Marine n-3 Polyunsaturated Fatty Acid Supplementation and Quality of Life After Kidney Transplantation

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Abbreviations: DHA: Docosahexaenoic acid, EPA: Eicosapentaenoic acid, KTR: Kidney transplant recipient, MCS: Mental component summary, PUFA: Polyunsaturated Fatty acid, PCS: Physical component summary, QoL: Quality of life, SF-36: Short Form 36, wt%: Weight percentage.

ABSTRACT

Introduction: Marine n-3 polyunsaturated fatty acids (PUFAs) may improve cardiovascular, renal and mental health. No previous trial has investigated the effects of marine n-3 PUFA supplementation on quality of life (QoL) indices after renal transplantation.

Methods: In this trial, 132 renal transplant recipients were randomized to receive daily either 2.6 g of marine n-3 PUFAs or an equivalent dose of olive oil (controls) on top of standard care for 44 weeks. We used a Short Form 36 (SF-36) questionnaire at baseline (8 weeks post-transplant) and end of study (one year after transplantation) to assess QoL. Results were expressed as net change (Δ) in SF-36 individual and composite mental and physical scores during follow-up.

Results: We found no improvement of Δ SF-36 individual or composite scores after marine n-3 PUFA supplementation compared with controls. In per-protocol analysis, patients who received marine n-3 PUFAs had a Δ emotional role function (mean 17% [SD 50%] vs 3% [SD 37%], p=0.11). In addition, plasma marine n-3 PUFA levels showed a weak but statistically significant correlation with Δ composite mental function score (r =0.18, p=0.04).

Conclusion: Marine n-3 PUFA supplementation did not improve QoL after renal transplantation.

INTRODUCTION

Quality of life (QoL) is an important patient related outcome measure in health interventions. The most common tool for QoL assessment is Short Form 36 (SF-36), which has been validated and used in various patient populations and geographical regions including Norwegian kidney transplant recipients (KTRs) (1). Patients with chronic kidney disease

have lower QoL than the general population, and QoL is particularly low in patients on hemodialysis therapy (2). Although receiving a kidney transplant significantly improves QoL, it still remains lower than in the general population (1).

Marine n-3 polyunsaturated fatty acids (PUFAs) have been extensively studied in relation to cardiovascular and inflammatory diseases (3). In recent years, there has also been focus on relationships between marine n-3 PUFAs and neuronal development, mental functions, attention deficit hyperactivity disorder, dementia and major depression (4-10). To our knowledge, no previous study has focused on the relationship between marine n-3 PUFAs and QoL in kidney transplantation. In this investigator initiated randomized controlled trial in Norwegian KTRs, we examined the effect of marine n-3 PUFA supplementation on QoL indices during follow-up.

MATERIALS AND METHODS

We included adults (≥ 18 years old) with a functional graft (estimated glomerular filtration rate > 30 mL/min/1.73m^2), who did not participate in another clinical trial, had no allergic reaction to fish or other seafoods and had a kidney donor < 75 years. From 176 eligible patients, transplanted at Oslo University Hospital, Rikshospitalet, between 15th of June 2013 and 15th of June 2014, 132 patients gave written informed consent to participate in the trial. The study was approved by the Regional Committees for Medical and Health Research Ethics in Norway and was performed in accordance with the Declaration of Helsinki and the Declaration of Istanbul (Clinical.Trials.gov identifier NCT01744067, ORENTRA).

Patients were randomly allocated to receive daily for 44 weeks either soft capsules containing 2.6 grams of marine n-3 PUFA ethyl ester ([Omacor®, Pronova Biopharma] containing docosahexaenoic acid [DHA] plus eicosapentaenoic acid [EPA]) or soft capsules containing

extra virgin olive oil. We used computer generated randomization codes and there were no code breaks before unblinding of the results at the 25th May 2017.

QoL was measured by a Short Form 36 (SF-36) questionnaire (Norwegian translation) at baseline (8 weeks post-transplant) and at the end of study (one year after transplantation). Study endpoints were net change (Δ) in SF-36 scores during follow-up. SF-36 is a generic tool, not specifically made for any disease and used to assess health related QoL during the past four weeks. It is self-administered and has been validated in various patient groups, including chronic kidney disease and renal transplantation (11). It contains eight scales: physical functioning, physical role functioning, bodily pain, general health perceptions, vitality, social role functioning, emotional role functioning and mental health. Scores are transformed to percent scale, ranging from 0 (minimum level of health) to 100 (maximum level of health). From the eight scales mentioned above, we can aggregate two composite scores: The physical component summary (PCS) includes the first four scales and the mental component summary (MCS) includes the latter four scales.

