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# Omega-3 and Renal Function in Older Adults

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## Abstract

Chronic kidney disease (CKD) is a major public health problem and can result in end-stage renal disease with need for dialysis or transplantation. In Europe up to 12% of the adult population had some renal impairment, while in the United States the end stage of CKD has increased dramatically from 209.000 in 1991 to 472.000 in 2004. Diabetes and hypertension are major causes of kidney pathology. Infection, particularly ascending infection, is more common with increasing age, as both immune function declines and associated pathology predisposing to infection, such as obstructive uropathy, becomes more common. Most pathological changes in the kidney appear to be initiated by oxidative stress, followed by an inflammatory reaction. Oxidative stress results from an imbalance between free radicals and their detoxification by endogenous and exogenous scavengers, including polyunsatured fatty acids (PUFA). Recent studies showed that PUFA supplementation slowed the rate of loss of renal function in patients with IgA nephropathy. Then, studies of omega-3 supplementation in dialysis patients describe salutary effects on triglyceride levels and dialysis access patency. We examined the relationship between total plasma PUFA levels and change in creatinine clearance over a three-year follow-up in the older persons enrolled in the InCHIANTI study, a population-based epidemiology study conducted in Tuscany, Italy. This study showed that older adults with low total plasma PUFA levels have a greater decline in creatinine clearance over three years of follow-up. These findings suggest that a higher dietary intake of PUFA may be protective against progression to chronic kidney disease.

### Keywords

Polyunsaturated fatty acids; renal function; chronic kidney disease; chronic renal failure

## EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is emerging as a major public health problem among older adults and can result in end-stage renal disease with need for dialysis or transplantation for kidney failure [1–2]. In the United Kingdom, the annual incidence of end stage renal disease

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is around 100 per 1.000.000 population [1]. The Prevention of Renal and Vascular End-Stage Disease study in Europe showed that up to 12% of the adult population had some renal impairment [3]. In the United States, an estimated 19 million adults are in the early stage of disease [1]. Then, the number of patients with kidney failure treated by dialysis and transplantation (the end stage of CKD) has increased dramatically in the United States from 209.000 in 1991 to 472.000 in 2004 [2]. Operationally, the CKD stages were categorized based on the classification system established by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative as: stage 1, persistent albuminuria (>300 mg/d or >200 μg/min), with an estimated GFR higher than 90 mL/min/1.73 $m^2$; stage 2, persistent albuminuria with an estimated GFR of 60 to 89 mL/min/1.73 $m^2$; stage 3, a GFR of 30 to 59 mL/min/1.73 $m^2$; stage 4, a GFR of 15 to 30 mL/min/1.73 $m^2$, and stage 5, a GFR lower than 15 mL/min/1.73 $m^2$ It is important to consider that CKD is high in older populations with “normal” serum creatinine value. CKD prevalence and risk of death associated with CKD stage vary widely according to the method adopted to estimate GFR. Both twenty-four hours Creatinine Crearance (Ccr), and Cockcroft-Gault (C–G) formula, but not MDRD derived equations, were significant independent predictors of all-cause mortality after adjustment for age, sex and other major confounding clinical characteristics [4].

## AGE-RELATED CHANGES IN RENAL STRUCTURE AND FUNCTION

Age-related changes in renal structure and function have been described, not just in humans [3,5–11] but in a wide range of other species, including rats, mice, hamsters, dogs and cats [12–20]. The decline of renal function with age in humans is well documented in a range of geographic settings, in different human populations and using a wide range of different methods and parameters. Since the kidney plays a fundamental role in the maintenance of biological homeostasis, not surprisingly renal function is a major predictors of longevity [21] and is often the limiting factor in choice of therapy for renal replacement therapy and for other disorders [22], as well as being one of the factors limiting transplantation options both as donor and recipient. As would be expected from the decline in renal function with age, the prevalence of chronic renal impairment, as well as end-stage renal failure (ESRF), rises sharply with age [23,24], although some authors have questioned the inevitability of the progression from renal impairment to renal failure [25]. With the increasing proportion of elderly people in the population of most of the Western world, there are profound implications for health care services in the provision of renal replacement therapy.

