EFFECT OF LOW-DOSE OMEGA-3 FATTY ACIDS SUBSTITUTION ON BLOOD PRESSURE, HYPERINSULINEMIA AND DYSLIPIDEMIA IN INDIANS WITH ESSENTIAL HYPERTENSION: A PILOT STUDY

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ABSTRACT

The present study comprised 100 patients of essential hypertension who were screened for fasting hyperinsulinemia, which was detected in 77% cases. Twenty such hyperinsulinemic cases were subjected to 4 weeks of dietary control phase followed by 6 weeks of omega-3 fatty acids substitution [either 0.6 g/d (group 1) or 1.2 g/d (group 2)]. The mean basal fasting plasma insulin levels were significantly higher ($p < 0.001$) in patients of hypertension when compared to normal controls (126.51 ± 80.36 and 19.35 ± 12.61 $\mu\text{U/ml}$ respectively). At the end of 4 weeks of diet control only, no significant change was observed in any parameter. After substitution of omega-3 fatty acid, a significant reduction of fasting plasma insulin levels in both group 1 (29%) and group 2 (22.8%) was observed ($p < 0.001$). Significant reduction of systolic and diastolic blood pressure (16.4% and 25% respectively), serum cholesterol, triglycerides and low density lipoprotein was also noted in both groups ($p < 0.001$), while high density lipoprotein increased by ~ 8 mg% in both groups. Thus omega-3 fatty acid substitution in low dose along-with curtailment of dietary omega-6 fatty acid may be used as an adjunctive measure in the management of essential hypertension.

KEY WORDS

Omega-3 Fatty acids, Hyperinsulinemia, Essential hypertension.

INTRODUCTION

An elevated arterial blood pressure is probably the most important public health problem throughout the world. Although our understanding of the pathophysiology of elevated blood pressure has increased, in 90-95% of cases the etiology is still largely unknown. Patients with arterial hypertension and no definable cause are said to have primary, idiopathic or essential hypertension. Insulin resistance and/ or hyperinsulinemia have been suggested as being responsible for the increased arterial pressure in some patients of hypertension. It is postulated that hyperinsulinemia can increase arterial pressure by one or more of following mechanisms (1):

1. Hyperinsulinemia produces renal sodium retention and increases sympathetic activity thus increasing arterial pressure.
2. Vascular smooth-muscle hypertrophy secondary to the mitogenic action of insulin.
3. Insulin also modifies ion transport across the cell membrane, thereby potentially increasing the cytosolic calcium levels of insulin-sensitive vascular or renal tissues.
4. Insulin resistance may be a marker for another pathological process, which could be a primary mechanism increasing blood pressure.

Studies have shown that Indians are genetically predisposed to hyperinsulinemia showing that ethnic background is an important determinant of insulin resistance (2, 3). Moreover, changes in lifestyle and faulty dietary pattern have led to the current epidemic of coronary artery disease and type 2 Diabetes Mellitus (DM). **Omega-3 fatty acids** (FA) viz. eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) administration in low doses ($< 3\text{g/d}$) has shown a BP lowering effect in subjects with type 2 DM (4, 5).

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There are few studies showing similar results of omega-3 FA therapy in patients of **essential hypertension** at a higher dose (> 5 g/d) of omega-3 FA (6,7), attributable to plasma membrane enrichment with EPA, which competes with arachidonic acid (AA) [an omega-6 fatty acid] as a potential substrate for the enzyme Cyclooxygenase. While the predominant product of arachidonic acid in the platelets, thromboxane A₂ (TXA₂) is a potent vasoconstrictor; the corresponding product of EPA is thromboxane A₃, which is virtually biologically inert. In contrast both prostaglandin I₂ (PGI₂), derived from AA, and prostaglandin I₃ (PGI₃), derived from EPA, are potent vasodilators. Thus, alteration of the omega-6 FA/omega-3 FA ratio in diet to near normal (8: 1) with dietary modification and supplementation of omega-3 FA, results in a shift of the net balance between PGI₂/PGI₃ and TXA₂/TXA₃ in the body to a more vasodilator state (8). Other possible mechanisms include effects on renal functions, lowering blood viscosity and a reduction in vascular responsiveness to systemic vasoconstrictors (9). Beneficial effects of omega-3 FA even in low doses have been seen on serum lipid profile of 935 NIDDM /IGT patients with hypertriglyceridemia (10). However, one study by Tsai *et al.* (11) had reported increased low density lipoprotein (LDL) susceptibility to oxidation in normolipidemic subjects after omega-3 FA therapy but studies by Wander *et al.* (12) and Jain *et al.* (5) using better techniques of measuring low density lipoprotein oxidation and low-dose of omega-3 FA have shown decreased oxidative susceptibility. Hence the present study was undertaken to determine prevalence of hyperinsulinemia in Indian subjects with essential hypertension and the effect of omega-3 FA in low-dose on blood pressure, hyperinsulinemia and dyslipidemia in them owing to paucity of data regarding effects of omega-3 FA on hypertension and hyperinsulinemia in Indian subjects.

