Omega-3 polyunsaturated fatty acids supplementation and blood pressure control

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ABSTRACT

Objectives: Determine the effect of PUFA supplementation on patients diagnosed with hypertension and are on treatment with antihypertensive drugs.
To identify if the response to PUFA differs according to gender and duration of hypertension.
To determine the effect of coexisting morbidities like diabetes and dyslipidemia on the hypertensive patients response to PUFA.

Materials and Methods: This observational study was conducted at the GMCH & RC during the period Jan 2012-Dec 2012. A total of 100 hypertensive patients on treatment, 50 of whom were taking n-3PUFA supplements along with their antihypertensive medications, were followed up for a period of 3 months. Comparisons were drawn between the BP recordings at the time of enrolment in the study and their follow up values 3 months after enrollment. Data analysis was done per protocol, excluding data from the drop out patients.

Results: There was a significant reduction in both the systolic and diastolic blood pressures after 3 months of n-3 PUFA therapy (mean reduction systolic 9.7 mmHg; diastolic 4.7 mm Hg). Males showed significant improvement in BP (systolic) compared to females. The BP of non-diabetic participants' improved significantly with PUFA therapy. The antihypertensive effect of PUFA supplement was more marked in patients with long standing hypertension.

Conclusion: Supplementation with omega- 3 PUFA causes a reduction in blood pressure in hypertensive patients.

Keywords: PUFA, omega 3 fatty acids, hypertension, dietary supplementation

INTRODUCTION

Hypertension has now become an increasing problem globally. Overall, 26.4% of the global adult population in 2000 had hypertension and this is predicted to rise to 29.2% by 2025, affecting a population of 1.56 billion[1]. There is not enough data regarding the prevalence of hypertension in UAE as a whole but report from the National Epidemiological Study of Hypertension in the United Arab Emirates (NESH-UAE) showed an overall prevalence in this screened sample of 3150 in Sharjah was 36.6%. Most of the study subjects were in the productive age, from 30-50 years[2].

Apart from genetic factors and stress, hypertension is often triggered by nutritional factors like increased consumption of carbohydrates, alcohol, salt, excess intake of saturated fatty acids (SFA) and reduced consumption of polyunsaturated fatty acids (PUFA)[3].

Rapid economic growth in UAE has, however, brought about marked changes both in lifestyle and in patterns of health and disease. Family history, lifestyle and socioeconomic factors are the major contributors to high prevalence of hypertension in UAE[4].

Certain dietary interventions and life style modifications have been shown to augment antihypertensive medication therapy in controlling hypertension. Diet that includes two to three servings of oily fish per week has been

often recommended by several health organizations[5,6] Such recommendations stem from the understanding that the intake of long-chain omega 3 (n-3) fatty acids- namely *Eicosapentaenoic acid* (EPA) and docosahexaenoic acid (DHA) confers cardiovascular protective effects that include but are not limited to blood pressure reduction[7] Omega -3 fatty acids are a group of biologically occurring Polyunsaturated Fatty Acids (PUFAs). DHA and EPA are two long chain omega-3 fatty acids that function as precursors to eicosanoids which are assumed to have anti-inflammatory, antithrombotic, antiarrhythmic, and vasodilatory's properties. DHA and DPA are biosynthesized (in-vivo) from a short chain fatty acid called alpha-linoleic acid (ALA). The rate of this biosynthesis mechanism, however, is extremely low in humans; which renders dietary supplementation the sole source of DHA and EPA for humans[8,9].

The purpose of our study is to verify whether there is an effective role for omega-3 PUFA dietary supplements in the treatment plans of hypertensive patients seen regularly at the outpatient department of Gulf Medical College hospital (GMCH) in Ajman, U.A.E in a scenario where such dietary supplements are not covered by most of our patients' health insurance plans and thus patients who opt to utilize those dietary supplements pay for them on an out of pocket basis and to examine if there exists unique effects of omega-3 PUFAs on BP in a certain gender or Ethnicity of patients, and in patients with a certain co morbidity, within the our population of patients. We found out that many small size randomized-controlled trails (RCTs) were conducted over time in different parts of the world to objectively investigate the relationship between consuming omega-3 PUFAs and blood pressure. In general, the results of such studies did not have rigorous external validities so they could not be extrapolated to various populations. Moreover, false negative findings were likely in those randomized controlled trials whenever sample sizes were not large enough or if blood pressure measuring techniques were sub-optimal[10].

