53	37.99 ± 8.24	29.61 ± 5.64***	39.62 ± 7.80

*p<0.05; **p<0.01; ***p<0.001, Wilcoxon test.

Table 3: Effects of n3-PUFAs supplementation on anthropometric parameters.

	Initial		3 Months		6 months		3 months post	
	Supplement	Control	Supplement	Control	Supplement	Control	Supplement	Control
E2 (pg/mL) (ND-60)	20.43 ± 9.84	21.43 ± 8.74	18.41 ± 8.79	20.98 ± 7.95	16.11 ± 12.90**	22.87 ± 8.82	24.79 ± 13.76	21.43 ± 10.84
TT (ng/ml) (0.1-1.1)	0.26 ± 0.10	0.25 ± 0.19	0.14 ± 0.10***	0.27 ± 0.32	0.20 ± 0.08**	0.24 ± 0.09	0.24 ± 0.11	0.25 ± 0.30
FT(pg/mL) (<4.6)	0.97 ± 0.52	1.12 ± 0.45	1.14 ± 0.56	1.13 ± 0.49	1.15 ± 0.56*	1.11 ± 0.45	1.93 ± 0.68*	1.12 ± 0.43
DHEA (µg/dL) (10-60)	64.34 ± 31.81	63.75 ± 13.28	43.93 ± 33.38***	62.15 ± 12.36	52.70 ± 23.74***	64.24 ± 12.35	48.85 ± 14.26	64.45 ± 12.15
Aromatase activity E2/TT	0.0769 ± 0.0020	0.0857 ± 0.0024	0.1315 ± 0.0019*	0.0777 ± 0.0028	0.1074 ± 0.0018**	0.0869 ± 0.0020	0.1032 ± 0.0021	0.0857 ± 0.0018

*p<0.05; **p<0.01; ***p<0.001. Wilcoxon test.

Table 4: Effect of w3 supplementation or no supplementation on plasma Sex hormones:Beta estradiol (E2), total testosterone (TT), free testosterone (FT) anddehydroepiandrosterone (DHEA).

especially n-3 fatty acids. The rate of n6-PUFAs/n3-PUFAs is high. There were not significant changes in these levels during the study.

Anthropometric results

Table 3 shows the anthropometric characteristics of women during the study.

In the SP group, weight increased significantly during the period of fish oil supplementation, which is maintained three months at the end of the study. Skinfolds measures decreased significantly (triceps and subscapular fold, p<0.001) after six months of supplementation and this decrease was maintained three months after the study ending. In the case of abdominal fold, significant decrease (p<0.001) was observed only after three months of the supplementation finish. No significant changes were observed in the control group.

Blood pressure levels

Table 1 indicate that in supplementation group, SBP decreased significantly at the third (p<0.001) and sixth (p<0.001) month after starting the study, and three months (p<0.01) since the end of supplementation. With regard to the DBP levels in the same group, it also produced a decrease that becomes significant (p<0.01) at the sixth month of supplementation and that is maintained three months after the completion of the supplementation, even without acquiring statistically significant. In the control group there were no significant changes in BP during the study.

Sex hormones

In Table 4, we present the results obtained for the sex hormones that may have an important role in the genesis and development of hypertension in the two study groups.

In the SG, β-estradiol experienced a decline in the first three months and was significant (p<0.01) at reaching the sixth month, returning to baseline after three months of leaving the supplementation. β-estradiol concentrations were maintained within the normal range in all the samples. However, DHEA at the beginning of the study was higher than normal values in the two study groups. The SG showed a significant decrease (p<0.001) after three months of the onset, maintained with the same significance degree at the sixth month of the supplementation.

Total testosterone decreased at the third (p<0.001) and sixth months (p<0.01), although in all cases was within the range considered normal. Free testosterone values increased statistically 6 months after beginning the supplementation, and maintained the same levels of significance at 3 months after the stop of supplementation, since in the previous case values were within normal limits.

The aromatase rate increased significantly at the 3rd, 6th months and after stopping the supplementation.

No changes were found in any hormone studied in the CG.

Discussion

The aim of the present study was to examine the effect of a moderate long-term supplementation with low doses of fish oil (1,5 g/day) on the development and treatment of hypertension in relation with sex hormones. All participants in this study were hypertensive and postmenopausal women, and significantly older than groups of others studies [20-22]. These women have clear risk factors for cardiovascular disease (CVD), menopause, obesity, high cholesterol levels and they intake small amounts of n-3 fatty acids in their diet (Table 2). They form two homogeneous groups that allow us study, in an appropriate

way, the effects that fish oil administration (n-3 fatty acids) as adjuvant therapy, has on BP and on their sexual hormones.

