



## Effects of omega-3 administration on homocysteine serum concentration in renal transplant recipient.

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### ABSTRACT

**Background:** It has been shown that serum total homocysteine (HC) is a risk factor for vascular disease which characterizes endothelial damage in the general and in the End-Stage Renal Disease (ESRD) population as well. Whether n-3 polyunsaturated fatty acids decrease homocysteine (Hcy) level has been a subject of controversy.

**Methods:** Renal transplant patients were randomized in 2 groups and received 6 months of dietary supplementation with 6 g/day of Fish oil or placebo. Homocysteine level and total cholesterol level were measured.

**Results:** In 40 renal transplant recipients, increase in homocysteine level was greater after Fish oil administration but not significantly, total cholesterol was decreased significantly.

**Conclusion:** Based on these data omega3 fatty acids supplementation doesn't decrease serum homocysteine in renal transplant recipients but decreases total cholesterol level.

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### Introduction

Cardiovascular complications are the leading cause of death in Renal Transplant Recipient (RTR) (1). Correlation between cardiovascular risk factors and outcomes in RTR patients has been reported (2). Therefore, aggressive intervention in first year of renal transplantation was suggested (3). There are several traditional (including hyperlipidemia which is a frequent complication after renal transplantation) and non-traditional risk factors predicting the risk of future cardiovascular events. Among the non-traditional risk factor is hyperhomocysteinaemia (1). Evidences from epidemiological studies suggested an association between elevated homocysteine levels and increased risk of cardiovascular disease (CVD) (4). Several retrospective and prospective studies showed

the predictive value of traditional and non-traditional (including homocysteine) risk factors in prediction of outcomes of transplant patients (1, 5). Homocysteine has numerous damaging effects on vascular cells promoting atherosclerosis and cardiovascular disease. Homocysteine promotes vasoconstriction, LDL-cholesterol modification, macrophage-foam cell formation, oxidative stress, pro-inflammatory response, atherosclerosis and also induces prothrombotic response (6). Importance of homocysteine level monitoring and prevention of hyperhomocysteinaemia was established. Studies also showed that hyperhomocysteinaemia is common in renal transplant recipients (7, 8). A prospective study including 733 patients showed that fasting plasma total homocysteine level was a predictor of allograft survival in RTRs (9). Higher levels of homocysteine was associated with hypercholesterolemia (10) and a higher risk of cardiovascular events in RTRs and homocysteine-lowering therapy was associated with decreasing of carotid intima-media thickness (5) as well as pro-inflammatory status (8).

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and endothelial damage(8,11) in RTRs .

Omega-3 fatty acids have been used in patients with cardiovascular diseases (CVD). Controversial results about effects of omega-3 intervention on homocysteine level have been reported. Omega-3 fatty acids administration adjunct to either simvastatin (12) or pravastatin (13) was more effective than simvastatin or pravastatin treatment alone for correcting the post renal transplantation hyperlipidemia. It decreased homocysteine level in diabetic patients (14) and patients with myocardial infarction (15). Due to lack of long-term study investigated the potential of omega-3 fatty acids in RTRs, we conducted a 6 months study investigating the effects of omega-3 fatty acids administrations in RTRs especially on homocysteine level.

### Patients and methods

This study was approved by the Ethics Commission of MUMS (Mashhad University of Medical Sciences). All Patients signed a consent form prior to entry into the study. Forty hemodialysis (HD) patients (all candidates for future transplantation) who fulfilled inclusion and exclusion criteria were selected. All patients were undergoing kidney transplantation; the patients were in the 19-62 age range, take the kidney from live subjects and treated by immunosuppressant drugs. Patients with heart failure, thyroid disease, liver dysfunction, diabetes, acute infection and acute rejection and who were treated by statins or changes in their immunosuppressive regimen, were excluded from the study. After transplantation all 40 HD patients were randomized into two groups. For one group (A) omega3 supplements (6g/day: 720mg of DHA and 1080mg of EPA daily (oral)) was administered for 6 month. Other group (B) treated by placebo in same condition. Blood samples were obtained from patients, just before and 6 months after transplantation. Demographic data and Para clinical test results including traditional cardiovascular risk factors and ESRD etiology were recorded. Peripheral blood samples were obtained after a 12-hour fast.

The homocysteine serum concentration of samples was determined by an Enzyme-Linked Immunosorbant Assay (ELISA) kit (Axis-shield, Dundee, Scotland).

### Statistical analysis

Two independent sample t test and Paired Student *t* test was used for data analyzing. *P* values < 0.05 were considered significant.

### Results

#### Characteristics of the study population

The median age was  $36.5 \pm 14.34$  years (range 19–62). We evaluated other risk factors, such as age, hypertension, hypercholesterolemia, smoking, diabetes, and previous CV disease (Table 1).

**Table1.** Demographic data, laboratory tests and traditional cardiovascular risk factors of patients.

Demographic data	
Age (year)	$36.5 \pm 14.34$
Female/Male ratio	0.57
<b>Laboratory tests</b>	
Calcium (mg/dl)	$9.5 \pm 0.50$
Phosphorus (mg/dl)	$6.8 \pm 6.9$
Parathyroid hormone (pg/ml)	$238.0 \pm 228.23$
HDL cholesterol (mg/dl)	$38.2 \pm 5.64$
LDL cholesterol (mg/dl)	$108.9 \pm 27.37$
Total cholesterol (mg/dl)	$168.4 \pm 35.93$
Triglycerides (mg/dl)	$174.3 \pm 112.79$
Mean CCIMT (mm)	$0.62 \pm 0.11$
<b>Traditional cardiovascular risk factors</b>	
Hypertension (%)	54.84
Dyslipidemia (%)	12.9
Positive family history (%)	25.8
Diabetes (%)	0
Current smoking (%)	9.68

HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, CCIMT: Common Carotid Intima-Media Thickness.