### Tubulo-Interstitial Changes with Age

The size of the kidneys rises until age 40–50 years and then decreases with age [26]. Much of this change is likely due to tubulo-interstitial changes, including infarction, scarring and fibrosis, rather than just loss of glomeruli [27,28]. Macroscopic scarring of the kidney is a frequent incidental finding at autopsy, and localized scarring increases with frequency in the elderly [29,30]. Simple cysts of the kidney are also more common in older subjects [31]. Tubular atrophy, with thickening of the basement membrane, is a common feature of parenchymal change in scarring, and tubular thyroidization, with dilatation of the lumen, flattening of tubular epithelium and accumulation of eosinophilic hyaline cast material within the tubule, is also a common feature of end-stage renal damage. More intricate studies of age-related changes in tubular morphology have shown that, in addition to tubule number decreasing with age, the volume decreases, length decreases, the number of diverticula increases and tubular atrophy increases [32]. There is also an increase in the interstitial volume associated with interstitial fibrosis. In experimental models of the ageing kidney, collagen deposition is increased in association with age-related expression of fibrosis-related genes, including fibronectin [33,34], as well as increased TGF- expression [35]. Other age-related changes in the extracellular matrix, including collagen alterations and reduction of tubular

metalloproteinases, have also been well described [36–38]. A causal relationship between hypoxia and resultant interstitial fibrosis has also been postulated, with up-regulation of hypoxia-induced genes in the ageing kidney, including hypoxia-inducible factor (HIF) vascular endothelial growth factor (VEGF) and glucose transporter-1 (GLUT1) [39]. Most authors have suggested that the damage to tubulo-interstitium is one of the major prognostic features in renal disease (not glomerular or vascular changes) and this would appear to be so, not just for the native kidney but also for the accumulated tubulo-interstitial scarring that can be present in the transplanted kidney [40]. Although there is considerable disagreement concerning this view, it is important to note that, especially at the initial stage, severe pathological changes in the interstitial tissue may not cause detectable changes in renal function and, therefore, may not be detected by screening based measures of GFR or albuminuria. Whether any aspect of the tubulo-interstitial injury is ultimately reversible remains to be seen.

## Glomerular Structural Changes with Age

Concomitant with a reduction in the number of viable glomeruli, there is an increase in the number and percentage of sclerotic glomeruli with age, with approximately 10% loss up to the age of 40 and highly variable individual rates of loss, after that age [41–43]. Subcapsular cortical glomeruli are particularly susceptible to sclerosis in comparison to juxtamedullary glomeruli [44–45]. Glomerular sclerosis is generally thought to be a non-specific end-stage morphological change resulting from a large range of insults, including ischaemia and a wide range of immunological disorders [46]; however, different types of segmental sclerosing lesions have been clearly shown to result from different stimuli [47].

In addition to alterations in overall numbers of glomeruli, there may also be an increase in the glomerular basement membrane and an increase in the mesangial matrix volume/material [48–49]. These are likely to result from alterations in the balance between formation and breakdown of the extracellular matrix in the glomerulus. It is important to note that although these pathological changes are often observed in the kidney of older persons, they also occur in the context of many kidney diseases and there is no robust evidence that they increase with age in healthy individuals.

