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Effect of diet and fluvastatin treatment on the serum lipid profile of kidney transplant, diabetic recipients: a 1-year follow up

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Abstract The effect of a cholesterol-lowering diet and subsequent fluvastatin treatment (Lescol, Novartis; 20 mg/day) on serum lipids and lipoproteins was investigated in 21 diabetic patients (eight women, 13 men, age range 31–63 years, BMI 25.9 ± 4.5 kg/m^2) who had undergone successful kidney transplantation. A cholesterol-lowering diet followed for 8 weeks had apparently no effect on serum lipid concentrations. Fluvastatin applied afterwards for 12 months significantly decreased the total cholesterol, triglyceride and LDL cholesterol levels from 7.7 ± 0.94, 2.84 ± 0.85 and 4.87 ± 1.05 mmol/l to 6.40 ± 0.74, 2.64 ± 0.86 and 3.52 ± 0.69 mmol/l, $P < 0.001$, < 0.05 and < 0.001, respectively, while the level of HDL cholesterol increased from 1.12 ± 0.28 to 1.52 ± 0.39 mmol/l, $P < 0.001$. Serum concentration of lipoprotein(a) remained unchanged. The serum level of apolipoprotein-A1 increased from 1.52 ± 0.28 to 1.83 ± 0.29 mmol/l ($P < 0.01$) and that of lipoprotein-B decresed from 1.37 ± 0.20 to 1.20 ± 0.36 mmol/l ($P < 0.05$). These maximum changes were achieved by the 12th week of fluvastatin treatment, and no further significant change was observed in the remaining part of the year. The other parameters that could have influenced lipid metabolism (doses of diuretics and steroid, daily dose and serum level of cyclosporin, kidney function, degree of proteinuria, HbA1c, etc.) remained unchanged throughout the study. Thus, the improvement in lipid concentrations can be ascribed exclusively to fluvastatin. No side effects were observed during the 1-year follow up. Liver enzymes and CPK remained within the normal reference limits. Fluvastatin proved to be an effective and safe drug for treating the dyslipidaemia of transplanted patients receiving steroid cyclosporin immunosuppression.

Key words Renal transplantation · Posttransplant diabetes mellitus · Cyclosporin · Dislipidaemia · Fluvastatin

Introduction

Deterioration in carbohydrate and lipid metabolism is frequently observed in patients who had undergone organ transplantation and have been treated with immunosuppressive drugs [1, 5, 14]. Both diabetes and dyslipidaemia facilitate the atherosclerotic process and increase the risk of cardiovascular morbidity and mortality. Epidemiological data suggest that cardiovascular death among kidney transplant recipients is 5–7 times higher than that of the general population [6, 1–3]. Therefore, correction of dyslipidaemia is of primary importance for these patients.

Our team has been caring for a great number of kidney transplant recipients with diabetes mellitus. The majority of these patients have dyslipidaemia. In this

Table 1 Clinical characteristics (± SD) of kidney transplant recipients included in the study (*IDDM* insulin-dependent diabetes mellitus, *PTDM* posttransplant diabetes mellitus)

Number of patients (M/F)	21 (13/8)
Age range (years)	31–63
BMI	25.9 ± 4.5 kg/m^2 (19–33)
Type of diabetes	
IDDM	3
PTDM	18 (onset 6–36 months after Tx)
HbA1c	6.64 ± 1.62 %
Serum cholesterol (mmol/l)	7.70 ± 0.87 (range 6.60–9.81)
Serum triglyceride (mmol/l)	2.85 ± 0.86 (range 1.30–3.98)

