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Effects of Omega-3 on Vitamin D Activation in Iraqi Patients with Chronic Kidney Disease Treated by Maintenance Hemodialysis

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Abstract

Background-Omega 3 had many effects on dialysis patients like dyslipidemia, blood pressure, dialysis access, immune response and inflammation, oxidative stress, uremic prurits and recently activation of vitamin D.The activity of 1α-hydroxylase increased to patients takes omega-3 supplement that will lead to increase levels to 1,25 dihydroxy vitamin D.

Materlias And Methods-The study is prospective, interventional, cross sectional, randomized, double blinded; placebo controlled clinical trial; held in medical city, Baghdad hospital; Iraqi center of dialysis in the period between May 2015 till July 2016.There were 74 patients enrolled in the study; 36 patients in group 1 received omega-3 and 38 patients in group 2 received placebo drug for 12 weeks.

Results-There were many changes in biochemical data including Cacium, Phosphate, Ca-Po4 product, albumin and Parathyroid hormone levels.The current study shows that there are significant increase in albumin level, significant increase in calcium level, insignificant difference in phosphate level, insignificant increase in parathyroid hormone in patients treated by omega-3.There was significant increase in 25(OH)D level and 1,25(OH)2D at the end of the study, the ratio of 1,25(OH)2D /25(OH)D significantly increased from omega-3 treated patients.

Conclusion-Omega-3 significantly increases level to 1,25dihydroxy vitamin D and increase activity of 1-alpha hydoxylase.

Keywords : Omega-3,Chronic kidney disease,vitamin D

INTRODUCTION

High level of parathyroid hormone (PTH) occurs early on as kidney utility begins to decline. Which affects bone turnover and lead to CKD-mineral and bone disorders (CKD-MBD) around 75% to 100% of patients with stage 3 CKD has CKD- MBD.(Francisco,2004)(Mohammed etal,2015)[1,2] . Current interest has focused on n-3 polyunsaturate fatty acids (PUFA) and vitamin D. Decreased renal utility is a powerful judge of cardiovascular morbidity,mortality and all cause mortality (Cunningham,2011) (Albader,2008)(Filion etal,2010)(Matsuyama,2005)[3,4,5,6] .Cardiovascular disease (CVD) is also a chief cause of mortality in patients that have declined renal function (Allawi,2013)[7] (Tonelli,2006)[8]. This perhaps relates to inflammation, malnutrition, atherosclerosis, dyslipidemia and vascular calcification (Vanholder etal,2005)(Vaziri,2013)(Mizobuchi etal,2009)[9,10,11]. In addition, vitamin D deficiency (VDD) is an identified risk factor of CVD in CKD patients VDD is linked with CVD even among the general people(De Brito etal, 2013)[12] . Several studies have shown a close relationship between VDD and increased possibility of CVD among CKD patients (Pilis etal,2011)(Cupisti etal,2015)[13,14] In particular, VDD was allied with an increased risk of CVD and mortality in hemodialysis(HD) patients(Wolf etal,2008)(Peovnik etal,2009)(Drechsler etal,2010)[15,16,17]. An earlier study has reported that extra-renal sources of 1,25(OH)2D can be amplified to usual serum 1,25(OH)2D levels in HD patients after administration of high doses of 25(OH)D (Matias etal, 2010)[18]. Recently 1,25(OH)2D levels appreciably increased in dialysis patients compared to baseline after three months of omega-3 fatty acid (FA) supplementations without 25(OH)D management(An W etal,2012)[19]. omega-3 FA, having an antiinflammatory effect and reducing oxidative stress, may adjust uremic condition and possibly adjust enzyme levels.(An W etal,2012) [19]

MATERLIAS AND METHODS

A prospective, interventional, cross sectional, randomized, double blinded; placebo controlled clinical study;in Baghdad teaching hospital, Iraqi center of dialysis from May 2015 till July 2016.There were 110 patients on maintenance hemodialysis at least one year in section of hepatitis C in dialysis unit randomly enrolled in the study , an approval for ethical committee of Iraqi boards of clinical pharmacy .Each patient signed A consent according to Helsinki law.Primary outcomes: completion of 12 weeks on drug supplied to patients (active drug or placebo).Secondary outcomes: any patient require termination of enrollment in the study to any reason. Patients excluded from this study include: history of vascular access active infection within 3 months, patients already take fish oil or omega-3 to 3 months,Patients with a history of fish, gelatine, and/or omega-3 fatty acid allergies, Patients with a history of hospital admission within 3 months, bleeding within 3 months, thrombocytopenia, use of Warfarin and Patients with malignancy and/or liver cirrhosis.The demographic variables included gender, age, past medical history, past drug history, dialysis

