Statins and Kidney

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ABSTRACT

Statins are widely used by cardiologists for their beneficial effects on lipid lowering and plaque stabilization. But they have found to have a significant role in various renal diseases due either to their lipid lowering effects or due to other non-lipid lowering actions. In this article we evaluate various uses of statins in renal diseases besides their traditional use.

A brief correlation between cardiovascular disorders and renal disorders have also been tried to establish as the major cause of death in patients of CRF is cardiac.

The incidence of atherosclerotic related vascular diseases is decreasing in United States of America, but coronary artery disease, ischemic cerebrovascular diseases etc. is still one of the major causes of morbidity and mortality.

Hypercholesterolemia is one of the major cause of atherosclerosis in the West. Genetic factors and diet both contribute to the elevated lipid levels. Lowering these levels can decrease the cardiovascular mortality by up to 30%-40% as has been proved by 4S[1] and LIPID[2] studies.

Hypercholesterolemia, if severe (>1000mg/dl), needs treatment to prevent pancreatitis. Moderate elevation may be a part of syndrome characterized by insulin resistance, obesity, hypertension and increased coronary heart disease risk.

Hyperlipidemia (increased levels of triglyceride or cholesterol) and decrease HDL-C level occur as a result of several factors that affect the concentration of various plasma lipoproteins. These factors vary from lifestyle (sedentary), behavior (type A personality) to metabolic and influence plasma lipoprotein metabolism.

Epidemiological studies have proved that higher the cholesterol level, higher the risk of CHD (Stambler et al.).[3] Several trials in 1970s and 1980s showed that average cholesterol reduction by 10% resulted in 20% reduction in nonfatal CHD events. (Lipid Research Clinics Programme 1984,[4] Fricket al[5]).

The 4S study showed that lowering LDL-C with simvastatin despite normal HDL decreased the mortality by 42%, non-fatal CHD events by 40% and total mortality 30%. The 4S, CARE and LIPID studies prove that lowering LDL-C value below 130 mg/dl benefits CHD patients.

DRUG THERAPY OF DYSLIPIDEMIA (STATINS)

Statins are the most effective and best tolerated agents for the treatment of dyslipidemia. They act by inhibiting HMG-CoA reductase which catalyzes a rate limiting step in cholesterol synthesis. Higher dose can also decrease triglyceride levels and also help in elevating HDL-C.

Statins were derived from *Penicillium citrinium* in 1976 by Endo and his colleagues. Brown et al[7] showed that they act by inhibiting HMG-CoA reductase. The first studied statin was compactin which was renamed mevastatin. Lovastatin became the first statin to be approved for human use. Pravastatin and simvastatin are chemically modified derivatives of lovastatin. Atorvastatin, fluvastatin and cerivastatin are synthetic compounds.

CARDIOVASCULAR DISEASE AND CHRONIC KIDNEY DISEASES

Cardiovascular diseases are the most common cause of death in patients with ESRD. The risk of cardiac complications is 30 times higher in ESRD than the age-adjusted general population.[8] Due to the advancement in renal replacement therapy (RRT) more and more patients are opting for RRT. However life-expectancy in ESRD patients on dialysis is reduced. Cardiovascular disease is emerging as the major cause of death. The risk of death due to cardiac complications is 65 times higher in dialysis patients between the age of 45-54 years and 500 times more than the general population.[9] This can be due to underlying cause of CKD e.g. diabetes mellitus, hypertension, dyslipidemia etc. Framingham study has shown increased risk of early renal insufficiency in patients with above disease.[8]

PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE IN KIDNEY DISEASE

Patients with CKD have the usual risk factors for CVD. Myocardial infarction is responsible for about 59% of all deaths in CKD, also the risk of CAD is 40% in patients on haemodialysis or peritoneal dialysis.[10] The incidence of unstable plaque is more in CRF. Intramyocardial arterial wall thickening is found which is independent of blood pressure and can interfere with vasodilatation. Capillary density also decreases leading to decrease in myocardial oxygen supply. There is an accelerated atherosclerotic change in aorta and peripheral arteries. Calcification of arterial media causes stiffness and is an independent predictor of cardiovascular mortality.[10,11]

Other factors leading to increased cardiovascular mortality and morbidity in CKD are hypertension, anaemia, calcium, phosphorus, parathyroid hormone, proteinuria, decreased albumin level, increased homocysteine levels and lipids.

ROLE OF STATINS IN CKD

Statins have been found to be useful in patients with various renal diseases. Let us consider them one at a time.

Chronic Glomerulonephritis

There is an increasing evidence that suggest that lipid abnormality plays a role in the progression of renal diseases.[12,13] In diabetic nephropathy, hyperlipidemia has been associated negatively with GFR[13] and simvastatin has been shown to reduce urinary albumin excretion.[14] Syrjanen et al[12] reported hypertriglyceride levels to be a risk factor for progression of IgA nephropathy. Statins have been found to be effective in the prevention of ESRD. Lipid lowering has a beneficial effect on declining GFR.[15] The major cell type responsible for the maintenance of the structure and function of the glomeruli are the podocytes. Glomerular injury is usually associated with the leakage of proteins across the glomerular basement membrane which occurs as a result of loss of podocyte foot process. It has been reported that urinary podocytes are a marker of acute glomerular injury and a possible predictor of disease progression.[16,17] Nakamera T et al[18] have found that cerivastatin decreases urinary podocytes excretion in patients of IgA nephropathy.