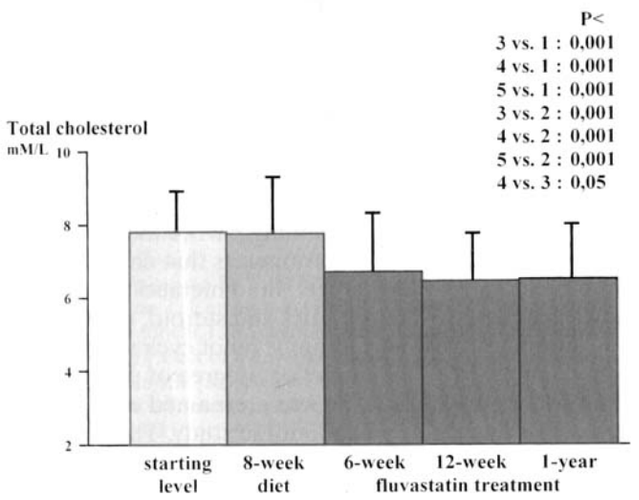

Fig. 1 Changes in serum total cholesterol levels (± SD) during diet and fluvastatin treatment. Only significant changes are indicated *(upper right)*

study we compared the efficacy of a cholesterol-lowering diet and a totally synthetic "statin"-type drug, fluvastatin (Lescol, Novartis), in reducing the hyperlipidaemia of such patients.

Materials and methods

The study was performed on 21 diabetic patients who had undergone successful kidney transplantation. Only those patients with elevated serum cholesterol (6.60–9.85 mmol/l) and normal to moderately elevated serum triglyceride (1.30–3.98 mmol/l) were included. All patients had good or acceptable kidney function (serum creatinine < 150 μmol/l) at the time of the study. Three of the patients had long-term insulin-dependent diabetes mellitus and their kidney transplantation was due to diabetic nephropathy. In the other 18 patients, diabetes developed 6–36 months after transplantation, i.e. in the course of the maintenance immunosuppressive therapy (so-called posttransplant diabetes mellitus). All but 1 of these patients had hypertonia. Five patients had microalbuminuria (albumin excretion between 30–300 mg/day), while the other patients had a daily protein excretion above this level. The clinical characteristics of the 21 patients are summarised in Table 1.

All patients were on a combined immunosuppressive regimen containing 8–10 mg methylprednisolone (Medrol, Upjohn) given as a single dose in the morning, and 2 × 100–175 mg cyclosporin (Sandimmun neoral, Novartis) daily. Thirteen patients received insulin therapy, in 4 patients diabetes was controlled by diet only, while, the other 4 patients received sulphonylurea drugs (Gilemal, Chinoin). Twenty patients were treated for hypertension with small doses of a beta-blocking drug (Betaloc, Astra) and calcium-channel blockers (Nifedipine, Pharmagen). Each patient received varying doses of loop diuretics (Furosemid, Chinoin)

At the beginning of the study blood was taken for the measurement of plasma glucose, HbA1c, total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglyceride (TG), apolipoprotein-A1 (Apo-A1), apolipoprotein-B (Apo-B), lipoprotein(a) [Lp(a)], liver enzymes (ASAT, ALAT), creatinine phosphokinase (CPK), uric acid, serum creatinine and blood urea nitrogen. Daily albumin excretion was also measured in the collected urine. After enrolment for the study, patients received a cholesterol-lowering diet containing no more than 250 mg of cholesterol daily. Each patient was educated by a trained dietist and patients' daily meals were regularly supervised. Following an 8-week dietary treatment, the laboratory measurements were repeated. Thereafter, the therapy was completed by adding fluvastatin at a dose of 20 mg/day, taken in the evening. This combined treatment was continued for 1 year. Laboratory examinations were again repeated at 6 and 12 weeks, and then 12 months after the initiation of fluvastatin therapy.

Laboratory measurements were performed on a Hitachi 704 autoanalyser. HbA1c and urinary albumin excretion, as well as the serum levels of TC, TG, Apo-A1 and Apo-B were measured with immunoturbidimetry using a Boehringer kit (Boehringer). Serum concentration of HDL-C was measured after phosphotungstic acid precipitation and LDL-C after precipitation with polyvinyl sulphate. The serum level of Lp(a) was determined with a Dako kit.