duration,sessions no. per week . patients included to take the same combination of drugs for chronic kidney disease: calcium supplement tablets 500mg one tablet three times a day, alfacalcidol tablets either 0.5 microgram tow times weekly or 0.25 microgram daily, MIRCERA syringe 0.75IU monthly, parenteral iron supplement as a dextran or sucrose, folic acid 5mg daily tablets. The patients included are randomized into two groups: group1 received omega- 3 and group2 received placebo, omega-3 were taken from company VITEX pharmaceuticals, patch number 21338, exp 10\2016 which is the only tested product in the National Centre of Drug Control and Research till the time of study by the number 4505 in 27\10\2014, while the placebo drug which is hard gelatin capsules contains glucose powder made by hand.The patients instructed to take one capsule per day after 2 hours of the main meal to insure complete absorption and avoid any drug food interaction. Patients in both arm with the study instructed to take their treatment for 12 weeks and; adherence was assessed by providing weekly supply of capsules and counting if there is remaining capsules in the pocket that was given to them. Patients in omega-3 arm of study would be termed group 1 and patients in placebo arm of study would be termed group 2. patients who couldn't tolerate the intervention or developed any of the exclusion criteria or not adheres to their treatment were excluded from the trial. Anderson Darling test for normality was done , t test (independent) was use to analyzed the differences in mean . Non parametric Kruskal Wallis tests were used to analyzed the differences in variables at baseline.Wilcoxon median ranks test used to analyzed the differences between baseline and end of treatment differences .Two ways Repeated to measure ANOVA was used to analyzed the differences between placebo and omega 3 groups .P values (level of significance) were considered to be significant at 0.05, all data were analyzed using SPSS 20 .

RESULTS

A total of 110 patients are randomized to receive treatment for either O3 (55)or Placebo (55) at ratio of 1:1.randomization was made by numbering each case and then by excel sheet,after randomization there were exclusion of 24 patients from study because of presence of one or more of exclusion criteria that was mentioned before. So there were 86 patients entered the trial (43) patients in the group1 and (43) patients in the group2. After initiation of trial; 1 patient in group1 died and 4 patients excluded because of inadherence, while 3 in group2 transferred to other hospital and 2 patients in placebo group excluded due to inadherence. The remaining 74 patients (36) patients in omega3 arm (group1) and (38) in placebo arm (group2) continued their treatment for 12 weeks and they enrolled in trial. There were 38 females (36%) in both arms with study divided as 22 (61.1%) in group1 and 16(42.1%) in group 2 with (P value 0.112) table- 1,table-2. Albumin was found to be significantly different from two arms of study [normal range 3.4-5.4g/dl]. After completion of 12 weeks of the study, there were many significant changes in biochemical data including Calcium, phosphate, Ca-PO4 product, albumin and PTH levels (table-3,table-4).It's found that 25(OH)D; 1,25(OH)2D and 1,25(OH)2D/25(OH).D ratio is changed into the study in both arms of the study. In group 1 there is significant increase in 25(OH) D levels at the end of the study .Level of 1,25(OH)2Ds increased significantly to the end of the study .The ratio of 1,25(OH)2D/25(OH)D significantly increased . In group 2 there is significant increase in D levels during study .Accordingly the ratio of 1,25(OH)2D/25(OH)D in group 2 reduced at the end of the study.(table -5). The net changes into vitamin 25(OH)D; 1,25(OH)2D and 1,25(OH)2D/25(OH)D in two groups we will find that there is significant increase in 25(OH)D levels in group 2; marked increase in 1,25(OH)2D in group 1 and marked increase in 1,25(OH)2D/25(OH)D ratio of group 1 at the end of the study table -6.

Table 1: Age of patients

Variables	Omega 3 (38)		Placebo (36)		P value (2 tailed)
	Mean	SD	Mean	SD	
Age	52.8333	13.94581	53.6579	10.15628	0.771

Table 2:Basic patients disease characteristics

Variables		Omega 3		Placebo		Total		P value
		No	Percent	No	Percent	No	Percent	
Gender	Female	22	61.1	16	42.1	38	36	0.112
	Male	14	38.9	22	57.9	51.4	48.6	

Table 3 Baseline laboratory data

Variables	Omega 3 (36)		Placebo (38)		P value
	Median	IQR	Median	IQR	
Albumin	4.77	4.22 – 5.72	3.81	3.186 – 4.77	0.002
Ca *	6.23	1.28	5.99	1.43	0.463
Ca x PO_4	17.44	13.32 – 22.4	13.9	9.12 – 25.2	0.165
Dialysis duration (months)	36	36 – 58.5	36	24 – 60	0.492
PO_4	3	2 – 4	3	2 – 4	0.253
PTH	182.6	88.7 – 277.8	150.5	103.9 – 272.3	0.393