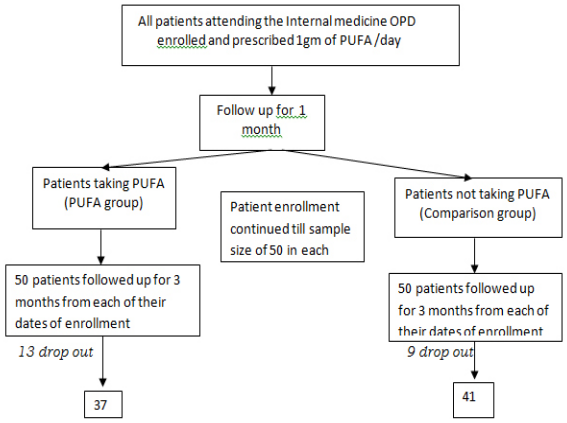
Our literature review suggests an overall small, yet useful, role of omega-3 PUFAs in reducing blood pressure in hypertensive patients. Due to conflicting results in we decided to conduct a prospective observational study that has an intervention group and a comparison group to look at the effect of omega-3 PUFA regular intake on the level of hypertension control in a group of hypertensive patients who are recurrently seen at the outpatient department in GMC.

MATERIALS AND METHODS

Study settings and population-This study was conducted among hypertensive patients visiting OPD of internal medicine department at the GMCH & RC during the period June 2011-Jan2013. Patients diagnosed with hypertension on treatment and prescribed PUFA were included in the study. Patients using hormone replacement therapy, and diagnosed with cardiac or c/c renal disease or complications of hypertension were excluded from the study. Based on evidence from available literature we expected a mean difference of 5 mm Hg and a SD of 8 and hence the estimated sample size was calculated to be 50 in each arm.

Study design and data collection - This observational study was approved by the Ethics committee of the University and therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. As a part of patient education, all hypertensive patients attending the OPD of Internal medicine are being educated by their attending physician about the health benefits of PUFA as a nutritional supplement and prescribed 1gm fish oil (Omacor tablets) daily. The researchers screened all the hypertensive patients attending the medicine OPD based on their inclusion and exclusion

criteria and enrolled them for the study. A validated questionnaire was filled by one of the researchers after interviewing the patient. The questionnaire recorded the socioeconomic variables; details of Hypertension-age of onset, duration; History of dyslipidemia /diabetes and Treatment history. Blood pressure was averaged across three readings were taken 2 min intervals and was recorded in the questionnaire. After a follow up of 1 month the participants who consumed PUFA supplement were categorized into PUFA group and the others into control group. All the patients were followed up for 2 more months. Enrollment of patients into the study continued till the sample size of 50 was attained in each group and each of the participants in both groups was followed up for 2 more months after being allocated into the groups. Comparisons were drawn between the BP recordings at the time of enrolment in the study and their follow up values 3 months after enrollment.



Data Analysis- Statistical analysis was done using PASW 19 version software. Only subjects who completed the study and had both baseline and final measurements were included in the analysis. Chi-square test was used to determine the association between the variables. Paired and unpaired t-tests were used to compare the variables within the group and between the groups both prior to and after the intervention. The significance level was considered as $p<0.05$.

RESULTS

Analysis of demographic data revealed that the participants of this study were of the mean age of 46.4 years and the mean duration of hypertension was 5yrs. Majority of them were males (73%). Of the total participants 66% were of Arab origin while the rest were Asians.

Table 1 shows the baseline characteristics of the PUFA group and control group. The two groups are found to be matched with regards to their mean age and mean duration of hypertension and their blood pressure values. There was a significant difference in the gender distribution among both the groups. The participants in the PUFA group were predominantly Arabs (94.6%) while Asians accounted for 58.5% of the control group. Prevalence of diabetes was 27% in PUFA group and 31% in control group. 89% of the patients in PUFA were on lipid lowering drugs.