MATERIAL AND METHODS

The present study was conducted at Department of Medicine, Maulana Azad Medical College (MAMC) and Lok Nayak hospital (LNH), Department of Biochemistry G B Pant hospital (GBPH), New Delhi. The study population included patients from Delhi and rural areas around Delhi with BMI ≤ 27 Kg/ m² with varied life style based on their occupation. Hundred cases with stage 1 and 2 essential HT (diastolic BP 90-109 and systolic BP of 140-179 mm of Hg) [JNC-VI (13)] in the age between 30-60 years were randomly selected based on the criteria of positive family history of hypertension and exclusion of secondary causes of hypertension clinically. Twenty age and sex matched normal healthy adults were taken as controls. The hypertensive patients were screened for hyperinsulinemia by taking samples for fasting and 2 hrs post-prandial plasma insulin levels along-with blood sugars and complete

lipid profile. The controls were also subjected to the above-mentioned tests.

It was a prospective, single blind, randomized study comprising twenty patients with essential hypertension randomly selected for omega-3 FA substitution from the above mentioned group based on the following inclusion criteria: cases either newly diagnosed or on irregular anti-hypertensive therapy demonstrating hyperinsulinemia (fasting plasma insulin levels > 45 μ U/ml) and BMI ≤ 27 Kg/m². The exclusion criteria included isolated systolic hypertension, secondary or severe hypertension, pregnancy and DM with nephropathy. The 20 patients were further randomized into **groups 1 and 2** of 10 cases each. Both the groups were age and sex matched.

Study design: The study consisted of 2 weeks of washout period followed by 4 weeks of control phase with dietary modifications as per the WHO recommendations including that for dietary fat intake. **Total fats:** 25-30% of total caloric intake with **Saturated fats:** 8-10% (visible and invisible), **Monosaturated Fats:** 8-10% and **Polyunsaturated fats:** 8-10%. Salt intake was restricted to 5 g/d.

Each case was provided with an appropriate diet chart prepared by a dietician with necessary adjustments regarding various oils used for cooking and any other changes in diet. Rapeseed oil/ Mustard oil was introduced in their diet to provide source of MUFA in appropriate amounts.

It was followed by 6 weeks of study phase with omega-3 FA substitution in the form of Cap MaxEPA (each capsule containing EPA 180 mg, DHA 120 mg, and cholesterol 6 mg) along-with proportionate curtailment of omega-6 FA in diet so as to maintain an omega-6/omega-3 FA ratio of 8: 1. **Group 1** was put on Cap MaxEPA 1 bid (0.6 g/d of omega-3 FA) and **Group 2** was put on Cap MaxEPA 2 bid (1.2 g/d of omega-3 FA). The patients were not on any antihypertensive drugs during the entire study.

Biochemical analysis: The biochemical profile was done at the beginning of the study (0 week) and repeated at the end of 4th week and 10th week. Plasma insulin was estimated by ELISA (Boehringer Mannheim) method (14) while blood glucose was estimated by glucose oxidase method in autoanalyser (15). Glycosylated HbA1c was measured by affinity chromatography method (16). Serum cholesterol and triglycerides levels were analyzed with commercial kit in autoanalyser (17, 18). High density lipoprotein was estimated by precipitation method with phosphotungstate and magnesium and then in autoanalyser with commercial kit. Low Density Lipoprotein was calculated by Friedwald's method (19).

Statistical analysis: All the individual data were statistically analyzed. Student's t-test and probability p value was applied and used for the data analysis. Comparison of diet alone (control phase) and diet + omega-3 FA (study phase) in two different doses on hyperinsulinemia, dyslipidemia and blood pressure was done and results expressed as mean percentage change.

RESULTS

Plasma insulin levels in normal and patients of essential hypertension

The mean fasting and post-prandial plasma Insulin levels in 100 patients of essential hypertension was significantly ($p < 0.001$) higher when compared to healthy controls (Table 1). Based on the mean $\pm$ SD criteria of controls ($> 45 \mu\text{U/ml}$), 77% of the patients had raised fasting plasma insulin levels.

