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Current Opinion in Food Science

Evaluating the therapeutic value of omega-3 polyunsaturated fatty acid supplementation on polycystic kidney disease and co-morbidities

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Polycystic kidney disease (PKD) is an incurable genetic disease characterized by multiple fluid-filled renal cysts and is a leading cause of renal failure. Medical treatment options for PKD are limited. Therefore, dietary intervention offers a potentially efficacious, cost-effective, and safe therapeutic strategy for PKD. The omega-3 polyunsaturated fatty acids (n-3 PUFA) regulates multiple steps in PKD cyst pathogenesis. The aim of this review article was to evaluate studies investigating the effects of different amounts of fat and n-3 PUFAs sources on PKD, co-morbidities, safety, and potential mechanisms of action. Renal effects differed depending on the type of fat consumed. The n-3 PUFA, alpha-linolenic acid provided as flaxseed was renal protective, but provided as soybean oil with lower ALA content had inconsistent effects. Long-chain n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), provided as fish oil produced anti-inflammatory actions that attenuated PKD progression and improved dyslipidemia. However, adverse renal effects and reduced survival in PKD rodent models provided DHA supplementation as algal oil raises potential safety concerns. A better understanding of the role of nutrition on PKD can contribute to the development of dietary recommendations and diet-based therapies to reduce PKD progression and severity.

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Current Opinion in Food Science 2015, **2**:20–28

This review comes from a themed issue on **Functional foods and nutrition**

Edited by **Chi-Tang Ho**

For a complete overview see the Issue and the Editorial

Available online 31st December 2014

http://dx.doi.org/10.1016/j.cofs.2014.12.007

Introduction

Increasing omega-3 polyunsaturated fatty acid (n-3 PUFA) consumption has been reported to be beneficial for treating a range of diseases [1] including diabetes and hypertension which are leading causes of chronic renal disease worldwide [2]. In a review by Shapiro *et al.* [3], dietary n-3 PUFA intake was shown to consistently reduce proteinuria in diabetic nephropathy. Clinical investigation of dietary n-3 PUFA effects on kidney disease has focused on immunoglobulin A (IgA) nephrology, an autoimmune disease characterized by IgA collection in the glomeruli resulting in chronic inflammation [4]. Guidelines suggest that dietary n-3 PUFA should be considered as a treatment for progressive IgA nephropathy [5••]. The importance of n-3 PUFA supplementation in other renal diseases is less studied although inflammation is a common source of tissue injury in the pathogenesis of various kidney disease [5••]. The anti-inflammatory properties of n-3 PUFAs are supported by numerous studies [6•]. Furthermore, the ability of n-3 PUFA to act at the gene level offers a potential therapeutic strategy for genetic diseases with few medical options.

Polycystic kidney disease (PKD) is a genetic disease characterized by the development of multiple fluid-filled cysts that contribute to massive kidney enlargement, structural damage, and loss of renal function at an early age [7]. The two main forms of PKD are autosomal dominant polycystic kidney disease (ADPKD) which manifests in early adulthood and the less prevalent autosomal recessive polycystic kidney disease (ARPKD) with infantile disease onset resulting in kidney failure within the first years of life [8]. PKD is the third leading cause of end stage renal disease with ADPKD patients comprising 6–8% of adult patients with end stage renal failure. ARPKD patients and children with juvenile nephronophthisis comprises 6–14% of pediatric patients with end stage renal failure [9••,10].

Common renal-related complication of PKD are onset of hypertension at an early age and greater risk of cardiovascular disease (CVD) [11]. The most common extra-renal tissue manifestation of PKD is the development of polycystic liver disease [12]. In ARPKD, approximately 30% of affected neonates die shortly after birth [13]. In those who survive the neonate stage, hepatic cyst lesions become a major cause of morbidity and mortality [14]. Pharmaceutical agents to treat PKD have yielded inconsistent results [15]. Typically, drugs target a single pathway, however PKD cyst pathogenesis involves multiple pathways [9••]. Ideally, a therapeutic agent should be effective at the disease site, alleviate disease-related

complications, and produce minimal side-effects. Bioactive compounds naturally present in foods have the potential to be both efficacious and safe. Additionally, diet modulation offers cost-effective lifelong therapy.

The n-3 PUFAs are bioactive nutrients found in variety of plant and marine oil sources. The n-3 PUFAs act on multiple pathways that include regulating the production of mediators of inflammation (i.e. eicosanoids), activation of transcription factors, and expression of various inflammatory genes [6•]. The aim of this review was to evaluate the therapeutic value of dietary n-3 PUFA in PKD and to identify potential mechanisms of action. A better understanding of the role of n-3 PUFA in PKD will contribute toward the development of recommendations and therapies for this incurable genetic disease.

