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Randomized control trials

A randomized controlled trial of the effects of n-3 fatty acids on resolvins in chronic kidney disease

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SUMMARY

Background and objective: The high incidence of cardiovascular disease (CVD) in chronic kidney disease (CKD) is related partially to chronic inflammation. n-3 Fatty acids have been shown to have anti-inflammatory effects and to reduce the risk of CVD. Specialized Proresolving Lipid Mediators (SPMs) derived from the n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) actively promote the resolution of inflammation. This study evaluates the effects of n-3 fatty acid supplementation on plasma SPMs in patients with CKD.

Methods: In a double-blind, placebo-controlled intervention of factorial design, 85 patients were randomized to either n-3 fatty acids (4 g), Coenzyme Q_{10} (CoQ) (200 mg), both supplements, or control (4 g olive oil), daily for 8 weeks. The SPMs 18-HEPE, 17-HDHA, RvD1, 17R-RvD1, and RvD2, were measured in plasma by liquid chromatography–tandem mass spectrometry before and after intervention.

Results: Seventy four patients completed the 8 weeks intervention. n-3 Fatty acids but not CoQ significantly increased ($P < 0.0001$) plasma levels of 18-HEPE and 17-HDHA, the upstream precursors to the E- and D-series resolvins, respectively. RvD1 was significantly increased ($P = 0.036$) after n-3 fatty acids, but no change was seen in other SPMs. In regression analysis the increase in 18-HEPE and 17-HDHA after n-3 fatty acids was significantly predicted by the change in platelet EPA and DHA, respectively.

Conclusion: SPMs are increased after 8 weeks n-3 fatty acid supplementation in patients with CKD. This may have important implications for limiting ongoing low grade inflammation in CKD.

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1. Introduction

Individuals with chronic kidney disease (CKD) have up to a 10–20 fold greater risk of cardiac death than age and sex-matched controls [1]. CKD is associated with significant patient morbidity and mortality and the treatment of CKD by dialysis makes a large contribution to the growing health care costs. More than 50% of deaths in stage 5 CKD patients receiving maintenance dialysis are due to cardiovascular disease (CVD), and the risk of coronary artery disease increases exponentially with declining kidney function [2,3]. In the National Health and Nutrition Examination Survey (NHANES II), renal function of less than 70 ml/min/1.73 m^2 associated with a 51% increase in CVD death risk [4], while the Atherosclerosis Risk in Communities Study [5] showed that GFR >15 and <59 ml/min/1.73 m^2 associated with a 38% increase in risk of CVD death. The increased incidence of CVD in CKD is explained in part, by an increased prevalence of traditional risk factors such as

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LC–MS/MS, liquid chromatography–tandem mass spectrometry; 18-HEPE, 18R/S-hydroxy-5Z, 8Z, 11Z, 14Z, 16E-eicosapentaenoic acid; 17-HDHA, 17S-hydroxy-4Z, 7Z, 10Z, 13Z,15E, 19Z-docosahexaenoic acid; RvD1, 7S,8R,17S-trihydroxy-4Z,9E,11E,13Z,15E,19Z-docosahexaenoic acid; 17R-RvD1, 7S,8R,17R-trihydroxy-4Z,9E,11E,13Z,15E19Z-docosahexaenoic acid; RvD2, 7S,16R,17S-trihydroxy-4Z,8E,10Z,12E,14E,19Z-docosahexaenoic acid; 10S,17S-diHDHA, 10S,17S-dihydroxy-4Z,7Z,11E,13Z,15E,19Z-docosahexaenoic acid; protectin D1, PD1, 10R,17S-dihydroxy-4Z,7Z,11E,13E,15Z,19Z-docosahexaenoic acid; LTB_4-d_4, leukotriene B_4-d_4; EDTA, ethylenediaminetetraacetic acid; CVD, cardiovascular disease; CKD, chronic kidney disease; SPM, specialized proresolving lipid mediator; CoQ, coenzyme Q10; ESRD, end stage renal disease; COX-2, cyclooxygenase-2; BHT, butylated hydroxytoluene; GSH, reduced glutathione; LTB_4-d4, leukotriene B4-deuterated; TNF-α, tumor necrosis factor-alpha; IL-10, interleukin-10; RvE1, resolvin E1; BMI, body mass index; eGFR, estimated glomerular filtration rate.

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hypertension, diabetes mellitus, dyslipidemia, smoking, obesity and physical inactivity, and non-traditional risk factors including anemia, abnormal calcium/phosphate metabolism, inflammation, malnutrition, oxidative stress, and elevated lipoprotein (a) [1]. CKD is now considered a risk factor for all-cause mortality independent of CVD risk [2,3,6,7].

Inflammation plays an important role in acute and chronic kidney injury and may contribute to glomerular and tubulointerstitial damage. Unresolved inflammation promotes progressive glomerulosclerosis and interstitial fibrosis manifest as proteinuria and eventual renal failure [8,9]. Resolution of inflammation is an active process regulated by novel autacoids known as Specialized Proresolving Lipid Mediators (SPMs) [10,11]. SPMs are generated locally by polymorphonuclear leukocytes during the resolution of inflammation and include lipoxins derived from the n-6 fatty acid arachidonic acid (AA, 20:4n-6), and resolvins, protectins and maresins derived from the n-3 fatty acids eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) [10]. Several families of chemically and functionally distinct SPMs have been identified including E-series resolvins derived from EPA via P450 metabolism or aspirin-acetylated cyclooxygenase (COX-2), and D-series resolvins, protectins/neuroprotectins and maresins derived from DHA via lipoxygenase or aspirin acetylated COX-2 [11]. SPMs act at picogram-nanogram concentrations *in vivo* and directly block and limit excessive polymorphonuclear leukocyte chemotaxis. They inhibit pro-inflammatory cytokine production, increase anti-inflammatory cytokine synthesis, and activate specific G-coupled protein receptors on neutrophils and macrophages to enhance clearance of cellular debris that is required for tissue homeostasis to be re-established [11,12].

