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Progression of alterations in lipid metabolism in kidney transplant recipients over 5 years of follow-up

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SUMMARY

Background: Alterations in lipid metabolism frequently affect kidney transplant recipients and contribute to the onset of metabolic and cardiovascular diseases that threaten graft integrity. The purpose of this research study was to investigate the pattern of hyperlipidaemia and its progression, as well as to study potential risk factors in kidney transplant recipients. **Methods:** In this study, 119 kidney transplant recipients of both sexes were monitored over a period of 5 years in our posttransplant clinic. During this period, all patients had pretransplant and post-transplant blood tests to measure levels of the following: total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL) and triglycerides. Furthermore, the subjects were also weighed and their height measured. Their body mass index was then calculated using the weight (kg)/height (m^2) formula. **Results:** In the 5 years following the transplant, the patients experienced a significant increase in the levels of their biochemical markers as well as in their BMI. Consequently, a greater number suffered from dyslipidaemia, diabetes and hypertension. **Conclusions:** Kidney transplants can often trigger hyperlipidaemia, as reflected in higher levels of total cholesterol, low-density lipoproteins and high-density lipoproteins. The results of our study also showed that despite statin therapy, the patients had higher triglyceride levels, which made them more vulnerable to diabetes, hypertension, cardiovascular disease and graft rejection.

What's known

Lipid and lipoprotein metabolism disorders are a significant problem for kidney transplant recipients because they can affect the survival of both the graft and the patient. Nevertheless, few studies have focused on the prevalence pattern and type of lipoprotein abnormality in renal transplant recipients.

What's new

After a kidney transplant, despite the ingestion of lipid-lowering agents, many patients are affected by lipid alteration, which is reflected in high levels of total cholesterol, low-density lipoproteins, and high-density lipoproteins. At the same time, the increase in triglycerides causes the patients to be at a higher risk of diabetes, hypertension, cardiovascular disease, and graft rejection.

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Disclosure
None.

Introduction

Lipid and lipoprotein metabolism disorders are a problem for kidney transplant recipients because they can affect the survival of both the graft and the patient (1–3). Such alterations often lead to atherogenesis and the subsequent development of coronary artery disease, which are the most common causes of long-term morbidity and mortality following transplants (4).

Of great interest is the close relationship between hyperlipidaemia and the progression of the graft. In fact, one of the most frequent complications brought on by hyperlipidaemia is acute rejection, which can lead to graft loss. In addition, hyperlipidaemia can even be conducive to chronic nephropathy (5,6). It is thus rather alarming that 16–78% of kidney transplant patients suffer from some degree of hyperlipidaemia. Factors that increase the risk of this disorder include age, diet, kidney function, obesity (7), diuretic use, proteinuria and immunosuppression treatment (steroids and cyclosporine A). However, the primary risk factor is insulin resistance (IR) and the resulting hyperinsulinaemia (8).

Kidney transplant patients are particularly vulnerable to cardiovascular morbidity following transplant, as well as to accelerated deterioration caused by dyslipidaemia (9,10). It is thus not surprising that this problem is now a prime focus of attention. Unfortunately, there are currently few studies on the prevalence and type of lipoprotein abnormality in kidney transplant recipients. To fill this gap, we have conducted a retrospective study on hyperlipidaemia, which analyses its pattern and progression and also examines the risk factors affecting kidney transplant recipients.

Materials and Methods

Subjects

The sample population of this study was composed of 119 transplant recipients of both sexes, who periodically visited the kidney transplant clinic at the

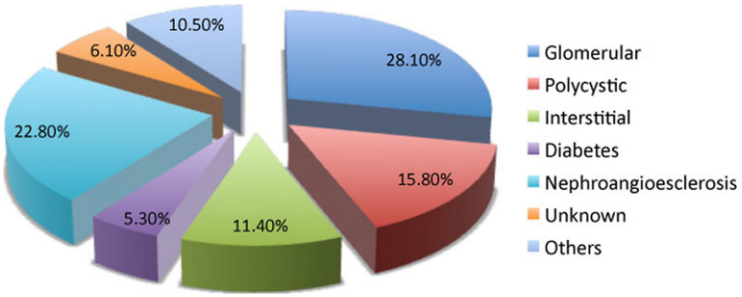

Figure 1 Causes of chronic kidney disease in the sample population

Virgen de las Nieves University Hospital in Granada, Spain. The subjects were not selected at random. Rather, their participation in the study was determined by their visits to the clinic for follow-up and monitoring during the 5-year period of the study (March 2006–2011). The sample was made up of 70 men and 49 women, of ages ranging from 18 to 74. Figure 1 shows the prevalence of the diseases which they were being treated for.

Methods

During the 5-year period of the study, all patients had pretransplant and posttransplant blood tests to measure the following: total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL) and triglyceride levels. Peripheral blood samples were taken at 8:30–9:00 in the morning. For this purpose, 6 ml of blood were extracted with a Venoject® II (Terumo; Autosep®). Biochemistry tests were conducted at 37° using the Roche/Hitachi 747 automated clinical chemistry analyser. The corresponding reagents were all supplied by Roche Diagnostic Systems. All assays were performed at the general laboratory of the Virgen de las Nieves University Hospital in Granada.