## Renal Disorders Associated with Increasing Age

Primary renal disease in the elderly has a spectrum of glomerular disorders similar to that seen in younger patients, although there is a two- to three-fold increased prevalence of membranous glomerulopathy and a four-fold increase in the incidence of crescentic glomerulonephritis, with decreased evidence of IgA nephropathy and minimal change nephrotic syndrome. Some of the membranous cases are obviously associated with the malignancies that, notoriously, are more prevalent in older than in younger patients. Thus, while it has been suggested that aging “per se” affects the probability of these lesions to develop, the role of aging has not been fully established. Diabetes and hypertension are major causes of kidney pathology, including glomerulosclerosis and arteriolosclerosis, which seem to accelerate age-related features. Infection, particularly ascending infection, is more common with increasing age, as both immune function declines and associated pathology predisposing to infection, such as obstructive uropathy, becomes more common. From the pathogenetic perspective, most pathological changes in the kidney appear to be initiated by oxidative stress, followed by an inflammatory reaction. Oxidative stress results from an imbalance between the levels of free radicals generated during aerobic metabolism, inflammation and infection and their detoxification by endogenous and exogenous scavengers, including superoxide dismutase, vitamins C, E, selenium and polyunsatured fatty acids (PUFA). Protein and other molecular damage can result from free radical damage, leading to toxic post-translational changes, such as carbonylation and nitrotyrosination [50–52].

## DEFINITE CAUSES OF CKD

Many cohort studies in the USA and Japan have identified hypertension, diabetes, hyperlipidaemia, obesity and smoking as risk factors for the development of CKD. It is generally hypothesized that these risk factors exert their effect both by increasing vascular pathology as well as by a direct damage kidney structures. Concerning the different etiopathogenetic forms, in a large clinical series the cause of CKD was glomerulonephritis in 59.6%, hydronephrosis in 9.7%, diabetic nephropathy in 7.6%, hypertensive renal disease in 6.6%, kidney malignancy in 5.2%, renovascular disease in 4.9%, and other in 6.4% [3].

The natural history of kidney disease is characterized by 10–15 years of stable renal function or even hyperfiltration, with sometime small amounts of albumin in the urine of 20–40% of patients with type 1 or type 2 diabetes. If left untreated, 80–100% of patients with microalbuminuria and type 1 or type 2 diabetes progress to overt nephropathy and macroalbuminuria. The ACE Inhibition in Progressive Renal Disease (AIPRD) meta-analysis confirmed that proteinuria is a strong risk factor for progression of chronic renal disease and those patients with more severe renal disease benefit most from ACE inhibitor treatment [3]. Nondiabetic glomerulopathies include IgA nephropathy. Progression to End-stage Renal Diseases (ESRD) occurs in 30% of patients after a follow-up of 25 years. Membranous nephropathy has a variable course with an insidious onset and increasing proteinuria up to nephritic ranges. In the long term, spontaneous remission occurs in up to 30% of individuals. Most patients with mesangial proliferative glomerulonephritis and isolated hematuria maintain normal renal function for years. Overall, approximately 30–40% of patients develop significant renal failure 10–15 years after the diagnosis of nephropathy.

### Mechanism of Kidney Scarring

Glomerulosclerosis (a syndrome characterized pathologically by diffuse inflammatory changes in the glomeruli and clinically by hematuria with red blood cell casts, mild proteinuria, and, often, hypertension, edema, and high serum BUN) [53]. Progressive glomerulosclerosis has many similarities to atherosclerosis. They are both characterized by endothelial damage and dysfunction, proliferation of smooth-muscle or mesangial cells, and injury to the pericyte or podocyte. As with atherosclerosis, hypertension-induced shear stress leads to injury, activation, and dysfunction of the glomerular endothelium, which is turn initiates glomerular microinflammation leading to interactions between inflammatory cells and mesangial cells with the activation, proliferation and dysfunction of the latter. Communication between cells depends on the release of a wide range of cytokines and growth factors. Under the influence of growth factors, especially transforming growth factor β1 (TGF β1), mesangial cells regress to an embryonic mesenchymal phenotype (mesangioblasts) capable of excessive production of extracellular matrix (ECM) leading to mesangial expansion, an early sign of glomerulosclerosis [54].

Tubulointerstitial fibrosis (Primary TIN is defined as injury that affects the tubules and interstitium without significant involvement of the glomeruli or renal vasculature. Drugs, infections and systemic diseases are the principal condition associated with TIN) [53].