n-3 fatty acids have been associated with cardiovascular protection and improve cardiovascular disease risk factors such as blood pressure, plasma triglycerides and inflammation [13,14]. We have also shown that n-3 fatty acid supplementation results in elevated levels of SPMs in healthy volunteers [15,16] suggesting that they may contribute to altered immune function. In a randomized controlled trial that examined the main and additive effects of n-3 fatty acids and coenzyme Q10 (CoQ) on cardiovascular risk in patients with CKD we showed that n-3 fatty acid supplementation reduced blood pressure, heart rate and plasma triglycerides [17]. As there is no evidence to suggest that CoQ affects SPM, this study utilized plasma samples from that trial [17] to assess how n-3 fatty acid supplementation affected plasma SPM using a main effects analysis.

2. Materials and methods

2.1. Study population

Men and women with chronic renal impairment, aged 25–75 years, were recruited from the renal units of Royal Perth, Sir Charles Gairdner and Fremantle Hospitals, in Perth, Western Australia. All participants had estimated (e) GFR >15 and <60 ml/min/1.73 m^2, and serum creatinine <350 mmol/l [18]. Patients were current nonsmokers and were excluded if they had angina pectoris; major surgery; a cardiovascular event or diagnosis of CVD; BP >170/100 mmHg; diabetes; liver disease; nephrotic syndrome (proteinuria >3 g/day or protein/creatinine ratio >300 mg/mmol); or hemoglobin <110 g/l. Patients were excluded if they regularly took nonsteroidal anti-inflammatory or immunosuppressive drugs, nitrates (including Viagra); ate ≥1 fish meal per week or regularly took fish oil supplements; or if they consumed an average of >4 standard alcoholic drinks/day. Antihypertensive or lipid-lowering medication were not criteria for exclusion. The study was approved by the ethics committees of the three hospitals in accordance with the declaration of Helsinki and all patients gave informed written consent. The study was registered with the Australian Clinical Trials Register (ACTRN012605000088640). The CONSORT statement for this trial has been published with the main outcomes from this trial [17].

2.2. Study design

During a 3-week familiarization period, participants continued their usual diet and alcohol intake. After collection of baseline measurements, they were stratified by age and BMI, and randomized to one of 4 groups to take either: n-3 fatty acids (4 g daily), coenzyme Q (200 mg/day), the treatments combined or control (4 g/day olive oil) in a double-blind, placebo-controlled intervention of 8 weeks duration. Randomization was conducted by a statistician not involved in the study using computer-generated random numbers. n-3 Fatty acid capsules (Omacor®, Solvay Pharmaceuticals, Pymble, NSW, Australia) contained 460 mg EPA, 38 mg docosapentaenoic acid, 380 mg DHA and 4.1 mg α-tocopherol per 1000 mg capsule. Control capsules were olive oil (1000 mg) (Cardinal Health Australia, Braeside, Victoria, Australia). CoQ and placebo capsules (50 mg) were provided by Blackmores Australia (Balgowlah, NSW, Australia). Capsules were taken as two 1 g n-3 fatty acids or control, and 2 × 50 mg CoQ or placebo, twice daily with meals.

Volunteers were asked to maintain their usual diets, medications, alcohol intake and physical activity and not to alter their lifestyle during the intervention. All measurements were performed at baseline and during the last week of intervention. Compliance with the supplements was monitored by capsule count and measurement of platelet fatty acids.

2.3. Measurement of fatty acid composition

Platelet phospholipid fatty acids are recognized as a reliable measure of compliance with fatty acids intake. This measure was used to determine the compliance with n-3 fatty acid intake in the patients. Platelet phospholipid fatty acids were measured by gas chromatography as previously described [19]. Samples were extracted with 2 ml chloroform/methanol (2:1; vol:vol). Fatty acid methyl esters were analyzed by gas liquid chromatography using an Agilent Technologies model 7890A gas chromatograph (Santa Clara, CA). The column was a Supelco SP-2560 (100 m × 0.25 mm ID × 0.20 μm; Bellefonte, PA) with a temperature program as follows: 180 °C (1.75 min), then 5 °C/min to 200 °C (held 1.75 min), then 10 °C/min to 240 °C (held 4.5 min) using hydrogen as carrier gas at a split ratio of 30:1. Peaks were identified by comparison with a known standard mixture.

2.4. Measurement of SPMs

Fasted blood samples were collected into EDTA/BHT/GSH for measurement of plasma SPMs. Baseline and end of intervention samples were measured in the same assay to minimize within-subject variation. Briefly, plasma (1 ml) and internal standard leukotriene B_4-d_4 (LTB_4-d_4) (500 pg) were acidified with 2 ml of 100 mM sodium acetate pH 3, applied to solid phase extraction cartridges (Bond Elut C18 500 mg, Agilent Technologies, Lake Forest, CA, USA), and washed with water and hexane. The SPMs were eluted with ethyl acetate (2 ml), dried under nitrogen and reconstituted in 120 μl of 5 mM ammonium acetate (pH = 8.9) and methanol (50/50; v/v) for analysis by LC–MS/MS (injection volume 50 μl). The standards 18R/S-hydroxy-5Z, 8Z, 11Z, 14Z, 16E-eicosapentaenoic acid (18-HEPE), 17S-hydroxy-4E, 7Z, 10Z, 13Z, 15Z,19Z-docosahexaenoic acid (17-HDHA), 7S,8R,17R-trihydroxy-

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