Results are expressed as mean ± SD. Changes in serum lipid levels during the study year were analysed by comparing each subsequent result with all of the previous ones (i.e. the results of the fifth examination at 1 year were compared with all those measured at the first to fourth examinations). Statistical analysis was performed by ANOVA. In addition, results obtained during the diet (first and second examinations) were compared with those obtained under fluvastatin treatment (third and fourth examinations) and analysed using the "Tukey" statistical program. Regarding the other laboratory parameters (ASAT, ALAT, CPK, HbA1c and daily dose and serum levels of cyclosporin), comparison between starting values and those obtained at the end of the study year was performed using Student's t-test. $P < 0.05$ was considered to be significant.

Results

The changes in serum TC concentration are shown in Fig. 1. As seen, the cholesterol-poor diet applied for 8 weeks did not cause any significant change. In contrast to this, the introduction of fluvastatin resulted in a highly significant fall in TC levels even after 6 weeks, and this was followed by a further significant decrease by the 12th week. Thereafter, TC levels remained unchanged until the end of the year. The initial value of se-

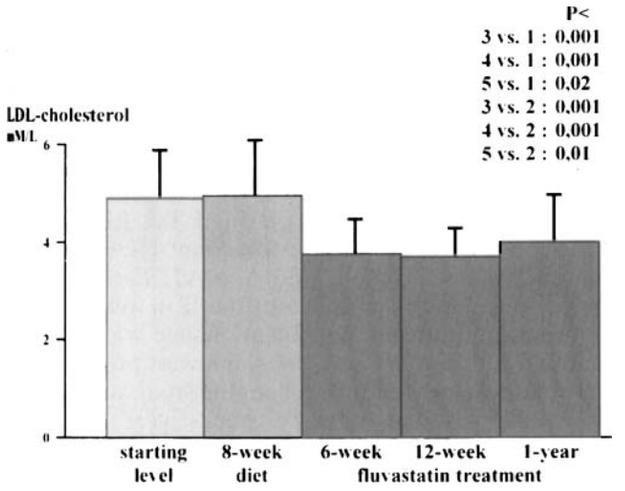

Fig. 2 Changes in LDL cholesterol levels (± SD) during diet and fluvastatin treatment

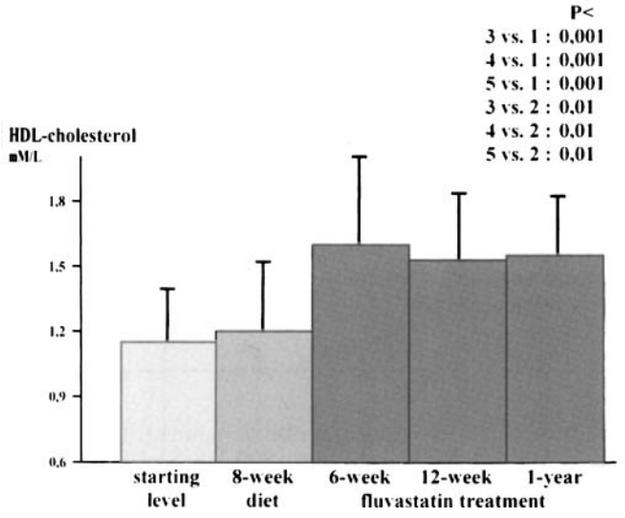

Fig. 3 Changes in HDL cholesterol levels (± SD) during diet and fluvastatin treatment

rum TG was 2.85 ± 0.85 mmol/l and the final value was 2.64 ± 0.86 mmol/l, $P \cong 0.05$. However, when values measured during diet and during fluvastatin treatment were summed and compared, the difference proved to be significant ($P = 0.48$). The changes in LDL-C are shown in Fig. 2. As with TC, LDL-C concentrations did not change significantly during the diet. Addition of fluvastatin caused, however, a significant drop in LDL-C levels. Maximum improvement occurred at the 12th week and no further significant change was observed until the end of the study. Figure 3 shows the changes in HDL-C concentration. Again, fluvastatin resulted in a highly significant increase, whereas diet alone failed to do so. Lp(a) did not change significantly throughout

Table 2 Changes in other laboratory parameters (± SD) during 1-year fluvastatin treatment (*CPK* creatinine phosphokinase, *Cy-A* cyclosporin A, *NS* not significant)