Tubulointerstitial scarring and fibrosis are associated with the impairment of renal function. As with glomerulosclerosis, tubulointerstitial fibrosis involves inflammation, proliferation, apoptosis and fibrosis. Experimental evidence suggests that proteinuria has an important role in the initiation of tubulointerstitial inflammation. Excessive reabsorption of albumin by proximal-tubule cells *in vitro* stimulates the release of various proinflammatory mediators including chemokines. Injured tubules undergo programmed cell death (apoptosis) leading to tubular atrophy and the formation of atubular glomeruli. Under the influence of TGF β1, some tubular become transformed into an embryonic phenotype, thus acquiring mesenchymal

properties similar to those of fibroblasts and myofibroblasts. Tubular cells could therefore contribute to the pool of cells directly involved in renal fibrogenesis [54].

Regardless of the primary cause of nephron loss, some usually survive or are less severely damaged [53]. These nephrons then adapt and enlarge, and the magnitude of clearance per nephron markedly increases, limiting the decline of global function. If the initiating process is diffuse, sudden, and severe, such as in some patients with rapidly progressive glomerulonephritis, acute or subacute renal failure may occur with the rapid development of ESRD. In most patients, however, disease progression is more gradual and nephron adaptation is possible. This process has been studied extensively in animals models. Glomerular hypertrophy, a marked increase in glomerular plasma flow and single-nephron GFR, and increased capillary pressure are noted. Focal glomerulosclerosis develops in these glomeruli, and they eventually become non-functional. At the same time that focal glomerulosclerosis develops, proteinuria markedly increases and systemic hypertension worsen. ACE inhibitors, slow this process and diminish proteinuria [54]. Other mechanism of progression, already mentioned above, are mesangial proliferation, glomerular coagulation and hyperlipidemic effects. It is likely that tubulointerstitial fibrosis contributes to nephron failure in the process of nephron adaptation. At this stage the release of the TGF β1 and nephron ischemia might contribute to arteriosclerosis. This process of nephron adaptation has been termed the “final common path”. The ability of nephrons to adapt by enlarging and increasing function has beneficial effects in maintaining whole-kidney GFR, as well as rates of solute excretion and the end products of protein metabolism that cause the uremic syndrome Fig. (1).

## EVIDENCE OF TREATMENT BY OMEGA-3 OF THE SPECIFIC KIDNEY DISEASES

Recent studies suggest that there may be an association between polyunsaturated fatty acids (PUFA) and the development of chronic kidney disease [55]. PUFA supplementation has been shown to reduce renal inflammation and fibrosis in animal models.

### IgA Nephropathy

Idiopathic IgA nephropathy is the most common glomerular disease in the world. Renal failure develops in 20 to 40 percent of patients 5 to 25 years after diagnosis. A randomized controlled trial of dietary fish-oil supplementation significantly slowed the rate of loss of renal function in patients with IgA nephropathy [56–59]. During the two-year treatment period patients in the treatment group received 1.87 g/d EPA and 1.36 g/d DHA. Only 6 percent of the fish-oil group had an increase in serum creatinine concentration of 50 percent or more, as compared with 33 percent of the placebo group. Dietary fish oil supplementation has been shown to reduce progression of renal disease among patients with IgA nephropathy [56] and to suppress mesangial cell activation and proliferation in animal models [60]. PUFA may reduce inflammation through several possible pathways, such as reduction of nitric oxide [61], down-regulation of TNF-α [62], and modulation of protein kinases [63].