Comparison of initial blood pressure values of the groups shows no significant difference between the two groups. The BP values of patients with diabetes and

Table 1: Gender, Ethnicity and Co-morbidity of Comparison group and PUFA group

Variables	Groups	PUFA group (N=37) N (%)	Comparison group (N=41) N (%)	p value
Gender	Male	22(59.5)	35(85.4%)	0.01
	Female	15(40.5%)	6(14.6%)	
Ethnicity	Arab	35(94.6%)	17(41.5%)	0.001
	Asian	2(5.4%)	24(58.5 %)	
Number of Diabetic patients		10(27%)	13(31%)	NS
Number of patients on lipid lowering drugs		33(89%)	23(56%)	0.001

Table 2: Blood pressure values at enrollment (mean ± SD)

Variables	Groups	PUFA group N=37	Comparison group N=41	p value
Blood pressure of all participants	Systolic BP	131.89±18.64	138.76±14.50	NS
	Diastolic BP	85.27±11.05	87.41±10.61	NS
Blood pressure of Diabetic patients	Systolic BP	140.00±25.386	141.54±15.730	NS
	Diastolic BP	87.50±15.855	88.46±12.810	NS
Blood pressure of patients on lipid lowering drugs	Systolic BP	133.33±19.15	137.09±13.52	NS
	Diastolic BP	86.21±11.25	85.04±9.89	NS

Table 3: Comparison of BP values at enrollment and at 3 months of follow up (mean ±SD)

Variables	Enrollment			Follow up		
	PUFA group (N=37)	Comparison group (N=41)	p	PUFA group (N=37)	Comparison group (N=41)	p value
Systolic BP (mm Hg)	131.89±18.68	138.76±14.50	NS	122.89±12.18	132.59±13.44	<0.001
Diastolic BP (mm Hg)	85.27±11.05	87.41±10.61	NS	80.05±6.33	84.78±8.28	<0.01

Table 4: Gender and changes in blood pressures following PUFA therapy

Gender	Variables	Enrollment	Follow up	p value
Males (n=22)	Systolic BP	132.27±17.34	123.64±13.99	<0.05
	Diastolic BP	83.65±10.02	80.45±6.53	NS
Females (n=15)	Systolic BP	131.33±21.00	121.80±9.26	NS
	Diastolic BP	80.33± 11.10	79.47±6.20	NS

Table 5: Diabetic status and changes in BP with PUFA therapy

Disease groups	variables	Enrollment	Follow up	p value
Diabetic participants(N=10)	Systolic BP	140.00±25.39	125.70±6.87	NS
	Diastolic BP	87.50±15.85	81.20±6.05	NS
Non Diabetic participants(N=27)	Systolic BP	128.89±15.02	121.85±13.60	<0.05
	Diastolic BP	84.44±8.91	79.63±6.50	<0.05

Table 6: Duration of hypertension and changes in BP with PUFA therapy

Duration of hypertension	Variables	Enrollment	Follow up	p value
<5years (N=17)	Systolic BP	125.88±10.04	121.59±7.93	NS
	Diastolic BP	82.94±7.71	79.53±5.81	NS
≥5 years (N=20)	Systolic BP	137.00±22.73	124.00±15.01	<0.05
	Diastolic BP	87.25±13.13	80.50±6.86	<0.05

Table 7: BP changes in patients on statins in PUFA and comparison group (mean ±SD)

Variable	Enrollment			Follow up		
	PUFA group (N=33)	Comparison group (N=23)	p	PUFA group (N=33)	Comparison group (N=23)	p value
Systolic BP (mmHg)	133.33±19.15	137.09±13.52	NS	123.24±12.63	131.13±14.25	<0.05
Diastolic BP (mmHg)	86.21±11.25	85.04±9.89	NS	79.76±6.47	83.91±7.22	<0.05

patients on lipid lowering drugs were also comparable at the time of enrollment. (Table2)

Table 3 shows the changes in blood pressure during the study. There was a significant reduction in both the systolic and diastolic blood pressures after 3 months of PUFA therapy. While the systolic BP showed a mean reduction of 9.7 mm Hg (95%CI of 2.3 -15.7), the diastolic pressure reduced by a mean of 4.7 mm Hg(95%CI of 1.6-8.8)after PUFA therapy, when compared to the patients on anti-hypertensive medications alone.