Comparison between groups 1 and 2 at baseline (0 week)

Twenty such cases of hyperinsulinemia with HT were randomized into 2 groups of 10 cases each that were matched at baseline with respect to all parameters (Table 2 and 3).

Comparison of Effect of omega-3 FA therapy at end of 4 weeks (control phase) and 10 weeks (study phase) in both groups 1 and 2

The effects of omega-3 FA on blood pressure and plasma Insulin levels (both fasting and post-prandial) in groups 1 and 2 are shown in Table 2, while those on S. Lipid profile in Table 3. As is noted in Tables 2 and 3, after dietary modifications only (control phase), no significant ($p > 0.05$) change was observed on any of the variable in either group.

After addition of omega-3 FA in the study phase, highly significant ($p < 0.001$) improvement was observed for all the variables in both the groups.

Comparison of effect of omega-3 FA therapy in two different doses [groups 1 (0.6 g/d) and 2 (1.2 g/d)] on BP, Plasma insulin levels and lipid profile at the end of 10 weeks

No statistically significant difference was noted for the above-mentioned parameters between the two groups at the end of 10 weeks (Table 4).

DISCUSSION

In the present study, the fasting plasma insulin levels ($> 45 \mu\text{U/ml}$) were raised in 77% of patients of essential hypertension compared to healthy controls. The results were similar to a study by Bhatnagar *et al.* (3) on 100 Indian hypertensive patients in which 75% of patients had fasting hyperinsulinemia while 85% had post-prandial hyperinsulinemia.

The two matched (Table 2) groups of 10 cases each of the hyperinsulinemic hypertensive patients showed no significant response to dietary modification alone for 4 weeks (control phase). However, after substitution of omega-3 FA during the study phase of 6 weeks, fasting plasma insulin levels decreased by 29% and 22.8%, while post-prandial decreased by 21.7% and 19.2% in groups 1 and 2 respectively (Table 3). Studies on effects of omega-3 Fatty acids on hyperinsulinemia in patients of essential hypertension are lacking. However, animal studies have shown that omega-3 FA enhances tissue sensitivity to insulin thereby decreasing insulin resistance in adipocytes and muscles (20).

Similarly, omega-3 FA substitution resulted in reduction of systolic BP by 16.4 % and diastolic BP by 25% (Table 2) in both groups, which is probably attributable to reduction in insulin levels (hyperinsulinemia has been shown to cause raised BP) as well as production of vasodilatory eicosanoids from omega-3 FA in platelet membrane by cyclooxygenase. In a study by Singer *et al.* (21) on 12 patients with mild essential HT, substitution of omega-

Table 1. Comparison of Plasma Insulin levels in Normal Controls (20) and Patients of Essential Hypertension (100)

Insulin Levels	Normal controls Mean $\pm$ SD	Hypertensive Patients Mean $\pm$ SD	p value*
Fasting ($\mu\text{U/ml}$)	19.35 $\pm$ 12.61	126.51 $\pm$ 80.36	< 0.001
2 hr Post-Prandial ($\mu\text{U/ml}$)	24.70 $\pm$ 10.29	149.41 $\pm$ 98.32	< 0.001
The mean fasting as well as 2 hr post-prandial plasma levels were significantly higher than the normal controls (* $p < 0.001$ highly significant)			

Table 2. Effect of omega-3 fatty acids on blood pressure and plasma insulin levels in both groups (10 cases each)

Parameter	Group	0 weeks	4 weeks	Mean percentage change between 0 and 4 weeks*	10 weeks	Mean percentage change between 4 and 10 weeks**
Systolic BP (mm of Hg)	1	152.3±7.5	149.6±6.8	-1.8	125.0±8.5	-16.4
	2	151.1±4.6	149.4±10.1	-1.1	125.0±10.8	-16.3
Diastolic BP (mm of Hg)	1	105.2±5.6	104.0±5.0	-1.1	78.2±3.3	-24.8
	2	105.8±3.5	104.4±3.6	-1.7	78.6±3.3	-24.6
Fasting Plasma Insulin levels (µU/ml)	1	178.8±67.9	166.2±65.1	-7.2	118.0±62.3	-29.1
	2	208.0±91.8	201.1±84.0	-3.4	155.5±85.8	-22.8
Post-prandial Plasma Insulin levels (µU/ml)	1	174.5±91.0	167.5±90.7	-4.01	131.2±89.1	-21.7
	2	213.0±83.1	204.1±84.2	-4.2	165.0±87.1	-19.2
* p value > 0.05 not significant, ** p value < 0.001 very significant						