From fasting blood samples, drawn at baseline and at the end of study, samples were immediately frozen and later analyzed for fatty acid analysis by gas chromatography at The Lipid Research Center, Aalborg University Hospital, Denmark. Levels of individual plasma phospholipid PUFAs were quantitated as weight percentage (wt%) of total fatty acids. Plasma marine n-3 PUFA level was defined as the sum of plasma phospholipid DHA and EPA.

We used Student's t-test to evaluate differences between the study groups. Outliers were truncated at 2 standard deviations from the mean to obtain normal distribution. We performed analyses in both intention-to-treat and per-protocol populations. Pearson's correlation analysis was used to assess the relationship between plasma marine n-3 PUFA level at the end of study, assumed to reflect stable levels during follow-up, and Δ SF-36 individual and

composite scores. A two-sided p-value of < 0.05 was considered statistically significant. PASW Statistics® version 24.0 (IBM, New York, US) was used for the statistical analysis.

RESULTS

There were no significant differences in baseline patient characteristics between the study groups (Table 1). Median plasma marine n-3 PUFA level at baseline was 6.0 wt% in both groups, increased with 4.0 wt% on average in the marine n-3 PUFA group during follow-up, while it remained stable in controls.

PCS increased by 26% and MCS by 3% during follow-up, with no difference between the study groups (Table 1). We found no significant improvement in individual Δ SF-36 scores in the marine n-3 PUFA group compared with controls (Table 2). In per-protocol analysis, patients who received marine n-3 PUFA supplements had a Δ emotional role function of 17% [SD 50%] vs 3% [SD 37%], p=0.11.

Plasma marine n-3 PUFA levels showed a weak, but statistically significantly correlation with Δ MCS (r=0.18, p=0.04), driven by trends between plasma marine n-3 PUFA levels and Δ emotional role functioning (r=0.17, p=0.06) and Δ social role functioning (r=0.15, p=0.10). There was no correlation between plasma marine n-3 PUFA levels and Δ PCS (r=0.05, p=0.57).

DISCUSSION

The main finding in the present study was that marine n-3 PUFA supplementation did not improve QoL during the first year after renal transplantation compared with controls. We found a weak positive correlation between plasma marine n-3 PUFA levels and improvement in mental health during follow-up.

Marine n-3 PUFAs are major components in cell membranes and influence cell activity in all organs, including the brain. Previous epidemiological studies report that low plasma levels of marine n-3 PUFAs are associated with major depression (7). Clinical trials focusing on the effects of marine n-3 PUFA supplementation in patients with depression have shown conflicting results. A recent meta-analysis of these trials concluded that marine n-3 PUFA supplementation is effective in the treatment of patients with major depressive disorder, while another meta-analysis concluded that the observed anti-depressive effect was very small, hence marine n-3 PUFA consumption could not be recommended for improvement of depressive symptoms (6, 10). Similarly, the weak, but significant, correlation between plasma marine n-3 PUFA levels and Δ MCS in the present study is probably not clinically relevant.

Many patients on hemodialysis therapy suffer depressive symptoms, leading to lower QoL (2). Clinical trials evaluating the effects of marine n-3 PUFA supplementation on QoL in patients on hemodialysis are scarce. One study reported significantly improved QoL after marine n-3 PUFA supplementation for four months compared to placebo (12). In this study, improvement in QoL was mainly driven by better mental health and a corresponding improvement in Beck Depression Score was shown (12).

Nearly all patients with end-stage renal disease improve their QoL after kidney transplantation (1). When we compared differences between the early and late post-transplant phase in the present study, we found a marked improvement of physical, but not mental composite score. Difference in Δ emotional role functioning between the groups showed a positive trend with marine n-3 PUFA supplementation and with plasma marine n-3 PUFA levels. However, baseline emotional role functioning scores were lower in the marine n-3 PUFA group and a spurious relationship caused by dependency of baseline values could possibly influence on results.

Strengths of this study include a well described cohort and fatty acid analysis performed at baseline and end of study. The high background consumption of marine n-3 PUFA in this Norwegian transplant cohort constitute a limitation of the present study, as it might minimize the effects of additional marine n-3 PUFA intake. In conclusion, marine n-3 PUFA supplementation did not improve QoL during the first year after renal transplantation.