As the groups were not comparable with regards to gender, we used paired t tests to analyze the response of different genders to PUFA therapy, with the intervention group.. Following PUFA therapy the systolic blood pressure in males showed a significant reduction of 9.63 (95%CI of 0.2 to 17.1) .Reduction was noted in the diastolic BP of males and both systolic and diastolic blood pressure values of the female participants as well, but this was not of statistical significance (Table3).

Hypertensive patients with diabetes showed reduction in their blood pressure values on PUFA therapy.(CI for Systolic BP -3.4 – 32.0,CI for diastolic BP -3.0 - 15.6). However the reduction was not statistically significant. The systolic BP of non-diabetic patients showed a mean reduction of 7 mmHg (95% CI of 0.22 -14.30) while the diastolic BP reduced by 5 mmHg (95% CI of 0.8 - 8.8) (Table 4)

Significant blood pressures reduction of 13 mm Hg systolic (95%CI of1.5 to 24.5) and 6.75 mmHg diastolic (95% CI 1.6 to 11.9) was recorded, following PUFA therapy in participants with hypertension of 5 years duration or longer . Though consumption of PUFA resulted in improvement of blood pressure values in patients with hypertension of less than 5 years duration, this was not statistically significant. (Table 6).

Consumption of PUFA along with statins resulted in a significant decrease in both systolic and diastolic BP of patients when compared to patients on statin therapy alone. Subgroup analysis could not be done to determine the difference in the effect of PUFA on the BP of patients who are on antihypertensives and patients who are on statin therapy along with antihypertensives due to insufficient sample size (Table7).

DISCUSSION

Dietary intake of □3 PUFA is known to reduce the incidence of mortality and morbidity from cardiovascular diseases. The reduction in the risk for arrhythmias, inhibition of growth of atherosclerotic plaques, anti-inflammatory effects and decrease in triglyceride levels caused by □3 PUFAs –DHA and EPA account for their advocated use in patients with cardiovascular diseases[11].

The reduction in Blood pressure caused by administration of PUFA to hypertensive patients on treatment, as observed in our study is in accordance with the Meta analysis findings of Morris *et al* ,that showed a significant reduction in blood pressure of 3.4/2.0 mmHg with

the consumption of omega-3 fatty acids[12]. While a systematic review of randomised controlled trials and cross over trials by Campbell et al(2013) reported significant reductions in systolic and diastolic BP ;2.56mmHg (95% CI 0.58 TO 4.53) and 1.47 mmHg (95%CI 0.41 to 2.53) of hypertensive patients, they did not find any significant reduction in BP values of normotensive patients[13]. Studies have also stated that the reduction in systolic pressure is noted earlier in the course of treatment with PUFA than the improvement in diastolic blood pressure values[11]. A cross sectional study conducted by Ueshima et al (2007) concluded that when compared to hypertensive individuals, consumption of foods containing PUFA had a stronger inverse association with blood pressure values of normotensives and in individuals who are not undergoing dietary and /or medical interventions[10].

The beneficial effects of PUFA on vascular function are mediated by a wide range of biochemical and physiological alterations. EPA and DHA are acted upon by cycloxygenase and *lipoxygenase* give rise to 3 series prostaglandins and 5 series leukotienes.TxA3 is biologically inactive while PGI3 is equipotent to PGI2 in causing vasodilatation and inhibiting platelet aggregation hence the overall balance is shifted from vasoconstriction to vasodilatation[14].