	At start	After 1 year	
HbA1c	6.57 ± 1.46	6.38 ± 1.62	NS
Hb	14.03 ± 2.20	13.49 ± 2.20	NS
Haematocrit	43.1 ± 6.3	41.65 ± 6.5	NS
ASAT	27.9 ± 21.7	224.8 ± 10.9	NS
ALAT	29.45 ± 14.6	29.3 ± 14	NS
CPK	45.4 ± 13.9	54.4 ± 11.9	$P < 0.01$
Cy-A level	199 ± 89	206 ± 28	NS

the study. A slight but significant change was observed in the serum levels of both Apo-A1 (from 1.52 ± 0.28 to 1.83 ± 0.29 mmol/l, $P < 0.01$) and Apo-B (from 1.37 ± 0.20 to 1.20 ± 0.36 mmol/l, $P < 0.05$).

No side effects were observed throughout the study year. None of the patients had any adverse reaction or claim which could have been attributed to fluvastatin treatment. The changes in other laboratory parameters are shown in Table 2. Serum levels of ASAT, ALAT, creatinine and blood urea nitrogen, as well as Hb and haematocrit remained unchanged and within the normal limits. Mean levels of HbA1c were 6.64 ± 1.62 % at the start and 6.67 ± 1.36 % by the end of the study. Serum levels of CPK rose slightly, but significantly by the end of the year. It should be noted, however, that these changes remained within the normal reference range (24–200 IU/l) and without any clinical symptoms. The mean serum concentration of cyclosporin – giving stable doses throughout the study year – did not change significantly either, indicating that concomitant fluvastatin treatment did not influence significantly cyclosporin clearance from the blood.

Discussion

Dyslipidaemia may develop for many reasons after organ transplantation. Recipients on immunosuppressive therapy usually receive steroid + cyclosporin medication and both of them are known to induce hyperlipoproteinaemia [7, 8, 10, 11]. Diabetes mellitus develops in about one-fifth of the transplanted patients [9] and it is also accompanied by lipid abnormalities. Many of such patients require antihypertensive treatment and some of these drugs (beta-blocking agents, thiazide diuretics) may increase the serum lipid levels. Proteinuria is present in the majority of patients with kidney grafts and this can also result in high TG and low HDL-C levels. Keeping in mind the well-documented role of dyslipidaemia in cardiovascular morbidity and mortality, it is no wonder that transplanted patients have a significantly higher figure of vascular death than that observed in the general population. Furthermore, accelerated

atherosclerosis will develop in the graft arteries leading to chronic vascular rejection (CVR). According to literature data, CVR accounts for about 50–80% of graft failures in the 2–8 posttransplant years [3, 4, 12]. Taken together, early and effective lipid-lowering therapy seems to be essential in organ transplant recipients. Unfortunately, the known interference of lipid-lowering drugs with cyclosporin, and, consequently, the increased risk of adverse effects such as myositis and rhabdomyolysis, limits their wide-spread use.

Fluvastatin is a totally synthetic HMG-CoA reductase inhibitor with relatively selective action on the liver. The drug has been shown to effectively reduce in the elevated TC, LDL-C and Apo-B levels with a concomitant rise in the serum levels of HDL-C and Apo-A1. In large studies, fluvastatin proved to be a safe and well-tolerated drug with negligible side-effects. Castelao et al. [2] supplied evidence that statin-type lipid-lowering drugs could be safely used in renal transplant recipients treated with cyclosporin. Although the interaction of fluvastatin and cyclosporin in the cytochrome P_{450} system is well established, it appears that the two drugs utilise different enzyme subunits for their metabolism. In pharmacokinetic studies, the disappearance rate of fluvastatin was significantly less prolonged by Sandimmun-Neoral than that of pravastatin and simvastatin. Thus, fluvastatin seems to be the therapy of choice in reducing the hyperlipidaemias of organ transplant recipients receiving cyclosporin.

