Lipid disturbances in chronic renal failure – patomechanisms and treatment

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Abstract

Lipid disturbances are a constant feature of chronic renal failure (CRF). They compose a significant risk factor for vascular complications, leading to increased morbidity and mortality in this patients group. The major lipid abnormality in the course of CRF is hypertriglyceridemia, but increased cholesterol level is also common. Numerous studies, including these from our Centre, point to the conclusion that hypertriglyceridemia is a consequence of both, increased TG production and impaired TG removal. In contrast hypercholesterolemia is mainly due to enhanced cholesterol biosynthesis. HMG-CoA reductase inhibitors (statins) compose the most promising group of drugs to treat lipid abnormalities in CRF. Apart from their lipid-lowering abilities they posses non-lipid, so called pleiotropic activities, which make them especially useful in proliferative and inflammatory kidney diseases.

Key words: chronic renal failure, lipid disturbances, fibrates, statins.

Cardiovascular and cerebrovascular complications are as much as 20 times more frequent in patients suffering from chronic renal failure (CRF), when compared to general population [1]. This is mainly due to accelerated atherosclerosis processes in this group of patients. Numerous risk factors for the development of atherosclerosis are present in patients with CRF. Among them lipid disturbances play a particularly important role. Described for the first time almost hundred years ago by Blackall et al. they were predicted much earlier by Richard Bright [2]. They consist mainly of hypertriglyceridemia [3]. This abnormality occurs in as much as 60% of CRF patients. Triglycerides (TG) content is increased in all atherogenic lipoprotein fractions (VLDL, IDL, LDL), and seems to be related to the progression of the disease. Hypercholesterolemia is less common, as it affects 20-30% of patients with renal insufficiency. This percentage is similar to the one observed in general population. However, even in cases of normal total cholesterol level shifts among particular lipoprotein fractions are often observed with a tendency to higher cholesterol concentrations in atherogenic VLDL and LDL, and lower in HDL fraction.

Lipoprotein disturbances in the course of CRF vary significantly depending on the stage of the disease and the method of treatment. On the basis of data obtained from the literature as well as the studies performed in our Department it can be stated that the abnormalities in lipid profile are still present in the course of renal replacement therapy. In hemodialysed (HD) patients they consist mainly of increased plasma TG levels and reduced plasma HDL cholesterol [4]. It is noteworthy that erythropoietin treatment has no impact on lipid profile in HD patients [5]. Impaired lipid metabolism is also common in patients on peritoneal dialysis (PD). Increased concentrations of TG, total and LDL cholesterol, decreased HDL cholesterol level are constant features of lipid profile in PD patients [6]. Probably, to some extent it is a consequence of increased absorption of glucose from the dialysate. But it is after renal transplantation when most severe changes in lipid metabolism occur. Our studies, among others indicate that cholesterol level begins to rise immediately after transplantation reaching the maximum after 2-3 months post transplant [7-9]. In the third month after transplantation total cholesterol level is approximately 20% higher, than pre-transplant. Cholesterol concentration is increased in all the lipoprotein fractions. In

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the course of further treatment the level of total cholesterol decreases, still, after six months after the transplantation it exceeds 200 mg/dl in 80% of patients. It is now well acknowledged that the mentioned above complications are caused by the immunosuppressive treatment, especially the use of cyclosporine and steroids [9].

Despite numerous studies performed in several nephrology centres all over the world the mechanisms of lipid disturbances in the course of CRF are still poorly understood.

