

Management of Dyslipemia in Heart Transplant Patients. Findings on New Risk Factors

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ABSTRACT

Coronary vascular disease is a frequent complication in heart transplant patients, and dyslipemia is one of its main predictors. Immunosuppressive drugs predispose to dyslipemia, complicating the use of hypolipidemic agents. In this particular group of patients therapeutic goals in secondary prevention should be achieved. Statins are the hypolipidemic agents of first choice. Still there are no clear recommendations on new risk factors such as homocysteine and Lp (a).

The aim of this study was to assess the lipid profile, the prevalence of high levels of homocysteine and Lp (a), the achievement of the therapeutic goals and the tolerance to the medication. Twenty-three heart transplantation patients were included. The results showed an acceptable achievement of the lipid objectives; 65% of patients were on hypolipidemic treatment. Statins were safe. A great prevalence of high levels of homocysteine and Lp (a) were reported. The consequences of these findings on a change of therapy are still unknown.

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Key words > Transplantation - Dyslipemia - Homocysteine - Lipoprotein (a)

Abbreviations >			
ApoB	Apoprotein B	AMI	Acute myocardial infarction
HDL-C	High density lipoprotein cholesterol	Lp(a)	Lipoprotein (a)
LDL-C	Low density lipoprotein cholesterol	TG	Triglycerides
HMG CoA	Hydroxymethylglutaryl-coenzyme A	VLDL	Very low density lipoprotein cholesterol

BACKGROUND

About 60% to 80% of transplant patients present lipid disorders. According to the International Society of Heart and Lung Transplantation, more than 60,000 heart transplants have been performed from 1982 to 2001. This society has reported that the 5-year incidence of dyslipemia in transplant patients is 81%.

Several studies have demonstrated an increase in the levels of LDL-C, total cholesterol, VLDL, ApoB and triglycerides in transplant patients, which is more evident during the first six months following transplantation. Cholesterol levels, triglycerides and LDL-C levels may increase up to 40%, 80% and 35%, respectively compared to lipid levels prior to transplantation. Nevertheless, the information available on HDL-C and Lp(a) levels is contradictory. (1)

Immunosuppressive drugs not only predispose to dyslipemia, but may also interfere with the use of hypolipidemic agents. Dyslipemia is one of the most consistent predictors of vascular disease in the transplant patient. (2, 3) Coronary artery disease is a frequent complication beyond the first year following

transplantation (incidence of 30-50% at 5 years) and is one of the predictors of graft survival.

Specific guidelines for management of dyslipemia in heart transplant patients are not available yet. Expert opinions recommend using the National Cholesterol Education Program (ATP III) guidelines in order to achieve similar percentages of therapeutic control objectives as compared to patients in secondary prevention. (4)

The aims of the present study were: to assess the lipid profile and achievement of therapeutic goals in a population of heart transplant patients; to identify hypolipidemic therapy and drug tolerance; and to evaluate the prevalence of other risk factors such as high levels of homocysteine and Lp (a).

MATERIAL AND METHODS

Twenty-three heart transplant patients from a congestive heart failure outpatient clinic were prospectively included. Heart transplant had been performed more than a year before inclusion. Lipid profile, homocysteine levels and Lp(a) plasmatic levels were determined. Therapeutic goals were

as follows: LDL-C < 100 mg/dl, total cholesterol < 200 mg/dl, HDL-C > 40 mg/dl in men and > 50 mg/dl in women, and triglycerides < 150 mg/dl. The presence of adverse events related to hypolipidemic therapy was also assessed.

RESULTS

Ninety percent of patients were male (mean age 51 ± 16 years; 50% had a history of coronary artery disease and 35% had dyslipemia prior to transplantation). Time since transplantation ranged from 14 months to 6 years. The lipid profile of this population is shown in Table 1. Fifty percent of patients achieved therapeutic control objectives of LDL-C < 100 mg/dl; 85% of men had HDL-C > 40 mg/dl and 80% of patients had TG levels < 150 mg/dl. High levels of homocysteine (> 15 mg/dl) were present in 45% of patients, and 44% had abnormal Lp(a) (> 30 mg/dl). One third of patients with Lp(a) > 30 mg/dl did not achieve the LDL-C therapeutic objective. Sixty-one percent of patients were under treatment with statins (simvastatin: n = 7, mean dose 23 mg; pravastatin: n = 4, mean dose 10 mg; atorvastatin: n = 2, mean dose 10 mg; and rosuvastatin: n = 1, dose 20 mg) and 13% were receiving ezetimibe (associated with simvastatin in 2 patients, and as monotherapy in 1 patient). Neither fibrates nor niacin were used. Immunosuppressants included cyclosporine (87%), steroids (73%) and everolimus (60%). High levels of creatine phosphokinase (CPK) and transaminases were present in 17% and 13% of patients, respectively. Nevertheless, no patient doubled the basal values or discontinued therapy for this reason. None of the patients complaint of myalgias.

DISCUSSION

In this series, we observed that 65% of patients were under drug therapy, and the proportion of patients at therapeutic target for the conventional parameters (LDL-C, HDL-C, triglycerides) was acceptable. One of every two patients had high levels of homocysteine and Lp(a). Hypolipidemic drugs were well tolerated and therapy was not discontinued due to adverse events.