### Chronic Renal Disease

We hypothesized that low total plasma PUFA levels were associated with an accelerated decline of kidney function in older adults. To test this hypothesis, we examined the relationship between total plasma PUFA levels and change in creatinine clearance over a three-year follow-up in the older persons enrolled in the InCHIANTI study, a population-based epidemiology study conducted in Tuscany, Italy [64]. This study showed that older adults with low total plasma PUFA levels have a greater decline in creatinine clearance over three years of follow-up than those with higher levels of total plasma PUFA levels. In addition, participants with lower baseline plasma PUFA levels and free of renal insufficiency were significantly more

likely to develop renal insufficiency at the three-year follow-up compared to those with higher plasma PUFA levels [64]. These findings suggest that a higher dietary intake of PUFA may be protective against progression to chronic kidney disease, and are consistent with observations from animal models that show that PUFA supplementation reduces progression of renal disease [65]. The observation that total plasma PUFA and not omega-3 fatty and omega-6 fatty acids separately (data not shown) appear to have a beneficial effect on renal function require consideration. In fact, omega-3 polyunsaturated fatty acids are generally considered more beneficial than omega-6 fatty acids [65]. However, recent data showed that both omega-6 [66] and omega-3 [65] fatty acids have anti-inflammatory properties. Our findings prompt the hypothesis that a diet rich in PUFA may be protective against the decline in renal function that is common with aging. A Mediterranean-style diet that is characterized by a relatively high consumption of fish and low consumption of saturated fats has been shown to be protective by reducing markers of inflammation and cardiovascular disease [67], and cancer [68]. Further work is needed to confirm the association between plasma PUFA and renal function in other cohorts of older persons and provide enough evidence to test translate these findings into clinical trials.

### Dialysis

Studies of omega-3 supplementation in dialysis patients describe salutary effects on triglyceride levels, dialysis access patency, and possibly uremic pruritus and oxidative stress [69–70].

Despite these advantages, omega-3 supplementation is neither routinely recommended nor used in the dialysis-dependent population [71].

### Renal Cancer

Renal cell carcinoma (RCC) of the renal parenchyma accounts for more than 80% of all kidney cancer, the majority of which are adenocarcinomas. The evidence that fish consumption, especially fatty fish, may be associated with low risk of several cancers is weak and not consistent. A recent study published by Wolk a *et al*. [72] found an inverse association of fatty fish consumption with the risk of RCC after adjustment for potential confounders. Compared with no consumption, the multivariate risk ratio (RR) was 0.56 (95% confidence interval [CI], 0.35–0.91) for women eating fatty fish once a week or more. Compared with women consistently reporting no fish consumption, the multivariate RR was 0.26 (95% CI, 0.10–0.67) for those women reporting consistent consumption of fatty fish at baseline and 1997 (based on a subset of 36 664 women who filled in the baseline and 1997 questionnaires, with 40 incident RCC cases during the 1998–2004 follow-up period). This study suggests that consumption of fatty fish may reduce the occurrence of RCC in women [72].

## POSSIBLE MECHANISMS BY WHICH PUFA MAY PREVENT CKD

### Omega-3 Fatty Acids Influence the Circulating Amount of Eicosanoids

Both omega-6 and omega-3 fatty acids and their longer-chain derivates are import components of plant and animal cell membranes. Arachidonic acid (AA) is found mostly in triglycerides, in cholestereryl esters, and only in very small amounts in phosplolipids. EPA and DHA is found mostly in phospholipides. There is plenty of evidence that consumption of essential fatty acids has a significant effect on the production and distribution of prostanoids and leukotriens [73–75]. AA is the precursor of the 2-series of prostanoids (prostaglandins and thromboxanes) and of leukotriens of the 4-series, which are both proinflammatory eicosanoids. EPA and DHA are precursors of the 3-series of prostanoids and leukotriens of the 5-series, which are anti-inflammatory, anti-trombotic and inhibit platelets aggregation. Both, omega-3 and omega-6 fatty acids increase levels of prostacyclin PGI3 and PGI2, respectively, which are active and

potent vasodilators. Interestingly, nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., aspirin, indomethacin, ibuprofen) exert a strong anti-inflammatory activity by blocking cycloxygenase isozymes and the release of prostaglandins derived from phospolipase-released arachidonic acid Fig. (2). Unfortunately, since they the contemporary block release of prostacyclin, these drugs are highly nefrotoxic [76].