Hypertriglyceridemia is the major lipid abnormality in CRF patients. It is believed that this disturbance is mainly a consequence if impaired TG removal. Studies by Bagdade et al. [3,10] demonstrated decreased activities of both lipoprotein and hepatic lipases. The impact of lipogenesis disturbances on hypertriglyceridemia was evaluated in our Centre on a rat model of chronic renal insufficiency. Experimental CRF was induced by our own modification of 5/6 nephrectomy model [11]. First studies, performed 25 years ago showed augmented lipid production in white adipose tissue of CRF animals [12]. This was most probably due to the observed increase in free fatty acid synthase activity. The studies on lipogenesis in experimental CRF were continued recently [13]. They confirmed that the activity of free fatty acid synthase activity was increased in CRF rats. Further, increase in the enzyme's mRNA level and protein abundance was demonstrated, both in liver and adipose tissue of CRF animals when compared to control group. Moreover, increased activities of malic enzyme, glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase were observed. As these enzymes play a significant part in lipogenesis processes, namely NADPH production, obtained results further support the role of increased lipid synthesis in development of hypertriglyceridemia in the course of CRF. The factors responsible for the stimulation of gene expression of enzymes engaged in lipogenesis include hyperinsulinemia and low leptin concentration. Indeed, results of our earlier studies demonstrate that leptin mRNA level is decreased by 50% in adipose tissue of CRF animals, while leptin is known to inhibit fatty acid synthase gene expression [14,15].

Hypercholesterolemia affects 20-30% of CRF patients. Though not as common as hypertriglyceridemia it is as dangerous, since it is acknowledged that hypercholesterolemia constitutes an independent risk factor for atherosclerosis development [1]. As atherosclerosis processes are enhanced in CRF population, leading to increased morbidity and mortality in this patient group, mechanisms leading to hypercholesterolemia deserve thorough evaluation.

Both in vitro and in vivo studies conducted in our Centre showed a significant impact of enhanced cholesterol biosynthesis on hypercholesterolemia in experimental CRF. The first set of experiments with the use of tritated water injected intraperitoneally proved that the rate of cholesterologenesis was increased both in liver and intestines of CRF animals [16]. Further studies evaluated in vitro incorporation of radioactive cholesterol substrates: [^{14}C]-acetate and [^{3}H]-mevalonate into liver cholesterol fraction [16]. Significantly higher activities of both 'compounds' incorporation were found in livers of CRF rats, when compared to control animals.

Since 3-hydroxy-3-methylglutaryl coenzymeA (HMG-CoA) reductase is the rate limiting enzyme in cholesterol biosynthesis pathway one can suppose that enhanced cholesterologenesis observed in our studies is a consequence of increased HMG-CoA reductase activity. This activity, as well as the whole cholesterologenesis process undergoes a significant diurnal rhythm. It is preserved in the course of experimental CRF, as demonstrated by studies from our Centre [16]. Our experiments on HMG-CoA reductase were, therefore, performed with regard to these diurnal changes in enzyme's activity. We found that liver microsomal HMG-CoA reductase specific activity in CRF rats was increased both during the day and in the night [17]. Similarly, values of HMG-CoA reductase mRNA level were higher in CRF group when compared to control animals.

Patients, as well as laboratory animals with CRF exhibit higher plasma mevalonate concentrations with a concomitant decrease in its urinary excretion [18]. Mevalonate is a direct product of HMG-CoA reductase activity. Therefore, in the presence of elevated mevalonate level HMG-CoA reductase activity and its mRNA level would be expected to be suppressed rather than stimulated. As it is not the case, it seems obvious that normal feedback regulation of HMG-CoA reductase is altered in CRF animals.

The etiology of the described disturbances is poorly understood. It has been suggested that CRF generates an undefined stimulus for HMG-CoA reductase activity in the liver. Feingold and Grunefeld [19] demonstrated that intravenous administration of Tumor Necrosis Factor-alpha (TNF-α) stimulated hepatic sterol synthesis and increased HMG-CoA reductase activity in livers of rats. It is noteworthy that plasma concentrations of TNF-α as well as soluble TNF-α receptors have been found to be increased in chronically uremic patients [20]. On the other hand, however, in the work by Feingold and Grunefeld stimulation of sterologenesis by TNF-α was specifically localized to the liver. Administration of TNF-α did not stimulate cholesterol biosynthesis in the small intestine, adipose tissue, muscle nor skin, while our results indicated that in experimental CRF cholesterolegenesis was stimulated both in liver and intestinal tissue [16]. Therefore, it appears that TNF-α might by just one of many factors responsible for the increase in HMG-CoA gene expression in CRF.

