REVIEW ARTICLE

Fatty Acids in Nephrotic Syndrome and Chronic Kidney Disease

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The role of fatty acids (FAs) in inflammation and in the related chronic diseases has been demonstrated. However, there is a lack of consistent and agreed knowledge about the role of FA profile and renal physiology and pathology, most articles focusing on the effect of polyunsaturated FAs supplementation, without considering the impact of basal FA metabolism on the efficacy of the supplementation. Here, we have summarized the specific literature concerning the assessment of circulating FA in 2 renal diseases, namely nephrotic syndrome and chronic kidney disease, also under hemodialytic treatment, and have received the most significant contributions in the last years. The effects of changes of FA profile and metabolism and the possible involvement of polyunsaturated FA metabolites in raising and modulating inflammation are discussed.

Introduction

ALTHOUGH FATTY ACIDS (FAs) play a clear role in chronic degenerative diseases with an inflammatory component in most organs and systems,[1] their role in the pathogenesis of diseases involving kidney is less evident.[2] As a matter of fact, scarce and scant data are available in this field, possibly explaining why the response to FA supplementation in renal diseases is not univocal.

Recent literature regarding FA and kidney disorders has mainly focused on FA ability to prevent kidney damage or to ameliorate kidney function in renal diseases than on the basic mechanisms of renal damage induced by alterations of their profile or metabolism.

This preference of describing putative preventive FA actions in the kidney to the assumed impact of their anomalous profile reverts the logical approach that would be based in the first place on biological plausibility and secondarily on intervention effects.

A substantial proportion of publications describes indeed a variation of FA profile in different forms of nephrotic syndrome, and furthermore experimental data underline the role of FA in the progression of renal damage in nephrotic patients.[3] Significant modifications in the FA profile of circulating lipids have been reported, in comparison to controls, in patients affected by chronic kidney disease (CKD), the most investigated renal condition as regards dietary and pharmacologic treatment aimed at increasing the n-3PUFA (polyunsaturated FA) intake.

Aim of the present review was to summarize the most relevant literature regarding changes in the profiles of FA and their metabolites in nephrotic syndrome and CKD, with the intent of elucidating their contribution in the development and progression of renal damage.

General Overview on FAs

FA profile in circulating lipids is an index of dietary intake, endogenous metabolism, and pathophysiological conditions, as suggested by the most recent scientific literature. Several studies have confirmed the relationship between health status and levels of selected FA and FA classes in various metabolic processes.[4] In particular, hard data are available on the association (either positive or negative) between PUFA metabolism and both developmental issues[5] and cardiovascular disease risk factors.[6,7]

The n-3 PUFA series has mainly positive effects on heart and brain-related functions,[8-11] while heterogeneous data are reported for the kidney, either considering CKD,[12] urinary tract inflammatory diseases,[13] or transplanted kidney.[1]

Because a positive role for dietary n-3 PUFA on health is even recognized by official institutions, such as the European Food Safety Authority,[14,15] a decrease in the level of omega-3, as reported in many diseases, needs monitoring and possibly supplementing.

On the other size, n-6 show a dualistic role, both positive and negative, that depends mainly on the effects of their metabolites.[16] Even considering several confounding factors,[17] a putative negative effect of n-6 in various diseases

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seems to emerge. Indeed, n-6 metabolites have a strong proinflammatory potential and are able to induce platelet aggregation and vasoconstriction.[18] While a diet rich of n-6 series is able to reduce LDL concentration in healthy subjects,[19] the value in preventing cardiovascular disease risk is still debated.[20,21] In kidney diseases, both n-6 and n-3 PUFA may act mainly through their metabolites,[22,23] by modulating inflammation and fibrosis, which may be important events both in nephrotic syndrome and CKD.[24] However, more data are necessary to clarify the role of either n-6 or n-3 in human diseases.

In contrast, there are few examples regarding the role of saturated FAs (SFAs) and/or monounsaturated FAs (MUFAs) in the kidney.

SFAs are collectively considered proinflammatory lipids, but biodiversity of metabolic by-products also characterizes single FA compounds.