Table 4. calcium, phosphorus, albumin and PTH changes throughout the study					
Variables	**Baseline**		**End of Tx**		**P value**
	Mean	**SD**	**Mean**	**SD**	
Omega 3 group (n=36)					
Albumin	2.86	0.83	4.36	0.72	0.004 [b]
Ca	6.23	1.28	8.19	1.09	0.001[a]
Ca x PO_4	9.80	8.34	26.25	8.20	0.012 [b]
PO_4	3.17	1.23	3.19	0.86	0.861[b]
PTH	127.33	18.70	233.13	189.63	0.144 [b]
Placebo(n = 38)					
Albumin	4.18	1.16	4.10	0.61	0.817 [b]
Ca	5.99	1.43	8.81	1.24	<0.001 [a]
Ca x PO_4	17.13	9.71	29.22	9.61	<0.001 [b]
PO_4	2.84	1.52	3.32	0.99	0.08 [b]
PTH	200.51	124.23	280.46	273.49	0.429 [b]

a paired t test b Wilcoxon Signed Ranks Test

Table 5. vitamin 25(OH)D and 1,25(OH)2D and their ratio throughout the study					
Variables	**Baseline**		**End of Tx**		**P value**
	Mean	**SD**	**Mean**	**SD**	
Omega 3 group (n=36)					
25(OH)D	27.71	20.11	35.23	26.55	0.015
1,25(OH)2D	153.94	121.15	244.11	137.61	<0.001
1,25(OH)2D/ 25(OH)D ratio	7.79	7.71	10.18	7.34	0.01
Placebo(n = 38)					
25(OH)D	27.29	16.29	53.31	26.02	<0.001
1,25(OH)2D	170.57	113.10	170.17	100.26	0.607
1,25(OH)2D/ 25(OH)D ratio	7.63	4.71	4.07	3.30	<0.001
Wilcoxon Signed Ranks Test					

Tx; treatment, SD; standard deviation

Table 6. comparison between the overall effect of omega 3 and placebo against each other	
Variables	P values
25(OH)D	0.002
1,25(OH)2D	<0.001
1,25(OH)2D/25(OH)D ratio	<0.001
Repeated measure MANOVA	

DISCUSSION

In current study females is found to be more than males 38 females (51.4%) vs. 36 males (48.6%).This is compared to nationwide survey of ESRD by the Japanese Society for Dialysis Therapy which revealed a higher incidence and prevalence in men than in women.The mean age at the start of dialysis are also higher in women than in men(Alwakeel ,2002)[20]. In Iraq the prevalence of CKD according to gender is similar to nationwide survey and is found to be higher in male than female with a male to female ratio of 1.17:1(Hanafusa etal,2015)[21].The demographic results of this study may be explained by many reasons like sample number, study held in one centre and patients only had chronic dialysis for period longer than one year are included in this study which represented a homogenous group of patients to exclude difference in viral type infection effect on our results because although it's found that low vitamin D 25(OH) D is found in patients with chronic hepatitis C but it is not related to any biochemical or virological variables also vitamin D therapy has no immediate effect on HCV-RNA serum levels (Jose etal,2013)[22].The study use 12 weeks duration of therapy because one prior study(An W etal,2012)[19] used this period to demonstrate the effect of omega3 on vitamin D activation..Exclusion criteria from this trial include Patients with history of active vascular access infection because as presented in the literature of the drug general side effects including infection (4.4%), flu syndrome (3.5%) have been reported.While we excluded patients with history of bleeding, patients already taken Warfarin or those with thrombocytopenia because omega3 may increase bleeding tendency and act as antiplatelet agent (Abbott)(Mitchell etal,2010)[23,24].The hypocalcaemia at the baseline may be attributed to many causes; phosphate retention, skeletal resistance to the calcemic action of PTH, and altered vitamin D metabolism (Allawi etal,2016)(Mohanad etal,2016)[25,26]. Most of the patients with hypocalcaemia are either in-adherent to their Ca supplements or take Ca supplement directly after meals which make it work as Phosphate binding agents instead of pure supplements.. Patients with Ca-P product of 72 (20% of all patients) had a 34% higher relative the risk of death compared to patients with Ca-P product of the range of 42 to 52.The increased risk was observed in proportion to the elevation of Ca-P product; indeed, for every increase in10 in Ca-P product, there was an 11% increase in relative risk of death (NKF ,2007)[27].It's found that phosphate level within normal ranges (3-4)mg/dl,This reflect the effectiveness of phosphate binding therapy that patients takes [patients were found to take Ca supplements as phosphate binders] , effective dialysis duration and schedule [they scheduled as two times weekly each session three to four hours] and Adherence to dietary program that is consist of low phosphorus, low sodium, low potassium and high protein diet.There were many changes occurred in laboratory data after completion of the course of treatment. Ca level increased from baseline in significant manner in both arms, This is may be attributed that to group 1 and due to the effect of intervention with omega-3 there is increase in the fraction of active D which will promote more calcium absorption from intestines, patients in both groups that found to be in hypocalcaemia at the baseline are educated to take their Calcium before meal in addition to Ca after meal but without exceed the maximum daily dose of 1500mg/day. It's found that Ca levels increased to group 2 more than group 1, this can be attributed to the gastrointestinal side effects of omega-3 which may reduce adherence of patients to Ca supplements.This effect is not presented in placebo drug so patients can tolerated higher doses of Ca supplements. This is compared to study(An W etal,2012)[19] in which Ca levels didn't differ either significantly between two groups or at beginning and at end of study.It's found that there is significant increase in albumin level in group 1 compared to insignificant change

