

Renal Transplant Alıcılarında Hiperkolesterolemi Tedavisi

Treatment of Hypercholesterolemia in the Kidney Transplant Recipient Population

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ÖZET

Renal transplant alıcılarında, dislipidemi prevalansı (özellikle total kolesterol ve düşük dansiteli lipoprotein artışı olarak) oldukça yüksek bulunmaktadır. Bu hastalarda hiperlipidemi varlığı, ateroskleroz ve kardiyovasküler ölüm riskine katkıda bulunmaktadır. Aterosklerotik koroner arter hastalığı için renal transplant alıcıları, en yüksek risk grubunda olup, dislipidemi değerlendirilmesi başlangıçta, durumda bir değişiklik olduğunda ve yıllık olarak yapılmalıdır. Renal transplant alıcılarında statin tedavisinin yararları, kardiyak olaylarda, akut rejeksiyonda, kan basıncı kontrolünde, kemik mineral dansitesi ve sağkalımda düzelmede gösterilmiştir. Bu derlemede, renal transplant alıcılarında hiperlipidemiyle ilgili tedavi stratejileri tartışılacaktır.

Anahtar sözcükler: hiperlipidemi, tedavi, renal transplant alıcıları

ABSTRACT

The prevalence of dyslipidemias in kidney transplant recipients is very high particularly common as increases in total cholesterol and low density lipoprotein. Hyperlipidemia contribute to the risk of premature atherosclerosis and cardiovascular death in these patients. Kidney transplant patients should be considered to be in the highest risk category for atherosclerotic coronary heart disease and evaluation of dyslipidemia should occur for kidney transplant recipient population at presentation, after a change in status and annually. Beneficial effects of statins specific to the kidney transplant population that have been demonstrated previously include favorable effects on cardiac events, acute rejection, associations with improved patient survival, lower blood pressure, and improved bone mineral density. In this review, the treatment strategy of hyperlipidemia in kidney transplant recipient population will be discussed.

Keywords: hyperlipidemia, treatment, kidney transplant recipients

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Introduction

Premature cardiovascular morbidity and mortality are still the major problems in the long-term after renal transplantation (1). The relative age-specific death rates due to cardiovascular disease are 5-10 times greater than in the general population (1-3). Hyperlipidemia is a major modifiable risk factor contributing to cardiovascular complications after renal transplantation (4). It has also been implicated

in the development of chronic allograft nephropathy and may jeopardize long-term graft outcome (5,6). Short-term studies have demonstrated that hypercholesterolemia with raised low density lipoprotein (LDL) represented the most frequent abnormality, which was associated with corticosteroid and cyclosporine treatment in a dose-dependent manner (7).

In this review, the lipid abnormalities and the use of anti-lipidemic treatment in renal transplant recipient population will be summarized.

Quality of life after renal transplantation

Renal transplantation improves quality of life and longevity compared with chronic dialysis (8), but nonetheless is an incomplete treatment for the mor-

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bidity and excess mortality of kidney failure. Because the half-lives of deceased donor and living donor allografts are currently 13.8 and 21.6 years, respectively, many transplant recipients will require retransplantation or return to dialysis during their lifetimes (9). Further, the survival of renal allograft recipients is significantly lower than that of age-matched controls in the general population due in large part to accelerated cardiovascular risk.

Statins and their functions

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [HMG-CoA]) lower the total cholesterol and its low density lipoprotein (LDL) fraction level in a dose-dependent manner. Statins competitively inhibit HMG-CoA reductase, an enzyme participating in cholesterol synthesis. They lower cholesterol concentrations in blood, by also increasing LDL-receptor expression on hepatocyte surfaces. The LDL-receptors scavenge LDL and its precursor molecules from blood (10). Additionally, statins have the potential to inhibit apolipoprotein B-100 hepatocyte synthesis and decrease production and secretion of very low density lipoproteins, which are rich in triglycerides.

In addition statins have several pleiotropic effects unrelated to lipid levels including reduced inflammation, improved endothelial function, and improved insulin sensitivity (11,12). Growing evidence suggests that statins have nephroprotective effects, evidenced by decreased glomerular damage (13). The effect of statins on the glomerular vasculature is probably mediated by reduced endothelin-1 concentrations and increased endothelial nitric oxide (NO) synthase expression (14,15). Statins can stimulate production of osteoblasts, increase apoptosis of osteoclasts in vitro, and influence bone-specific isoform of alkaline phosphatase, thus exerting antiosporotic effects (16).