Studies in both humans and animals have revealed that long chain n-3 PUFAs inhibit the synthesis of TxA2 –a potent vasoconstrictor[15] This effect maybe produced by altering the enzymes for its biosynthesis[16]. Antagonism of TxA2 and PGH2 receptors is also another mechanism by which the blood vessel is kept dilated by n-3 PUFA[17]. Another endothelium derived vasoconstrictor inhibited by EPA is Endothelin -1.

n-3 PUFAs increase endothelium-dependent relaxation by enhancing the release of NO[18].The antioxidant action of n-3 PUFA is also known to reduce endothelial free radical damage and thus restore the balance between VD and VC[19]. Activation of vascular K+ channels and inhibition of Ca2+ channels leads to hyperpolarisation and relaxation of vascular smooth muscle was noted with treatment with PUFA[20].

The metabolism of n-3 PUFAs can be modified by genetic and epigenetic factors. Genetic p*leomorphism* of genes for these enzymes result in altered content of n-3 PUFA in membrane phospholipids and hence their response in different individuals [21].This could be postulated to be the reason for the less improvement in BP values of females when compared to males in our study. In contrast to our findings there has been data suggesting no significant interaction between BP and gender[10,11]. Results of meta-regression analysis conducted by Geleijnse (2002) suggest more significant reduction in women than in men. In the view of these conflicting results more studies have to be conducted to analyse the interactions between female hormones and effect of PUFA[22].

A rich source of dietary n-3 PUFA is known to reduce the increased systolic blood pressure associated with long-term diabetes in rats [23]. Blood pressure also decreases in type 1 diabetic patients receiving supplements of n-3 PUFA[24]. This is consistent with the findings of our study where a reduction was noted in the blood pressure values of hypertensive patients with diabetes. Obesity, malignancies and insulin resistance are among the acquired causes of modifications in the rate limiting enzymes of n-3 PUFA metabolism[7,25]. This could probably be the reason why the improvement seen in non-diabetic hypertensives on PUFA therapy was significant when compared to patients with diabetes co-existing with hypertension in our study.

Endothelial dysfunction is present in various forms of cardiovascular disease. Long standing hypertension compounds endothelial dysfunction, decreasing responsiveness to medications. In hypertension, reduction of BP *per se* does

not seem to restore endothelial function. Restoration of endothelial function is seen following treatment of only few underlying diseases[26]. PUFAs by their mechanism of action reduce the endothelial damage and hence maintain responsiveness to antihypertensive therapy.

Treatment with 3 hydroxy 3 methylglutaryl-coenzyme A reductase inhibitors (statins) has a relatively small but statistically significant effect on blood pressure. A meta-analysis of the effect of statins on blood pressure in patients on concomitant antihypertensive treatment revealed significant reductions in both systolic and diastolic BP of patients taking statins, in comparison with placebo group[27]. In our study, it was found that stains when consumed along with PUFA supplements caused significant reduction in blood pressures as compared to the group taking satins alone. This is in accordance with the findings of Cicero AF(2010)who found that PUFA supplementation for 1 year duration in *hypertriglyceridemic* patients on statin therapy with high normal blood pressure resulted in a significant reduction in their systolic BP, diastolic BP and pulse pressure[28].

LIMITATIONS

Randomization was not performed, due to the fact that there were financial; constraints in making the PUFA supplement available to the patient. It was in such a scenario more feasible to observe patients who were in a position to pay for the same by themselves. We were not able to control the effect of the confounding factor of diet, due to lack of a validated questionnaire which is standardized for recording of dietary data of the population based in UAE.

CONCLUSION

From our observational study we found that supplementation with n-3 PUFA (1g/d) for 3 month causes significant reduction in BP of patients with hypertension on treatment. The effect of PUFA was more pronounced in patients with long standing hypertension. Co-existence of diabetes causes a decrease in response of patients to n-3 PUFA supplements. Hence we like to conclude that in accordance with data already available Omega-3 PUFA dietary supplements have a beneficial effect as add-on modalities to augment pharmacotherapy in hypertension. However the observation that BP of females of Arab ethnicity shows a less response to PUFA is a finding which needs to be investigated by genetic studies.

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