Administration of 1.5 g/day of fish oil to the SG, decreased systolic ($p<0.001$) and diastolic blood pressure ($p<0.01$) (Table 1). Some data proved the reduction of BP by n-3 PUFAs in essential hypertension [17,18] in doses ≥ 3 g/day. *In vitro* animal and human studies have shown that EPA and DHA are differently incorporated into plasma [23,24] platelet, membranes [25] and tissue lipids [26]. We think this waning of SBP in the SG, could be due to a progressive accumulation in the body of n-3 PUFAs during the supplementation period and it is needed to remember that this women have a low dietary ingestion of n-3 PUFAs, so this low doses of fish oils can reduce significantly the SBP, and this reduction is higher when the supplementation period is longer. This accumulation can maintain the significant decrease in SBP during twelve weeks after treatment ends.

Regarding DBP, which decreases during the study, is only statistically significant ($p<0.05$) after 6 months of treatment only in the SG. As happening to the SBP, after 3 months of completing treatment the decrease in DBP remained, although it did not reach statistical significance. These data may indicate the need to maintain, for the longest time, the supplying of n-3 fatty acids in order to get major accumulations in tissues, especially subcutaneous and in cell membranes and obtain with them largest decreases and sustained reductions on BP, without giving high doses that may lead to side effects and difficult their destination.

Weight suffered a slight increase, statistically significant in the SG during the study (Table 3). The decrease in skin folds indicates that this is probably due to an increase in free-fat weight induced for the increased levels at this time in total testosterone and free testosterone that promotes increases in the muscular cells synthesis. This gain of weight is also seen in the study by Gray et al. [22]. The skinfolds decreases were statistically significant on triceps and subscapular skinfolds (Table 3) in the SG, indicating a decrease in peripheral fat body as a result of taking n-3 fatty acids, because there were no changes in nutritional habits during the study and in the CG no changes were found. This decrease of subcutaneous fat has great significance related to health, since subcutaneous fat is known to be a great strain on the person's cardiovascular system, increasing its cardiac output, leading to a BP increase. This lessen in peripheral fat can improve BP levels, causing too a decrease in it through this way. It should be noticed that in the other reviewed studies, there was no measure of skin folds in patients to assess changes in body weight.

Regarding the hormonal levels on the CG and SG, it led us to a number of important changes only with the fish oil supplementation.

Prior to menopause, blood pressure is lower in women compared with age-matched men [27,28]. During the menstrual cycle, blood pressure levels are inversely related to circulating estrogen concentrations and lower when β-estradiol levels peak [28], reflecting the vasodilator activity of endogenous β-estradiol [29]. The first decade after menopause is accompanied by an increase in BP. In the seventh decade of life, the prevalence of hypertension among women is even higher than in men, regardless of ethnic background [27,30].

The protective effects of β–estradiol on hypertensive women are based on the acute and long-term vasodilator effects of estradiol mediated in part via generation of endothelium-derived nitric oxide (NO), and they are attenuated by NO inhibitors [31,32]. β-estradiol induces an increase in intracellular free calcium concentration in endothelial cells [33,34], which could contribute to the increase in endothelial-derived NO. Since inhibition of NO synthesis promotes arterial hypertension [35], it is conceivable that estradiol protects against hypertension by increasing NO synthesis.

About β-estradiol in our women, a decrease occurred in β-estradiol, ovarian steroid hormone, reaching statistical significance at the 6th month in the SG, returning to the initial values at the third month after the supplementation period. This decrease was accompanied with a significant decrease of total testosterone, its precursor. We think, actually recognized, that n-3 PUFAs supplementation can raise NO synthesis by the endothelial cells, improving the activity of cell membrane, (calcium Channels and the cells receptors for hormones) [17] and the n-3 PUFAs can act as endogenous enhancers of parasympathetic tone, suppressing inflammatory events and inhibiting sympathetic over activity; and they can block β-receptor action. The endothelium cells, with good levels of n-3 PUFAs, need low levels of β-estradiol to produce a good control on the BP. On the other hand, in the Table 4, we can see an aromatase activity increase, due to the low levels of total testosterone above all, its precursor, indicating more disposition and anti-hypertensive activity of β-estradiol by the cells.