Table 3. Effect of omega-3 fatty acids on serum lipid profile in both groups (10 cases each)

Parameter	Group	0 weeks	4 weeks	Mean percentage change between 0 and 4 weeks*	10 weeks	Mean percentage change between 4 and 10 weeks**
S. TC (mg/ dl)	1	195.4±30.9	189.334.2	-3.1	164.3±41.2	-13.2
	2	210.7±34.2	205.432.9	-2.5	188.8±42.2	-8.3
S. HDL (mg/ dl)	1	27.5±4.1	27.5±4.1	0.0	35.5±2.4	+29.1
	2	30.9±3.2	31.0±3.3	+0.3	38.6±3.5	+24.5
S. LDL (mg/ dl)	1	132.6±31.9	127.0±35.7	-4.2	102.4±42.9	-19.4
	2	144.7±33.3	140.1±23.0	-3.2	124.5±32.9	-11.1
S. TG (mg/ dl)	1	174.7±39.0	170.7±41.0	-2.3	131.0±32.9	-23.3
	2	175.3±55.1	167.9±49.6	-4.2	131.4±46.6	- 21.7
* p value > 0.05 not significant, ** p value < 0.001 very significant						

3 FA in the dose of 5 g/d for 8 weeks (period A) resulted in lowering of systolic BP by 9 mm of Hg and diastolic BP by 11 mm of Hg. When the patients were followed up with 1.2 g/d for 8 months (period B), the BP still remained significantly lower.

In the present study, beneficial effects of omega-3 FA was also noted on Total Cholesterol (TC), Serum Triglycerides (TG), low density lipoprotein and high density lipoprotein in both the groups (Table 4). These beneficial effects of omega-3 FA on serum lipid profile

of hypertensive patients are probably due to blunting of the stimulatory action of insulin on hepatic lipogenesis (22). A previous study by Singer *et al.* (21) also observed the same results during period A of their study however the levels slowly returned to near baseline at the end of period B of their study. The difference in the results in the two studies can be explained by the fact that various doses of omega-3 FA produce different results on serum lipids and blood pressure, depending on the basal levels of the parameters (21), and that the patients in the study by

Table 4. Comparison of Blood Pressure, Plasma Insulin levels and Lipid Profile in Group 1 (10) and Group 2 (10) at the end 10th week (study phase)

Parameters	Mean difference between 4 and 10 weeks in Group 1 Mean±SD	Mean difference between 4 and 10 weeks in Group 2 Mean±SD	p value*
- Systolic BP (mm of Hg)	-24.6±1.7	-24.4±0.7	0.92
Diastolic BP (mm of Hg)	-25.8±1.7	-25.8±0.3	0.98
Fasting plasma Insulin levels (µU/ml)	-48.2±2.8	-45.5±1.8	0.28
Post-prandial plasma Insulin levels (µU/ml)	-36.3±1.6	-39.1±2.9	0.41
S.TC (mg/ dl)	-25.0 + 7.0	-16.6 + 9.3	0.77
S. HDL (mg/ dl)	+8.0 + 2.7	+7.6 + 0.2	0.89
S. LDL (mg/ dl)	-24.6 + 7.2	-15.6 + 9.9	0.22
S. TG (mg/ dl)	-39.7 + 8.1	-36.5 + 3.0	0.89
*ns: not significant for all parameters			

Singer *et al.* (21) had near normal lipid profile at baseline compared to the present one.

In the present study no statistically significant difference was noted on the effects of two different doses of omega-3 FA (0.6 and 1.2 g/d) on BP, lipid profile and hyperinsulinemia (Table 4). Thus, both the above doses are optimal as long as omega-6: omega-3 FA ratio in diet is maintained at 8: 1.

The present study suggests that prevalence of hyperinsulinemia in Indian patients with essential hypertension is very high and that omega-3 FA substitution in low-dose and normalization of ratio of omega-6: omega-3 fatty acids in diet to 8: 1 resulted not only in improvement of blood pressure (systolic and diastolic) in patients with mild to moderate essential hypertension, but also in a significant decline in plasma insulin levels (fasting and post-prandial) and favorable alteration in serum lipid profile of these patients, which are desirable for comprehensive management of essential hypertension.

CONCLUSION

Thus, it may be concluded that low-dose omega-3 Fatty Acid substitution along-with dietary curtailment of

omega-6 Fatty Acid may be used as an adjunctive measure in patients with essential hypertension.

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