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Table 1: Baseline characteristics

Variables	All patients	Marine n-3 PUFA group	Control group
Number of patients	132	66	66
Recipient age, *years*	53.4 (13.8)	52.8 (13.5)	54.1 (14.2)
Recipient gender, Female, *%*	25.8	28.8	22.7
Ethnicity, Caucasian, *%*	92.4	90.9	93.9
Marine n-3 fatty acids, *wt%*	6.3 (2.1)	6.4 (2.2)	6.3 (2.1)
mGFR, *mL/min/1.73m^2*	55.5 (16.0)	56.2 (15.3)	54.9 (16.8)
Body mass index, *kg/m^2*	26.0 (3.9)	25.7 (3.8)	26.3 (4.0)
Pre-transplantation disease, *%*			
Hypertension	71.2	78.8	63.6
Diabetes mellitus	16.7	13.6	19.7
Coronary disease	12.1	12.1	12.1
Cancer	10.6	7.6	13.6
Dialysis vintage, *months*	8 (0 – 20)	7 (0 – 19)	9 (0 – 22)
Dialysis mode, *%*			
Hemodialysis	45.5	40.9	50.0
Peritoneal dialysis	23.5	28.8	18.2
Preemptive transplantation	31.0	29.3	31.8
Physical exercise, *%*			
High intensity ≥ twice per week	38.6	37.9	39.4
High intensity once per week	3.8	7.6	0.0
Low intensity ≥ twice per week	41.7	45.5	37.9
Low intensity once per week	8.3	4.5	12.1
None	7.6	4.5	10.6
Smoking habits, *%*			
Daily smoker	15.2	15.2	15.2
Non-daily smoker	2.3	3.0	1.5
Former heavy smoker	8.3	6.1	10.6
Former light smoker	32.6	31.8	33.3
Life-long non-smoker	41.7	43.9	39.4

Baseline characteristics presented as percentage for categorical data, median (interquartile range) or mean value (standard deviation) for continuous variables. Abbreviations: mGFR: Measured glomerular filtration rate. wt%: Weight percentage of total plasma fatty acids.

Table 2. Effects of marine n-3 fatty acid supplementation on quality of life indices

	Baseline SF-36 scores ITT population, n=132			Δ SF-36 scores ITT population, n=126			Δ SF-36 scores PP population, n=101		
	n-3 FA	Control		n-3 FA	Control		n-3 FA	Control	
Variables	Mean ± SD		p	Mean ± SD		p	Mean ± SD		p
MCS, *%*	75 ± 17	76 ± 19	0.78	4 ± 16	2 ± 17	0.58	5 ± 16	1 ± 18	0.28
Emotional role functioning, *%*	64 ± 43	78 ± 35	0.04	12 ± 39	4 ± 34	0.17	15 ± 40	3 ± 33	0.10
Mental health, *%*	86 ± 12	83 ± 15	0.18	-2 ± 14	-1 ± 15	0.41	-1 ± 14	0 ± 15	0.65
Social role functioning, *%*	83 ± 18	80 ± 24	0.50	5 ± 21	3 ± 20	0.62	7 ± 20	2 ± 19	0.20
Vitality, *%*	66 ± 21	62 ± 19	0.30	-1 ± 17	1 ± 19	0.48	0 ± 17	1 ± 19	0.75
PCS, *%*	67 ± 19	65 ± 18	0.48	10 ± 16	9 ± 17	0.88	10 ± 17	10 ± 16	0.89
Physical role Functioning,*%*	35 ± 41	37 ± 38	0.77	25 ± 37	27 ± 42	0.71	25 ± 38	28 ± 41	0.73
General health Perceptions, *%*	69 ± 19	66 ± 21	0.54	2 ± 19	2 ± 20	0.95	4 ± 21	3 ± 18	0.89
Physical functioning, *%*	82 ± 14	82 ± 15	0.98	5 ± 12	2 ± 11	0.13	5 ± 12	2 ± 11	0.23
Bodily pain, *%*	76 ± 24	75 ± 21	0.78	7 ± 22	6 ± 22	0.81	7 ± 22	6 ± 20	0.75

Differences between the marine n-3 polyunsaturated fatty acid group (n-3 *FA*) and the control group was evaluated using Student t-test. Abbreviations: MCS: Mental component summary. PCS: Physical component summary.