These beneficial power of statins are beyond their cholesterol reducing effects. The effects of statins on nitric oxide are the basis of the well described favourable effects of statins on endothelial dependent vasomotor function (17). In patients with documented coronary artery disease, statins reduced transient myocardial ischemia. Their anti-ischemic properties are thought to be consequence of protein kinase Akt activation, subsequently promoting collateral growth and increasing capillary density. In addition, oral treatment with statins reduces

angiotensin II induced NADPH oxidase activity, and subsequent oxidative stress (17). Statins can also modify the sympathetic system. They decrease sympathetic activity and inhibit apoptosis. Also statins have been shown to reduce left ventricular mass in patients with hypertension and hyperlipidemia, on top of anti-hypertensive treatment (17).

Alterations of lipid profile in end stage renal disease and renal transplant patients

Dyslipidemia is one of the most important and prevalent risk factors for atherosclerotic cardiovascular disease in the end stage renal disease (ESRD) population. Classically, patients with ESRD have been shown to have low levels of HDL, increases in very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) leading to elevated triglyceride levels, and either no change or a slight increase in LDL (18). Hemodialysis patients display elevated VLDL and IDL, decreased HDL, and a shift of LDL particle size toward a small, dense apo-B-rich LDL predominance. On the other hand, peritoneal dialysis patients demonstrate a reduction of apoA-containing lipoproteins (HDL), enrichment of triglycerides in especially VLDL and IDL, with a concomitant elevation in small triglyceride rich LDL particles (18). In general in patients on peritoneal dialysis, hypertriglyceridemia is as common as in patients on hemodialysis, but tends to be more severe, and hypercholesterolemia (especially elevations in LDL) is much more prevalent.

In renal transplant patients, the most frequent alterations of lipid profile are elevations of total cholesterol, LDL cholesterol and triglycerides and a decrease of HDL-cholesterol (19). Kasiske reported recently the combined results from five studies showing that 63% of patients had total cholesterol >240 mg/dL. LDL cholesterol was >130 mg/dL for 60% of the patients, while only 12% had HDL cholesterol <35 mg/dL, triglyceride levels were >200 mg/dL in 36% of patients (20). These alterations can persist chronically during the post-transplant period even 10 or more years after transplantation (21).

Several well known causes can contribute to these lipid alterations, such as older age, male gender, obesity, diabetes mellitus, proteinuria, anti-hypertensive medication (diuretics and beta blockers) and mainly immunosuppressive therapy (22). In many cases, several factors are involved in the same patient.

In general population, it is well accepted that hyperlipidemia (increased serum cholesterol and LDL-cholesterol) is one the most important factors for developing coronary disease (23). Evidence indicates that dyslipidemia plays a role in initiating and sustaining chronic kidney disease as well (24). While Schaeffner ES et al found that elevated levels of TC or its subfractions and elevated TG levels are not associated with increased risk for patient mortality or allograft loss in these kidney transplant recipients (25). Nevertheless, HMG-CoA reductase inhibitors have noticeably improved cardiovascular outcomes in patients lacking significant kidney disease and show promise of doing as much in renally compromised patients (24).

Treatment of hypercholesterolemia in renal transplant recipient population

In ALERT study, it was founded that treatment with fluvastatin reduced the incidence of major adverse cardiovascular events (cardiac death, non-fatal myocardial infarction and coronary revascularizations) by 17% in renal transplant recipients (26). A further finding of this study was to demonstrate the safety and efficacy of fluvastatin when administered together with immunosuppressive therapy and a wide range of cardiovascular medication in renal transplant recipients. It has been shown that lipid levels rise immediately following transplantation, reaching a maximum after 2-3 months, nearly 20-30% higher than pre-transplant levels (27). However despite compelling evidence that statin therapy is beneficial and reduces the risk of cardiovascular complications, treatment with these drugs has not yet become routine practice following transplantation and in many cases the initiation of statin treatment is delayed until clinical manifestation of hypercholesterolemia or the occurrence of the first cardiovascular event (28). But it was reported that the incidence of cardiac death and non-fatal myocardial infarction was reduced consistently in patients who started fluvastatin therapy in the first 4.5 years following transplantation (29). In the same study, those patients who started the therapy later had a smaller, statistically insignificant benefit. The risk of fatal and non-fatal cardiac events was higher in the first 6 years from last transplant in the placebo control group and the risk reduction seen with fluvastatin was larger during this same period.