### Comparison of homocysteine level between two groups

After 6 month of treatment of group A and B, the increase in homocysteine level was greater in group A than group B but not-significantly ( $P>0.05$ ) (Figure 1).

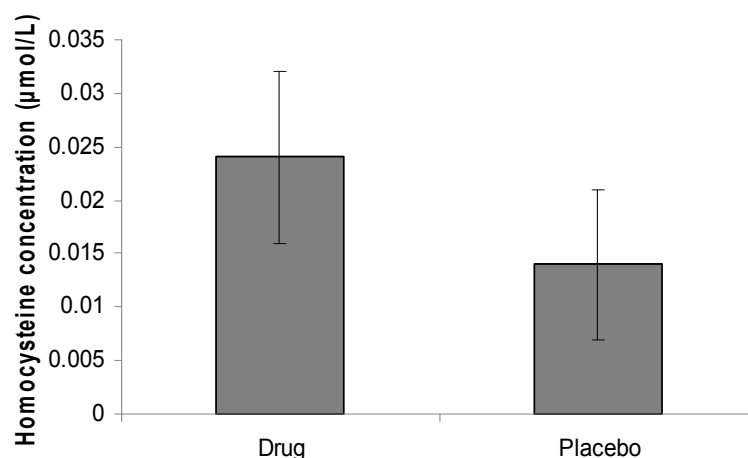
### Comparison of total cholesterol level between two groups

After 6 month of treatment of group A and B, the significant decrease in total cholesterol level was observed in group A compared with group B (Figure 2).

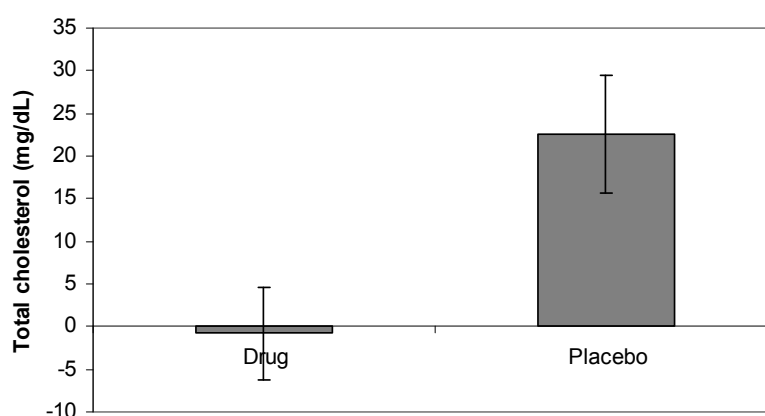
### Discussion

Our results indicate that omega-3 administration did not have any beneficial effects on evaluated end points including homocysteine level in RTRs except on lipid profile. In our experiments we did not find any significant differences between homocysteine levels of control and omega-3 groups. We also investigated the effects of omega-3 on lipid profile in RTRs and similarly no significant difference was observed between groups except on total cholesterol level.

Omega-3 administration in previous studies showed a good effect on lipid profile of transplant patients. Fish oil administration in high doses (6g/day) for 3 month reduced the TG and LDL level in post-renal transplantation (12). Omega3 also reduced homocysteine level in small group



**Figure 1.** Mean of homocysteine levels in two groups  $\pm$  SE ( $\mu\text{mol/L}$ ).  
SE: Standard Error of Mean



**Figure 2.** Comparison of total cholesterol level between two groups  $\pm$  SE (mg/dL).  
SE: Standard Error of Mean

of hyperlipidemic men after 3 weeks (16). Combined treatment with low-dose of pravastatin and fish oil changed the lipid profile after transplantation more effective than pravastatin alone (13).

Despite of these favor effects of omega-3 intervention on transplant patients our results and some previous studies demonstrated that omega-3 fatty acids could not decreased the homocysteine level in those patients. Omega-3 could not inhibit the increase of homocysteine in continuous ambulatory peritoneal dialysis (17). Homocysteine level was not changed after administration of compound of 85% Eicosapentaenoic acid (EPA)/

Docosahexaenoic acid (DHA) after 12 weeks in subjects with hyperlipidemia(18). Omega-3 fatty acid supplementation could not decrease total homocysteine levels in end-stage renal disease patients (19). A double-blind clinical trial including 86 patients randomly received either 6 g/day of fish oil during the first 3 months post-transplantation did not influence acute rejection rate and graft survival(20); However, it decreased homocysteine level in patients with other diseases. n-3 polyunsaturated fatty acids administrated followed an acute myocardial infarction decreased homocysteine level(15). n-3 polyunsaturated fatty acids supplementation resulted in

the decrease of homocysteine concentration (-29%) and TG (-28%) in plasma in diabetic patients(14) and also in healthy subjects (21).

In conclusion, according to previous studies and our results, it seems that omega-3 administration in post-transplantation does not have significant effect on homocysteine level, but it could decrease total cholesterol level. To decreasing other cardiovascular risk factors other than LDL and TG, we suggested the concomitant administration of other supplements with omega-3. We postulate that the mechanism that omega-3 whereby decreased homocysteine level in other patients is diminished in transplant patients and omega-3 could not decrease homocysteine level in these patients.

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