Taking into consideration unfavorable impact of lipid disturbances on CRF patient survival it seems advisable that they should be adequately treated. Dietary guidelines state that total calorie intake should be chosen to attain/maintain a desirable body weight and to prevent weight gain, daily total fat intake should not exceed 35% of total calories: (a) saturated fats < 7% of total calories, (b) polyunsaturated fat up to 10% of total calories, and (c) monounsaturated fat up to 20% of total calories, daily carbohydrate intake should range between 50 and 60% of total calories (predominantly from foods rich in complex carbohydrates, including grains, fruits, and vegetables), and daily protein intake is expected to be about 15% of total calories [21]. But dietary restrictions are usually insufficient in correcting lipid profile, and pharmacological treatment is often indispensable. Fibrates are often introduced, especially in patients with predominant hypertriglyceridemia. How fibrates exert their hipolipidemic action is still unclear. However, it is known that they act as peroxisome proliferator-activated receptor alpha

(PPAR-α) agonists [22]. By activating these nuclear transcription factors they have an impact on free-fatty acid transport. Further, they enhance β-oxidation process, increase the activity of lipoprotein lipase and the expression of apolipoproteins: apoA1 and apoA2, thereby increasing HDL production. Finally, they decrease VCAM-1 and interleukine-6 synthesis, and, therefore, act as anti-inflammatory agents [23,24].

But the most potent drugs lowering plasma lipid concentrations are HMG-CoA reductase inhibitors, i.e. statins. They inhibit endogenous cholesterol synthesis on the level of HMG-CoA reductase. Statins bind to this enzyme at nanomolar concentrations, whereas the natural substrate, HMG-CoA binds at micromolar concentrations [25]. This leads to competitive displacement of HMG-CoA and inhibition of the synthesis of cholesterol precursor, mevalonate. Active cholesterol synthesis is a requirement for VLDL assembly and secretion [26]. As VLDL are precursors of IDL and LDL, statins, by inhibiting cholesterol synthesis decrease the concentrations of all these lipoproteins. Further, reduction of intracellular cholesterol concentration by statins leads to activation of compensating mechanisms to assure intracellular lipid homeostasis. Namely, it activates membrane-bound transcription factors called sterol regulatory element binding proteins (SREBPs) that regulate multiple genes involved in cholesterol homeostasis [27]. SREBPs directly stimulate the expression of more than 30 genes dedicated to the synthesis and uptake of cholesterol, fatty acids and TG, among them the LDL-receptor gene. This leads to an increase in the number of LDL-receptors and intensification of LDL clearance from the plasma providing yet another mechanism, by which statins decrease plasma cholesterol concentration [26]. Lipid lowering properties of statins do not restrict themselves solely to cholesterol. More potent drugs, e.g. atorvastatin or rosuvastatin have been shown to decrease TG levels by 20-30% [28,29].

Beneficial effects of statins in decreasing the risk of coronary complications and prolonging survival have been documented in many large trials, with thousands of patients participating [30-33]. Statins appear also to have a positive impact on the prevention of other vascular complications, e.g. strokes [34]. Similar results have been obtained in patients with kidney diseases, both in persons with mild chronic renal insufficiency, as well as in end-stage renal disease (ESRD) patients [35,36].

Potential usefulness of statins in treating kidney diseases has been investigated by several authors. Kasiske et al. [37] introduced lovastatin in rats with experimental CRF. After 10 weeks of therapy urine albumin excretion was significantly reduced, as compared to the control group. Moreover, the percent of glomeruli with focal glomerulosclerosis was 3 times smaller in the group treated with the statin. In an experiment by O'Donnell et al. [38], after 22 weeks of treating rats with experimental CRF with lovastatin the animals had a 76% reduction in urine albumin excretion and one-sixth the incidence of focal glomerulosclerosis, compared with the vehicle-treated control rats. Other studies dealing with the use of lovastatin in rats with experimental CRF showed decrease in blood urea concentration, mesangial cell proliferation, and glomeruli sclerosis [39,40]. Clinical observations provided similarly promising results. Shoji et al. [41] introduced pravastatin in patients with microalbuminuria in the course of diabetic nephropathy. After three months of such treatment they observed decrease in albumin excretion in all patients. In the work by Rabelink et al. [42] partial remission of nephrotic syndrome was achieved in all patients after 48 weeks of treatment with simvastatin. However, patient groups were small in these studies.