### Omega-3 Fatty Acids Increase Endothelium-Derived Relaxing Factor (EDRF)

EDRF, presumably nitric oxide, facilitates relaxation in large arteries and vessels. In the presence of EPA, endothelial cells in culture increase the release of relaxing factors, indicating a direct effect of omega-3 fatty acids on the cells [77].

### Omega-3 Fatty Acids Influence Cytokine Levels

Using data from the InCHIANTI study, we found that the relative concentration of n-3 fatty acids is independently and significantly associated with low circulating levels of IL-6, IL-1ra and TNF-alpha, and high circulating levels of sIL-6r and TGF-beta. The anti-inflammatory properties of TGF-beta are well known. TGF-beta is a potent immunomodulatory cytokine that self-limit the acute inflammatory response, contributes to the development of immunotollerance, and is major signaling molecule for the activation of T-suppressors lymphocytes. Our study provides solid evidence that higher n-3 fatty acids relative concentration, well within the normal physiological range, have anti-inflammatory effects in humans. Since, these levels can be easily modified by a different selection of foods in the diet, physicians should always consider dietary interventions for the prevention and treatment of diseases where inflammation plays a pathophysiologic role [77].

### Omega-3 Fatty Acids Influence Blood Pressure

Omega-3 fatty acids seem to have a small, dose-dependent, hypotensive effect, the extent of which seems to be dependent on the degree of hypertension [78–79]. In a meta-analysis, Morris *et al*. found a significant reduction in blood pressure of −3.4/−2.0 mmHg in studies with hypertensive subjects who consumed 5.6 g/d of omega-3 fatty acids. DHA seems to be more effective than EPA in lowering blood pressure [80].

### Omega-3 Fatty Acids Influence the Levels of Tryglicerides and Cholesterols

The hypotriglyceridemic effects of omega-3 fatty acids from fish oils are well established. In a comprehensive review of humans studies, Harris reported that 4 g/day of omega-3 fatty acids from fish oil decreased serum triglyceride concentrations by 25% to 30%, with accompanying increases in LDL cholesterol of 5% to 10% and in HDL cholesterol of 1% to 3%. A dose-response relationship exists between omega-3 fatty acids intake and triglyceride lowering [81].

### Omega-3 Fatty Acids Influence Thrombosis and Hemostasis

Omega-3 fatty acids decrease platelet aggregation, resulting in a modest prolongation of bleeding times. Then, some evidence indicates that fish oil supplementation may enhance fibrinolysis [82].

## CONCLUSIONS

The intake of omega-3 fatty acids in the United States is 1.6 g/d (almost 0.7% of energy intake). Of this, ALA acids accounts for 1.4 g/d, and only 0.1 to 0.2 g/d comes from EPA and DHA. The major food sources of ALA acid are vegetable oils, principally canola and soybean oils. Other food sources that are rich in ALA acid include flaxseed and English walnuts.

Typical recommendations are 0.3 to 0.5 g/d of EPA+ DHA and 0.8 to 1.1 g/d of ALA acid. Recently, the Food and Nutrition Board, Institute of Medicine, and The National Academies, in collaboration with Health Canada, released the Dietary Reference Intakes for Energy and Macronutrients. The Acceptable Macronutrient Distribution Range (AMDR) for ALA is estimated to be 0.6% to 1.2% of energy, or 1.3 to 2.7 g/d on the basis of a 2000-calorie diet. This is almost 10 times the current intake of EPA+DHA. These recommendations can easily be met by following the AHA Dietary Guidelines to consume two fish meals for week, with an emphasis on fatty fish (e.g. salmon, herring and mackerel), and by using liquid vegetable oils containing ALA. The changes in food consumption in Poland, corresponding with increases in the ratio of polyunsaturated fat to saturated fat in people's diet and fruit consumption, seem to be related to a rapid decline in mortality due to coronary heart disease between 1991 and 1994 [67]. This type of diet should be used worldwide also for obtaining a significant reduction of the chronic kidney disease and associated cardiovascular disease.