Dehydroepiandrosterone (DHEA), adrenocortical hormone and possible precursor in the synthesis of total testosterone, presented levels above the normal values in the two groups. The SG suffered a significant decline throughout the study at the 3rd and 6th month ($p<0.001$). According to Cleare, this hormone has a positive correlation with blood pressure, meaning that higher DHEA levels associates with higher BP levels [36]. This relationship would be due to structural similarity that mineralocorticoid aldosterone have with DHEA. This could be another mechanism by which the fish oil intake could low blood pressure, and mainly the SBP, being the most sensitive to increase fluids and leading us to this hormone increases. On the other hand, blood pressure can be modulated indirectly by the action of the enzyme steroid sulfatase (STS) that catalyzes the conversion of estrone sulfate, DHEA sulphate, testosterone sulphate and other forms of conjugated steroids to the free form and to active steroid hormones. When this enzyme acts, potently lots of active steroids, estrogen, DHEA, testosterone and mineralocorticoids are released; because of this, we could observe an increase in BP, due to an increased extracellular volume. When we give an inhibitor of this enzyme, the presence of free hormones is inhibited and thus its activity; and in our case, an increase in BP is prevented as well [37]. On the other hand, administration of DHEA and Testosterone in normotensive rats produced renal hypertension [38]. Because of it, the decrease on DHEA and total Testosterone for taking fish oil would lead us to a decrease in BP by directly decreasing its action on the kidney. Schunkert et al. [39] showed also a positive association between endogenous DHEA and SBP and it is independent of the other adrenal steroids. In this way, lower levels of DHEA, as in our study, drops levels of BP. Barna et al. [40] found a highly positive correlation ($p<0.001$) between levels of DHEA sulfate and BP. Therefore, we believe that the DHEA decrease in serum levels would be largely responsible on BP decreases.

In the other hand, some of the advantageous effects of testosterone observed in males (decrease of BP) may be due to its conversion to estradiol and estradiol metabolites that can induce an increase in the synthesis of NO [41]. This hypothesis is supported by the finding that the inhibitory effects of dehydroepiandrosterone, a precursor of androstenedione, on atherosclerosis are blocked by the aromatase inhibitor fadrozole [41]. This finding suggests that the sequential conversion of several androgens to estradiol is responsible for their anti-atherosclerotic actions, but whether estradiol is the ultimate mediator remains unclear.

Total testosterone, steroid produced in women ovaries, had a highly significant decrease throughout the study. This hormone, like estrogen, has by its structural similarity with mineralocorticoid, similar actions to them, producing hypertension; and it is because of this their decline that it would lead to decreases in BP, especially systolic pressure. Reckelhoff et al. [15] showed that androgens in general may raise BP by increasing fluid reabsorption in the proximal tubule, or either by activating the renin-angiotensin system, meaning therefore that the decline in testosterone levels in our women would, by this mechanism, decrease BP. For the foregoing reasons, we believe that the decreases in estradiol, total testosterone and DHEA, observed in our study could be due to an inhibition of the enzyme steroid sulfatase (STS) for taking fish oil, and this would lead to a BP decrease, shown in our study.

Both estradiol and testosterone are present in both sexes, in different concentrations and ratios. Endogenous androgens (dehydroepiandrosterone, androstenedione, and testosterone) are readily converted to estradiol by the sequential actions of 17β-hydroxysteroid dehydrogenase (17β-HSD) and aromatase [14]. In our study, in the SG, the aromatase activity actually increases at 3rd ($p<0.01$) and 6th month ($p<0.01$), fact that can justify the decrease experimented by the DHEA and TT in our supplemented with n-3 PUFAs women.

For all these reasons, we conclude that taking a low dose of fish oil (1.5 g/day), as adjunctive therapy in hypertensive postmenopausal women, can produce decreases in BP both systolic and diastolic, and these decrease can be produced in the case of SBP in the third months of the intake, but more months of supplementation are required to produce similar changes in DBP. These decreases in BP could be due to changes in levels of sex hormones such as DHEA, β-estradiol, total testosterone or free testosterone. It also could be due to changes in the cellular receptors of these hormones, induced by the fish oil supplementation. More studies are needed in this line to clarify the influences these fatty acids can involve on sex hormones.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Authors Contributions

Maynar designed the study; data were collected and analyzed by Maynar, Robles, Grijota and Figuero; Muñoz, Robles and Maynar undertook data interpretation and manuscript preparation. All authors approved the final version of the paper.

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