PKD pathogenesis and potential for diet therapy

The genetic mutations and molecular mechanisms in ADPKD and ARPKD have been detailed in Torres *et al.* [9••]. Shown in Figure 1, cyst development and growth in PKD involve epithelial hyperproliferation, increased apoptosis, and fluid accumulation. Progressive increase in cyst number and expansion results in tissue injury, oxidative stress, interstitial inflammation, fibrosis and damage that impairs kidney function and ultimately leads to renal failure. Animal models of PKD have been useful for advancing knowledge regarding underlying molecular mechanisms and for generating evidence in support of human clinical trials. Currently, the only dietary factors that have been assessed in clinical drug trials of ADPKD are protein restriction and increased water intake [16••].

Epidemiological studies have demonstrated a positive correlation of a Western-style diet and higher incidence of chronic kidney disease [17]. The Western diet is high in fat (>35% kcal) with the type of fat being high in n-6 PUFA and low in n-3 PUFAs [18]. The n-6 PUFA, linoleic acid (LNA, 18:2n-6) and the n-3 PUFA, alpha-linolenic acid (ALA, 18:3n-3) cannot be synthesized by the body and therefore, are essential in the human diet. LNA is widely distributed in plant foods while ALA sources are more limited with flaxseed oil being the richest source and with soybean oil being the most common source in the diet [19•].

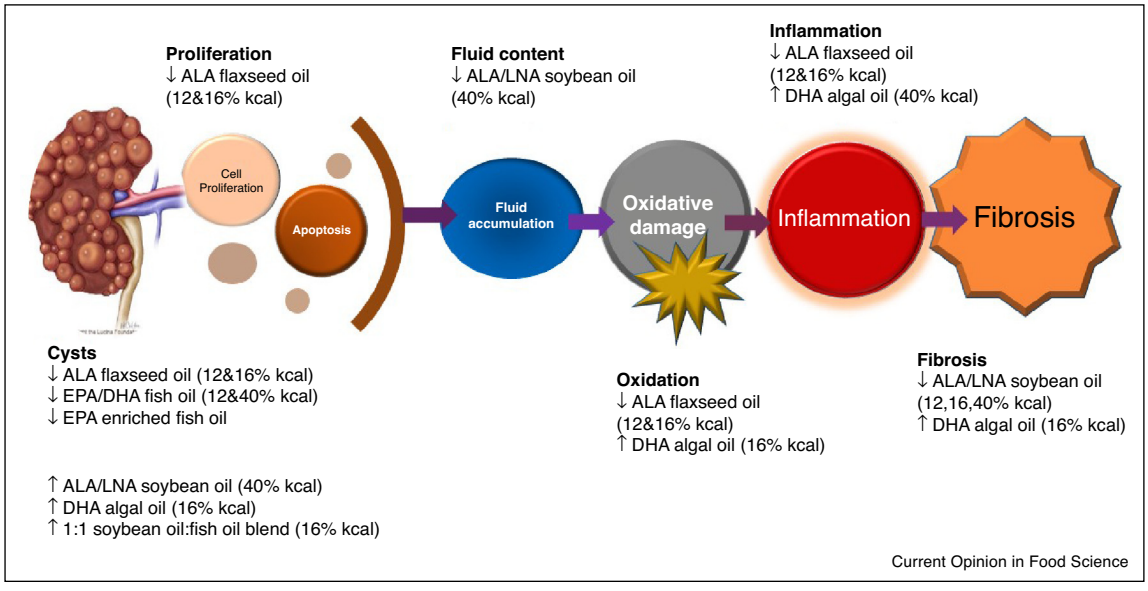
In the body, ALA can be converted by desaturase and elongase enzymes to the longer chain n-3 PUFA, eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) which are more bioactive. However, mammalian conversion of ALA to EPA and DHA is inefficient with ≤5% conversion by adults [20]. Therefore, consumption of foods containing pre-formed EPA and DHA such as fatty fish and other marine sources or supplements and fortified foods are being recommended in order to optimize health and to prevent disease.

Effect of amount and type of fat on PKD

Different amounts of fat

Feeding high fat diets produced adverse renal effects in animal models of PKD. Lu *et al.* [21] reported that feeding weanling male Han:SPRD-*cy* rats a high fat (40% kcal)

Figure 1



Summarizes the effect of different dietary omega-3 polyunsaturated fatty acids on cyst pathogenesis. Abbreviations are: ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LNA, linoleic acid.