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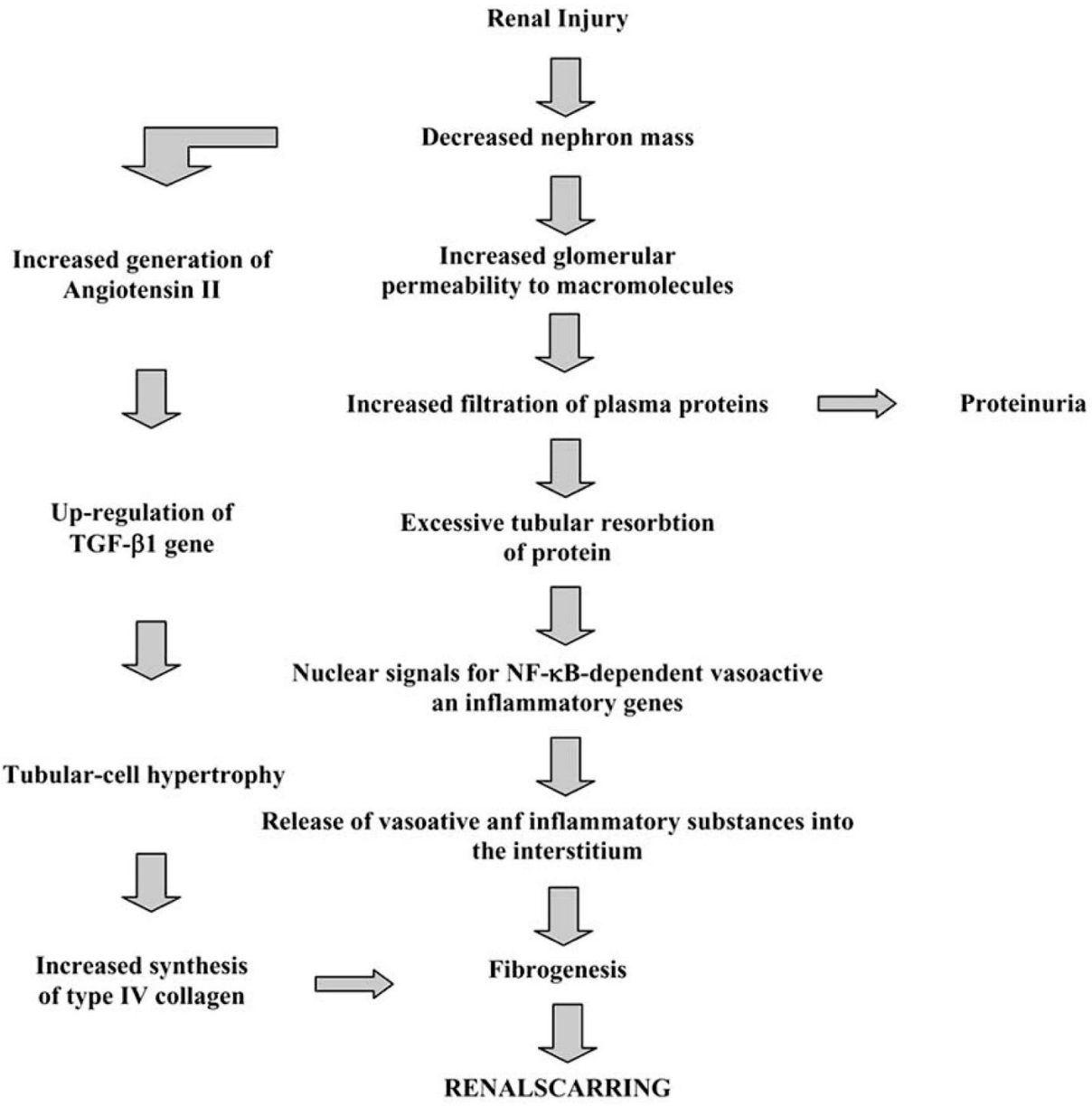