For instance, palmitic acid (16:0) has a proinflammatory characterization, by increasing interleukin (IL)-6,[25] activating the toll-like receptor 4 (TLR4), and nuclear factor kappa B (NF-κB) pathway[26,27] and is positively associated with all markers of inflammation.[28] In contrast, stearic acid (18:0), inversely associated with high-sensitivity C-reactive protein and RANTES,[28] shows upregulated in vitro expression of genes related to mammalian target of rapamycin (mTOR) signaling on adipose tissue, that is, adipocytokine, peroxisome proliferator-activated receptor (PPAR) signaling, and insulin signaling pathways, but no effect on TLR4 pathway.[29] In experimental studies, stearic acid upregulates IL-10[30] and accelerates the recovery of hepatic dysfunction in a rat model of liver injury.[31]

Finally, the most important MUFA, oleic acid, shows a powerful anti-inflammatory action for its ability to downregulate TLR4,[29] intercellular adhesion molecule 1, and NF-κB[32] pathway.

Kidney Disorders Associated With FA Profile

Nephrotic Syndrome and CKD

Idiopathic nephrotic syndrome is the most common glomerular disorder in childhood,[33] characterized by proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Although the majority of patients with idiopathic nephrotic syndrome is steroid sensitive and presents a favorable course as regards long-term renal function, patients with steroid-resistant nephrotic syndrome are at high risk of developing CKD and eventually end-stage renal disease.[34]

There are 2 main reasons to explain steroid resistance, the first one is the "immune dysregulation," involving an abnormality of T cells subset and their function,[35,36] the second one is the "congenital," related to a genetic defect, where the primary mutation is at the level of the podocyte.[37,38]

Adult-onset nephrotic syndrome differs from the pediatric counterpart because it is more etiologically heterogeneous compared with children[39] and membranous nephropathy is the most common cause, followed by minimal change disease and focal segmental glomerulosclerosis.[40] The disease shows a benign or indolent course in the majority of patients, with a rate of spontaneous complete or partial remission as high as 30% or more. Despite this, 30% to 40% of patients progress toward end-stage renal disease within 5 to 15 years.[41]

CKD is characterized by a progressive loss of kidney function over a period of months or years and is classified into 5 stages, with Stage 1 being the mildest, usually asymptomatic, and Stage 5 representing the most severe illness, requiring dialysis and/or renal transplantation. The main causes of CKD, which is a rare condition in children, are represented for the pediatric age by renal hypodysplasia, possibly associated with urinary tract malformations, gene-related kidney diseases and glomerular diseases, like steroid-resistant nephrotic syndrome and glomerulonephritis.[42,43]

CKD affects 8% to 16% of adults worldwide and is associated with multiple adverse outcomes. It includes a heterogeneous group of conditions with widely varied associated risks.[44] The main causes of CKD in adults are represented by diabetes, nephroangiosclerosis, infection, reduced blood supply to the kidneys, obstruction of the urinary tract, and genetic alterations.[45]

Circulating FA Profile and Possible Correlations in Nephrotic Syndrome and CKD

In spite of the many reports on the effects of FA supplementation on kidney function,[2] only few studies have checked FA levels in plasma/blood lipids in patients in comparison with healthy subjects before any treatment and compared them with those of healthy subjects. It is therefore difficult to draw any conclusions about the relation between measured changes of circulating FA because of a specific treatment and outcome variables.

As regards nephrotic syndrome, studies of changes of FA profile are few and based on small cohorts.

Aldamiz-Echevarria[46] studied both congenital and idiopathic nephrotic syndrome, comparing their FA profiles with those of healthy controls. He observed an increase in the MUFA levels in both conditions. Total SFA and stearic acid decreased in both types of nephrotic syndrome; moreover, a decrease in the levels of PUFA and arachidonic acid (AA) was observed in the case of congenital nephrotic syndrome. Regarding enzymatic activities, lower 20:4n6/18:2n6 ratio and EFA index (n3 + n6)/(n-7 + n-9) were observed in both cases, whereas a lower 18:0/16:0 ratio was found only in late onset idiopathic nephrotic syndrome.

Das[47] observed fewer differences between healthy subjects and patients with nephrotic syndrome than Aldamiz-Echevarria, consisting mainly in a lower level of 18:0, 18:3n3, and 20:5n3 and a higher level of 16:0 in nephrotic patients. Interestingly, even after remission of proteinuria,