There is also some clinical evidence that statins may slow down the progression of renal insufficiency [43]. These observations gain more importance in the light of the hypothesis that mechanisms leading to glomerulosclerosis are very similar to those responsible for the development of atherosclerosis [44].

Knowing that lipoprotein disturbances lead to atherosclerosis, and given the information that they can also have an injurious impact on kidneys, it would seem self-evident that the mentioned above beneficial effects of statins are related solely to their lipid lowering properties. However, analysis of large clinical trials shows that the advantages of statin use are not associated with the degree of cholesterol reduction [30-32]. In fact, they exceed it by far. Furthermore, a growing number of experimental studies indicates that many actions of HMG-CoA reductase inhibitors are independent from cholesterol lowering. For instance, Hidaka et al. [45] observed inhibition of the migration of cultured porcine smooth muscle cells stimulated with PDGF by simvastatin. This effect was reversed by the addition of mevalonate to the culture. However, supplementation with LDL was unable to reverse the effect of statin. In another work vascular smooth muscle cell proliferation was inhibited by lovastatin [46]. Addition of mevalonate completely reversed this effect, whereas supplementation with cholesterol had no impact on lovastatin induced action. Similar results were obtained in rat mesangial cells, where exogenous LDL did not prevent lovastatin inhibition of cell proliferation [47]. These investigations, as well as many others, show clearly that some effects of statin use are not related to cholesterol lowering.

It is known, however, that by inhibiting HMG-CoA reductase activity statins influence the biosynthesis of more compounds than merely cholesterol.

Mevalonate is the direct product of HMG-CoA reductase activity. Not all mevalonate molecules, however, participate in cholesterol formation. Some of them join together to form 15-carbon, and 20-carbon compunds – isoprenoids, named farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), respectively (*Fig. 1*). These two compounds play a major role in a process called protein prenylation [48]. It consists in post-translational modification of certain proteins by isoprenoids, leading to protein activation. Both, FPP and GGPP have the ability of covalent addition to cysteine residues at the carboxy-terminus of the proteins. The process is mediated by two enzymes, farnesyl transferase and geranylgeranyl transferase. The enzymes recognize a specific sequence at the carboxy-terminus, named CAAX motif, where C means cysteine, A an aliphatic amino acid, and X the carboxy-terminal amino acid, which determines which isoprenoid is to be added. In situations where X is methionine or serine, preferential protein prenylation occurs via farnesyl transferase, and where X is leucine, GGPP addition occurs. The enzymes

Figure 1. **Farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) synthesis**

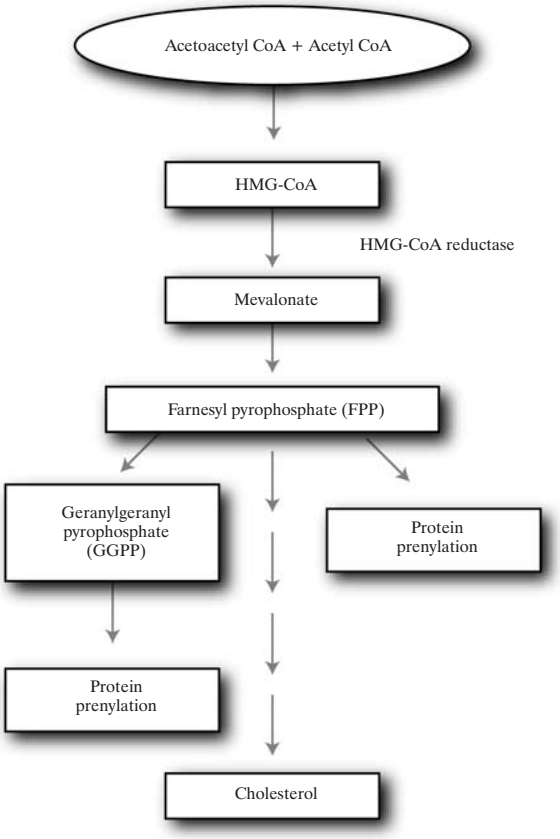
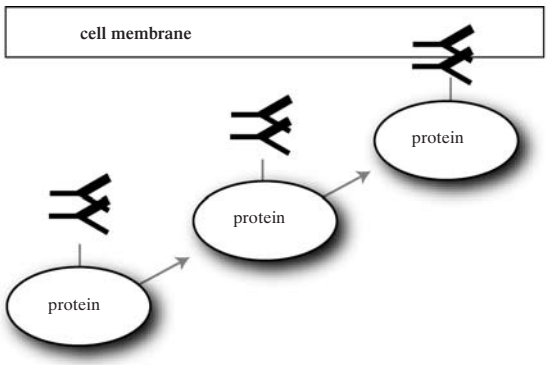