**Fig. 1.**
Process of nephron adaptation to a renal injury defined the “final common path”.

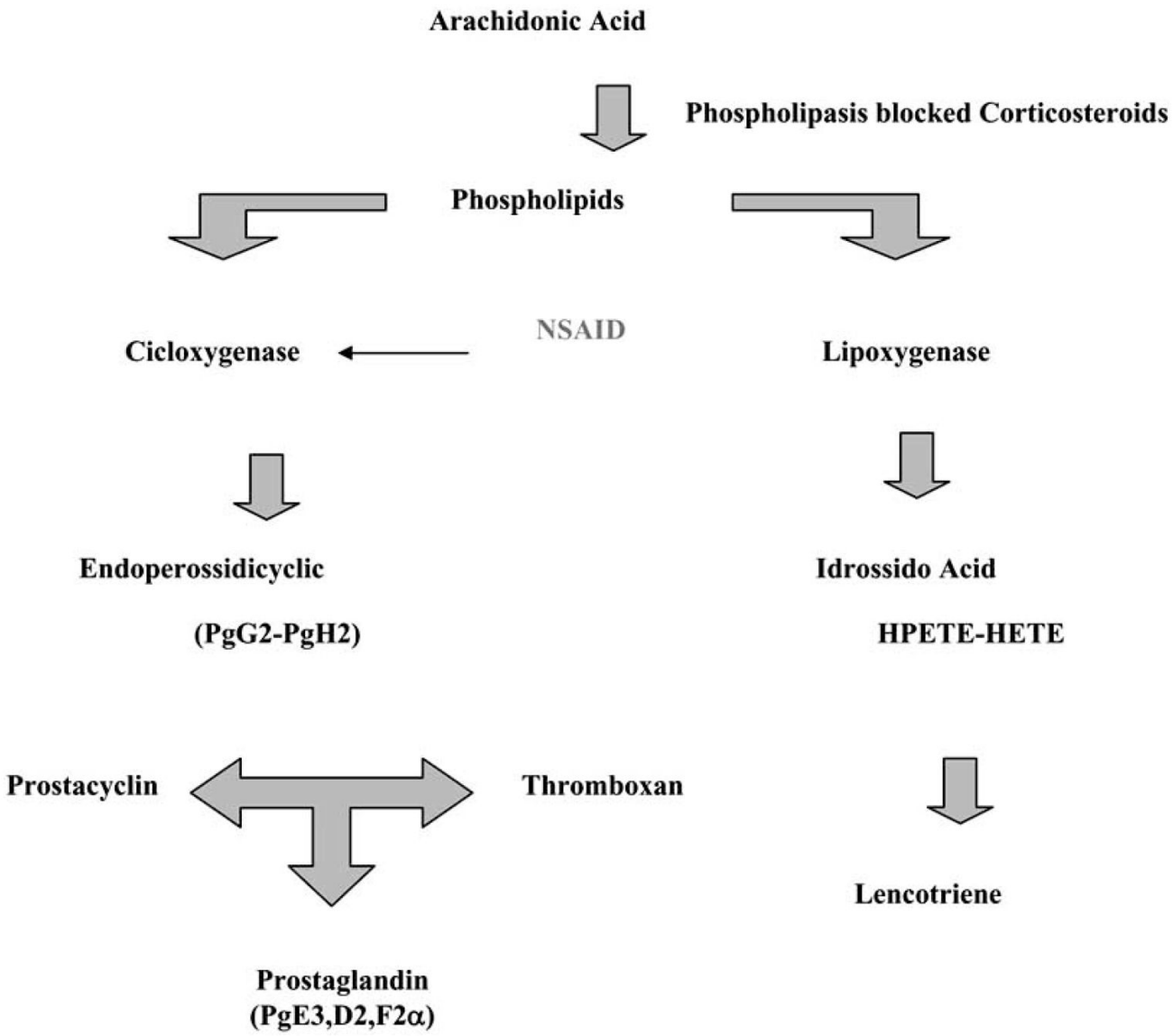


**Fig. 2.**
Prostaglandins pathways derived from phospolipase-released arachidonic acid.