We compared the efficacy of a cholesterol-poor diet and fluvastatin in the treatment of dyslipidaemia of renal transplant diabetic recipients. It was a bit surprising that diet had apparently no influence on the lipid levels. It had to be taken into account that our diabetic patients have had a low calorie diet with precisely calculated carbohydrate content even before the study. Thus, the introduction of a cholesterol-poor diet did not bring about a big change for these patients. By contrast, fluvastatin decreased significantly the elevated TC, LDL-C, TG and Apo-B levels, with a concomitant increase in the concentration of HDL-C and Apo-A1. The maximum improvements were achieved by the 12th week of treatment, and no further significant change was observed thereafter. For safety reasons, the lowest possible dose (20 mg/day) was used throughout the study year. During the study period, laboratory checks were repeatedly performed with special emphasis on liver enzymes and CPK. The serum levels of ASAT and ALAT remained unchanged, whereas the level of CPK rose slightly, but significantly. This elevation was not accompanied by clinical signs of myositis or myoglobinuria, and even elevated levels remained within the normal reference range. In accordance with this, none of the patients reported any symptoms or adverse reactions that could have been attributed to fluvastatin treatment. Therefore, fluvastatin can be regarded as a preferable drug in the treatment of dyslipidaemias in kidney transplant recipients with diabetes mellitus receiving cyclosporine + steroid immunosuppression.

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References

1. Brown JH, Anwar N, Short CD (1993) Serum lipoprotein(a) in renal transplant recipients receiving cyclosporin monotherapy. Nephrol Dial Transplant 8: 863–867
2. Castelao AM, Grino JM, Andres E, Gilvernet S, Seron D, Castineiras MJ (1993) HMGCoA reductase inhibitors lovastatin and simvastatin in the treatment of hypercholesterolemia after renal transplantation. Transpl Proc 25: 1043–1046
3. Dimény E (1994) Metabolic factors and outcome of organ transplantations. Scand J Urol Nephrol Suppl 159: 1–74
4. Dimény E, Fellström B, Larsson E, Tufveson G, Lithell H (1993) Chronic vascular rejection and hyperlipoproteinaemia in renal transplant patients. Clin Transpl 7: 482–490
5. Drueke TB, Abdulmassih Z, Lacour B, Bader C, Chevalier A, Kreis H (1991) Atherosclerosis and lipid disorders after renal transplantation. Kidney Int 31: 24–28
6. Hill MN, Grossman RA, Feldman HI, Hurwitz S, Dafoe DC (1991) Changes in causes of death after renal transplantation, 1966 to 1987. Am J Kidney Dis 17: 512–516
7. Ingulli E, Tejani A, Markell M (1993) The beneficial effects of steroid withdrawal on blood pressure and lipid profile in children posttransplantation in the cyclosporine era. Transplantation 55: 1029–1033
8. Isoniemi H, Tikkanen MJ, Ahonen J, Hayry P (1991) Renal allograft immunosuppression. IV. Comparison of lipid and lipoprotein profiles in blood using double and triple immunosuppressive drug combinations. Transpl Int 4: 130–135
9. Isoniemi HM, Ahonen J, Tikkanen NJ, Willebrandt EO van, Krogerus L, Eklund BH, Hockerstedt KV, Salmela KE, Hayri PJ (1993) Long-term consequences of different regimens for renal allografts. Transplantation 5: 494–499
10. Kasiske BL, Tortorice KL, Heim-Duthoy KL, Awni WM, Rao KV (1991) The adverse impact of cyclosporine on serum lipids in renal transplant recipients. Am J Kidney Dis 17: 700–707
11. Kuster GM, Drexel H, Bleisch JA, Rentsch K, Pei P, Binswanger U, Amann FW (1994) Relation of cyclosporine blood levels to adverse effects on lipoproteins. Transplantation 57: 1479–1483
12. Paul LC (1993) Chronic rejection of organ allografts. Magnitude of the problem. Transpl Proc 25: 2024–2025
13. Paul LC, Fellström B (1992) Chronic vascular rejection of the heart and kidney – have rational treatment options emerged? Transplantation 53: 1169–1179
14. Webb AT, Plant M, Reaveley DA, O'Donnel M, Luck VA, O'Connor B, Seed M, Brown EA (1992) Lipid and lipoprotein(a) concentrations in renal transplant patients. Nephrol Dial Transplant 7: 636–641