Figure 2. **Prenylation process. Isoprenoid (FPP or GGPP) is attached to the CAAX motif of a protein. This enables attachment of the protein to the inner cell membrane, and protein's activation**



catalyze the attachment of isoprenoid to the cysteine residue of the CAAX motif, and the –AAX moiety is removed. It is now known that prenylation is not confined to proteins containing the CAAX motif. Still, in such cases isoprenoids are also attached to cysteine residue at, or very near the carboxy-terminus of the protein. Prenylated protein is translocated to the inner cell membrane or plasma membrane, where isoprenoid serves as an "anchor" to fix the protein on the membrane's surface, thereby activating it [48] (*Fig. 2*). About 0.5% of the proteins in animals cells are activated through prenylation [49]. Some of them, as Ras or rho proteins are indispensable for cell growth and proliferation [50,51]. Therapeutic strategies that aim at prenylation inhibition can, therefore, have a crucial impact on inhibiting cell growth and proliferation, for instance in primary glomerulonephritis. Results of numerous studies demonstrate that the antiproliferative activity of statins is related, at least in part to inhibition of protein prenylation [51-53].

Cell proliferation is a part of a general inflammatory process which affects kidneys in response to injurious factors. This process, apart from cellular proliferation includes: release of several adhesion molecules, chemokines, pro-inflammatory cytokines, activation of inflammatory enzymes, oxidative stress, alterations in nitric oxide (NO) synthesis, coagulation disturbances etc. One of the markers of the ongoing inflammation is increased plasma concentration of C-reactive protein (CRP). It has also been demonstrated that levels of CRP are associated with increased risk of myocardial infarction and stroke among apparently healthy individuals [54]. The impact of pravastatin on CRP level was evaluated in a group of patients taking part in Cholesterol and Recurrent Events (CARE) trial [55]. After five years patients on pravastatin treatment had median CRP levels 21.6% lower than those on placebo ($p = 0.007$). This effect was, at least to some extent, independent from cholesterol lowering, as the magnitude of CRP reduction associated with pravastatin use did not correlate with the magnitude of LDL reduction. In an interesting study by Sirken et al. [55] statin therapy was demonstrated to decrease erythropoietin (EPO) requirements in hemodialysed patients. Increased levels of CRP have been associated with relative EPO resistance in dialysis patients. Therefore, the authors suggest that the improvement in EPO responsiveness may be caused by the effect of statins on CRP. These observations raise the possibility that HMG-CoA reductase inhibitors may have clinically important anti-inflammatory actions.

Despite potential benefits, statin treatment in CRF patients is still related to many fears and controversies. Numerous reports on myopathy, including rhabdomyolysis after statin treatment are available in the literature [56-58]. This is especially true for patients after renal transplantation, since some statins posses the same path of metabolism with immunosuppressive agents, mainly with cyclosporine and tacrolimus [59,60]. It has to be stressed, however, that statins are safe, when administered in adequate doses. Their ability to lower cholesterol level, as well as their pleiotropic abilities make statins a group of drugs worth considering in CRF patients.

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