Nephrotic Syndrome

Hyperlipidemia is a well known metabolic complication of nephrotic syndrome. Nephrotic individuals are at a high risk for cardiovascular diseases. Hyperlipidemia may exacerbate renal injury.[19] It has been shown that reduction in the level of lipids slows the progression of glomerular and tubulointerstitial disease.[20] In short term studies statins have been shown to be highly effective against adverse lipid profile associated with nephritic syndrome.[21]

Hyperlipidemia complicating nephrotic syndrome is characterized by increased plasma concentration of VLDL, LDL and Lp(a) with normal or slightly low HDL-C.[22] Hypercholesterolemia is seen in almost 90% of patients of urinary protein excretion of >3gm /24 hr. Plasma lipids correlates inversely with serum albumin but directly with urinary albumin excretion. It has been assumed by the result of retrospective and prospective studies that hypercholesterolemia in nephrotic syndrome represents a risk factor for atherosclerosis and that correction of lipid abnormality may be of benefit and is therefore recommended. Studies have shown that correction of lipid levels in progressive renal disease will slow the progression of renal failure.[23] Lipid-induced renal injury is caused by the accumulation of lipoproteins within the mesangium and tubulointerstitium, this initiates a chronic inflammatory response with infiltration of macrophages, disturbed mesangial cell function and accumulation of matrix components leading to irreversible functional loss.

Possible beneficial actions of Statins in Nephrotic Syndrome

- Correction of dyslipidemia
- Reduced platelet aggregation
- Reduced levels of procoagulant factors
- Inhibition of mesengial cell
- Inhibition of matrix accumulation
- Anti-inflammatory effects

Potential non-lipid lowering actions of statins in patients of Nephrotic Syndrome

They inhibit mesengial cell proliferation and accumulation of matrix in murine mesengial cell cultures. They also have a potential role as immunomodulators.

Clinical benefits of Statins in Nephrotic Syndrome:

Short term studies have suggested a significant reduction in albuminuria.[24] and increase in GFR. However long term studies are needed. Another study [25] did not find any change in either urinary protein excretion or creatinine clearance. However, a recent meta-analysis of 13 small prospective studies showed that statins do reduce the rate of decline of renal functions.[15]

Other methods of lipid lowering like lipopheresis may be used particularly in patients with focal segmental glomerulosclerosis.

Conclusion

The association between hyperlipidemia and nephrotic syndrome is well established however the underlying mechanism is not fully understood, but they may enhance renal injury and increase risk of cardiovascular events. Effort should be made to correct these abnormalities. Statins appear to be the most effective therapy on the basis of short-term studies. Long-term studies are still needed.

Renal Ischemic - Reperfusion Injury

Inflammation plays an important role in the pathogenesis of renal ischemic-perfusion injury (IRS). Statins have shown to have anti-inflammatory effects whish is independent of their lipid lowering effects. It was found that the mechanism of proteinuria in renal IRS was by reducing neutrophil and macrophage infiltration and by up regulating the anti-inflammatory cytokine IL-6. In a study by Yokota et al[26] it was found that pretreatment with cerivastatin for three days led to a significant improvement in renal functions, tubular injury as well as survival after IRS.

End Stage Renal Disease (ESRD)

Statins have been associated with significant reduction in cardiovascular mortality and morbidity in patients with ESRD. Besides this non-lipid lowering effects like endothelial stabilization, anti-inflammatory, anti-thrombotic etc. may

be important in modulating their effectiveness. Cerivastatin possesses some unique non-LDL-C mediating properties that may contribute to a reduction in coronary events in patients of ESRD. CHORUS[27] study has demonstrated beneficial non-lipid lowering effects of cerivastatin on inflammatory proteins like IL-6, oncostatin-M, intra-cellular adhesion molecule-1 and monocyte chemoattractant protein-1.

Effect on Erythropoiesis

Erythropoietin (EPO) is decreased in patients of CRF and has to be supplemented. The requirement varies from patient to patient but in our country it is still a costly proposal. In CRF it has been shown that inflammatory cytokines induce EPO resistance, anoxia and suppression of hepatic albumin synthesis. An increased level of CRP has been associated with relative EPO resistance in patients on dialysis. Study by Sirken G et al[28] has shown that statins decrease CRP and in turn decrease the requirement of EPO.

Van Den Akkar J M[29] showed that both simvastatin and atorvastatin showed favorable effect on lipid profile in the patients of ESRD. Moreover reduction of oxidatively modified LDL may indicate that statins exhibit favorable effects on oxidative stress also.

In CKD patients' connective tissue growth factor (CCN; CTGF) gene expression is upregulated in fibrotic renal glomeruli leading to increased mesengial fibrosis. Statins have been found to inhibit (CCN; CTGF) m-RNA expression in mesengial cells and thus decrease glomerular fibrosis.[30]

Cholesterol-independent inhibition of AT1 receptor-mediated vascular smooth cell proliferation by statins may contribute to the beneficial effects of statins when combined with ARB on vascular disease.[31]

Renal Transplant Patients

Hyperlipidemia is more common after renal transplantation, immunosuppression with corticosteroids, cyclosporine or sirolimus. ALERT trial showed that treatment of renal transplant patients with fluvastatin showed a reduction is secondary end-points of cardiac death and non-fatal myocardial infarction.

Cosyo FG et al[32] showed a 24% better survival in post-transplant patients treated with statins as compared to those who did not take statins after transplant.

CONCLUSION

It can be safely concluded that statins are a very useful drugs not only in cardiovascular disorders but also in chronic kidney disorders. They help not only by their lipid lowering action thereby reducing cardiac related mortality in CKD patients but also by their non-lipid lowering actions.

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