Table 1. Lipid profile in the population (mean \pm SD)

	Mean (mg/dl)	SdE (mg/dl)
Total cholesterol	193.1	38.6
LDL-C	99.3	30.9
HDL-C	57.85	17.9
Triglycerides	117.65	55.5
Lp(a)	51	67.9
Homocysteine	13.91	5.19

Immunosuppressive drugs predispose to dyslipemia. Steroids increase insulin resistance, free fatty acids and VLDL, activate HMG-CoA reductase and inhibit lipoprotein lipase. (5) Cyclosporine inhibits cholesterol-21-hydroxylase impairing bile acid formation and raising LDL-C levels. High Lp(a) and homocysteine levels have also been reported with cyclosporine. (6-8)

Tacrolimus seems to have less adverse events in lipid profile. Sirolimus and mycophenolate may alter triglyceride levels.

Several randomized trials have demonstrated that statins reduce the incidence of progressive atherosclerosis, endothelial dysfunction, graft rejection, early AMI and death in transplant patients. Only pravastatin and simvastatin have demonstrated a reduction in survival in randomized clinical trials. (9-11) Other clinical trials reported that therapy with atorvastatin or rosuvastatin reduced cholesterol levels with an incidence of adverse effects similar to placebo. (12)

Interestingly, in trials that used clinical endpoints, LDL-C levels following treatment were greater than 100 mg/dl. Wouldn't it be possible for patients to benefit with greater doses of statins in order to reduce LDL-C below 100 mg/dl? Extrapolating the results of other studies in secondary prevention, it seems that the answer would be affirmative, but what about the adverse events? There are no current studies to answer this question.

There is not enough evidence to recommend the use of fibrates. Both gemfibrozil and fenofibrate reduce cholesterol and triglyceride levels in transplant patients. Only gemfibrozil reduced mortality in an observational study.

Ezetimibe seems to be a safe drug; nevertheless, its plasmatic levels may increase when it is associated with cyclosporine. Omega-3 fatty acids reduce triglyceride levels up to a 30%, and they improve endothelial dysfunction. (13)

There is no evidence available regarding the use of nicotinic acid. Although no interactions with cyclosporine have been reported, patients with renal failure or liver diseases should be treated with caution.

Several epidemiological studies have reported an association between high levels of homocystein and Lp(a) with early or accelerated atherosclerotic disease. Half of the patients in our series presented high values of homocystein and Lp(a), a number considerably higher compared with other populations (general population, patients with coronary artery disease). Our findings might be explained by the effects of the therapy or by the presence of these risk factors before transplantation. Which might be the impact of these findings in the treatment of dyslipemias? The administration of vitamin supplements to reduce homocysteine levels in high-risk patients (secondary prevention) showed no benefits in the incidence of

cardiovascular events, as it has been recently published. (14) A small study performed on heart transplant patients failed to demonstrate any impact on early vascular disease. (15) Should we prescribe nicotinic acid for Lp(a)?

According to the evidence available, the recommendations are as follows: statins are the first-choice drugs (pravastatin 20-40 mg/day or simvastatin 10-20 mg/day with or without concomitant cyclosporine); in high-risk patients with LDL-C > 100 mg/dl, consider using other statins; fish oil should be added in patients who also have hypertriglyceridemia. Ezetimibe and fibrates should be prescribed with caution. Niacin might be prescribed; however there is no evidence available in heart transplant patients.

The strong association between dyslipemia and graft vascular disease reinforces the need of detecting lipid disturbances and treating them in this particular group of patients.

CONCLUSION

HDL-C and triglyceride levels were adequately controlled in this population; however, only half of the patients reached the LDL-C therapeutic objective. As the use of statins was safe and well tolerated in most cases, therapy should be optimized to improve the therapeutic goals; 57% of patients did not achieve the therapeutic control objectives and they were on low doses of statins (10 mg). The prevalence of high levels of homocysteine and Lp(a) was high; nevertheless these findings should be confirmed with a greater number of patients. The consequences of these findings on a change of therapy are still unknown. The absence of practice guidelines in this group of patients encourages conducting further research studies in order to elaborate evidence-based consensus. Physicians should use their energy not only "to protect the myocardium" but also to perform an aggressive management of the lipid profile "to protect" the coronary arteries.

RESUMEN

En pacientes cardíacos trasplantados, el desarrollo de enfermedad vascular coronaria es una complicación frecuente y la dislipidemia es uno de los predictores más importantes. Los inmunosupresores predisponen a las dislipidemias y dificultan la utilización de hipolipemiantes. En este grupo particular de pacientes se recomienda alcanzar las metas terapéuticas de prevención secundaria. Las estatinas son los hipolipemiantes de elección. No existen recomendaciones claras sobre nuevos factores de riesgo, como la homocisteína y la lipoproteína (a) [Lp(a)]. Con el objetivo de conocer el perfil lipídico, la prevalencia de homocisteinemia y de Lp(a) elevadas, el cumplimiento de las metas terapéuticas y la tolerancia a la medicación, se

incluyeron en el estudio 23 pacientes cardíacos trasplantados. Los resultados mostraron que el cumplimiento de las metas lipídicas fue aceptable y que el 65% recibía tratamiento hipolipemiente. El uso de estatinas fue seguro. Se encontró una prevalencia alta de homocisteína y Lp(a) elevadas. Su implicación en la modificación del tratamiento se desconoce.

Palabras clave > Trasplante - Dislipidemias - Homocisteína - Lipoproteína (a)

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