in group 2 and it's apparent that albumin level increased from deficient level to normal level in group 1 while it remain in normal range in group 2. This is compared to one study (Cabre etal, 2012)[28] Which found no effect of omega-3 on albumin level. This is can be explained by the fact that is omega-3 had anti-inflammatory effect (NKF,2007)[27](M H. Comment,2013)(Zulfitri etal,2012)[29,30] which may increase albumin level to normal range.

Reduce protein intake and an increase in inflammatory response is two important factors that lead to a decrease in serum albumin.However, (Kaysen et al,2004)[31] had noted that low serum albumin in dialysis patients may be attributed to systemic inflammation rather than nutritional inadequacy as a causative factor per se.(Friedman and Fadem ,2010)[32] suggested that serum albumin should be taken as a marker of illnesses rather than nutrition. This is due to the fact that serum albumin has a strong ability to predict mortality but rather limited prediction for nutritional status due to significant influence of non-nutrition causes (such as inflammation)(shaymaa etal, 2017)[33].Using repeated measure ANNOVA; we will find that there is significant difference in serum calcium with more increment in group 2 than group1. The effects of omega-3 on 25(OH)D and its active form are that there is significant increase in 1,25(OH)2D in group 1compared to group 2 is caused by effect of omega-3 on 1α-hydroxylase represented by ratio of 1,25(OH)2D/25(OH)D which increased significantly in group 1 compared to group 2; which is similar to study(An W etal,2012)[19] .This shows that omega- 3 had a positive effect of 1α-hydroxylase activity that convert 25(OH)D to its active molecule 1,25(OH)2D.

In patients with end stages renal disease production of activated vitamin D is regulated by extra-renal production of 1α-hydroxylase, and its' level is measured in anephric patients treated by hemodialysis (Koren etal ,2006)[34] . Previous investigations have reported a positive correlation between circulating proinflammatory cytokines and serum 25(OH)D levels, (Dobnig etal,2008)(Peterson etal,2008)[35,36] and that vitamin D inhibits experimental activation of NFκB, as well as IL-6 release, in endothelial cell culture. (Suzuki etal,2009)(Equils etal,2006) [37,38]Also it's noted that in patients on hemodialysis and healthy young adults with severe vitamin D deficiency found that brachial artery flow-mediated dilation was positively related to both serum 25(OH)D and 1,25(OH)2D levels.(London etal,2007)(Tarcin etal,2009)[39,40] It's found that vascular endothelial cells express vitamin D receptors and 1-α hydroxylase and there is an association between serum 25(OH)D level and flow-mediated dilation and it could be mediated in part by vascular endothelial cell conversion of 25(OH)D to 1,25(OH)2Ds. also endothelial cells from vitamin D deficient subjects had reduced expression of vitamin D receptors and 1-α hydroxylase compared with vitamin D–sufficient subjects and that -α hydroxylase was strongly related to flow-mediated dilation. This mechanism where circulating vitamin D deficiency may be linked to vascular endothelial dysfunction.

CONCLUSION

Omega-3 has a positive effect on patients with end stages renal disease on maintenance dialysis .These effects include increase the activity of 1-alpha-hydoxylase demonstrated by increase in 1,25 vitamin D concentrations, increase to ratio of 1,25D/ D.This increase in the active form of vitamin D will promote more calcium absorption and help to correct hypocalcaemia.Omega-3 results in no effect on phosphate level, no effect on parathyroid hormone, and minimal effect on Calcium- phosphorus product. Good patients education and making them part with action plan will increase their adherence to drug therapy.

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