In a recent review of data about renoprotective effects of statins reported that the renoprotective effects of statins in patients with diabetic nephropathy or recipients of renal transplants were less apparent than patients with nondiabetic nephropathy who require lipid lowering therapy (24).

Still, kidney transplant recipients have a higher incidence of dyslipidemia compared with the general population. According to national kidney foundation, kidney transplant patients should be considered to be in the highest risk category for atherosclerotic coronary heart disease. Evaluation of dyslipidemia should occur for kidney transplant recipient population at presentation, after a change in status and annually. Drug therapy should be used for LDL >130 mg/dL together with lifestyle changes (diet, weight reduction, increased physical activity, abstinence from alcohol, and treatment of hyperglycemia if present). Initial drug therapy should be with a statin. Drug therapy should be used for LDL 100-130 mg/dL after 3 months of lifestyle changes. Fibrates may be used for patients with triglycerides \geq 500 mg/dL and for patients with triglycerides \geq 200 mg/dL with nonHDL cholesterol \geq 130 mg/dL, who do not tolerate statins. Clinical practice guidelines recommend that transplant recipients have their LDL cholesterol below 100 mg/dL (30).

Statins are the group of hypolipemic drugs that best control dyslipidemia in kidney transplant recipients (31). However there are some side effects of these drugs. For example hepatic cells damage in the course of statin therapy is a well-known side effect, which appears in 1% to 3% of treated patients (32). Usually signs of hepatotoxicity are first observed within 3 months of drug introduction and disappear 2-3 months after withdrawal. Another side effect which requires cautious approach during statin use is myopathy. Because cyclosporin raises statin blood levels and thereby increases the risk of toxicity including myositis, aggressive dosing of currently available statins above the moderate range in patients taking calcineurin inhibitors is not recommended (30).

Beneficial effects of statins specific to the kidney transplant population that have been demonstrated previously include favorable effects on cardiac events (26), acute rejection (33), associations with improved patient survival (34), lower blood pressure (35), and improved bone mineral density (36). It has also been demonstrated that statins have a favorable influence on the development of new-onset

diabetes after transplantation (37). This effect appears to be independent of their lipid lowering effect.

Even though statin therapy are suggested to lower the risk of graft rejection after solid organ transplantation (38), when used at low to moderate doses among patients with renal transplants receiving cyclosporin-based immunosuppression, there is inadequate evidence to support use of statins for lowering the risk of acute allograft rejection (31).

In the treatment of hyperlipidemia, ezetimibe is a new agent with a different way of action selectively blocking absorption of dietary and biliary cholesterol by the small-intestine enterocyte brush-border (39). Ezetimibe, the first selective cholesterol absorption inhibitor, has been examined in the renal transplant population and offers a new option for the management of hyperlipidemia (40,41). This drug does not inhibit or induce the cytochrome P450 system and should be safe with calcineurin inhibitors and sirolimus. Although early evidence provides that ezetimibe is effective in lowering total and LDL cholesterol and has no marked toxic effects and no obvious drug interactions with primary immunosuppressive medications, it may be the best to increase the dose of the statin to more modest levels before considering adding ezetimibe. For patients who continue to have LDL ≥ 100 mg/dL despite optimal treatment with a statin, consideration should be given to adding a bile acid sequestrant. However bile acid sequestrants are contraindicated in patients with triglycerides ≥ 400 mg/dL. They are relatively contraindicated for triglycerides ≥ 200 mg/dL (30).

Very high triglycerides are not unusual in kidney transplant recipient population as a consequence of the effects of immunosuppressive medications. For individuals with very high triglycerides, the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. Fibrates and nicotinic acid lower triglycerides by 25-50% (30). Even though it has been reported that combined treatment with fluvastatin and gemfibrosil of renal transplant recipients who take cyclosporine and do not respond satisfactorily to fluvastatin monotherapy is effective and safe (42), 3 cases of reversible acute renal allograft dysfunction were published in patients treated with fenofibrate discontinuation of which resulted in the resolution of renal dysfunction (43). Although the control of hyperlipidemia is crucial in the transplant patient population, the authors suggest that caution be exercised and serum creatinine levels be closely monitored in patients started on fibrates.

In summary, despite statin use among renal allograft recipients grows in popularity for pleiotropic indications, there is a need for an individual approach to drug choice and further research on the use of statins for acute allograft rejection and cardiovascular protection.

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