The hypotensive agents used were beta blockers, diuretics, ACE inhibitors and calcium blockers. The immunosuppression therapy protocol consisted of a triple therapy based on prednisone, cyclosporine (CsA) or tacrolimus and mycophenolate mofetil (MMF) or azathioprine (AZA). The immunosuppressant dosage complied with the standard protocol used at the Virgen de las Nieves University Hospital for this purpose. It is worth mentioning that 80% of the patients had taken lipid-lowering agents, namely, rosuvastatin, atorvastatin and simvastatin.

At the same time as the subjects were having their blood tested, they were also weighed in kilograms with a Perperson 113,481 scale/stadiometer and their height was measured in centimetres. Their body mass index (BMI) was then calculated using the weight (kg)/height (m^2) formula. Data were also collected regarding the diagnosis of hypertension and diabetes.

Dyslipidaemia was defined in terms of the following values: total cholesterol > 200 mg/dl (5.17 mmol/l) and triglycerides >200 mg/dl (2.26 mmol/l). Diabetes was characterised by fasting blood glucose >126 mg/dl. The criteria used to define hypertension were those approved by the American Heart Association (NHBPEP) in 2010. More specifically, readings greater than or equal to 140/90 mmHg were considered high blood pressure.

Statistical analysis

The SPSS 15.0.1 software package was used for the statistical analysis. Differences in body mass index, biochemistry parameters, and the data for each year were evaluated by analysing means and percentages. All data were expressed as a mean value + standard deviation ($X \pm$ SD).

Results

The results of the study reflected a significant increase in BMI, which is especially evident from the pretransplant phase to the first year after transplant. However, as can be observed, in subsequent years, the BMI value slowly but steadily continued to rise (Figure 2).

The mean total cholesterol levels were also higher 1 year after transplant. Although the values decreased slightly from the second to the fifth year, they were still much higher in comparison to the levels prior to transplant (Table 1). In this regard, total cholesterol levels of the sample population were higher than the laboratory reference range (200–240 mg/dl). More specifically, this was the case of 18% of the patients in the pretransplant stage. The percentages in the subsequent 5 years were 49%, 42.2%, 30.8%, 43% and 43% respectively.

Mean HDL levels became significantly higher from the pretransplant stage to the years after transplant, showing similar values for each year (see Table 1). The total HDL cholesterol levels of the sample population were below the laboratory reference range

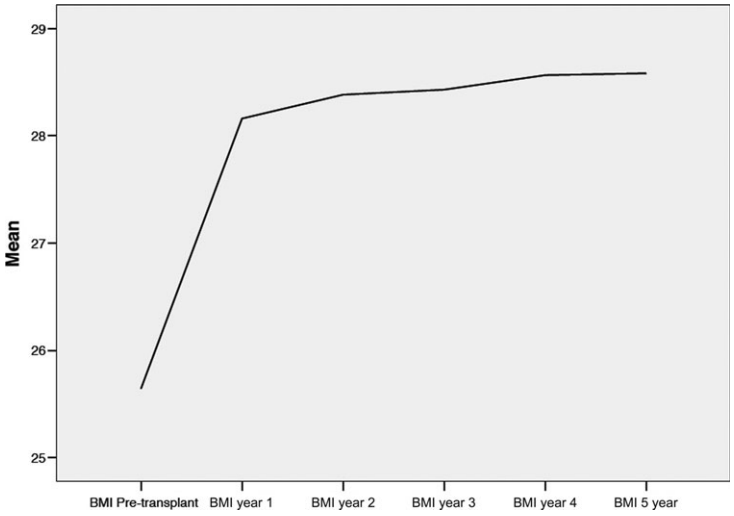

Figure 2 Evolution of the mean annual values of the pretransplant and posttransplant body mass index in the sample population

Table 1 Measurements of pretransplant and posttransplant biochemical parameters in the sample population in each year of the study

Biochemistry	Year	Mean	Std. Deviation	Minimum	Maximum
Total Cholesterol	Pretransplant	155.74	46.52	85	334
	Year 1	202.55	35.76	117	289
	Year 2	193.67	35.31	113	304
	Year 3	189.93	37.59	104	342
	Year 4	189.59	36.72	112	271
	Year 5	192.55	40.06	103	305
HDL	Pretransplant	47.43	17.07	23	97
	Year 1	59.72	16.27	25	99
	Year 2	61.53	20.91	30	159
	Year 3	59.12	17.74	21	113
	Year 4	59.62	17.9	26	107
	Year 5	59	25.78	31	104
LDL	Pretransplant	89.16	36.43	29	204
	Year 1	118.61	43.2	10	353
	Year 2	115.32	39.78	25	359
	Year 3	112.18	40.07	39	338
	Year 4	108.57	32.16	52	188
	Year 5	113.24	32.41	55	192
Triglycerides	Pretransplant	143.42	75.41	52	479
	Year 1	144.05	81.28	49	543
	Year 2	144.41	77.92	46	473
	Year 3	149.37	78.10	52	528
	Year 4	154.90	88.9	40	511
	Year 5	157.72	63.37	49	342

(40–60 mg/dl). This was true for 35% of the patients in the pretransplant stage. Percentages in the following 5 years were 10%, 11%, 12%, 12% and 14.3% respectively.

Mean LDL levels also increased in the first year after transplant, with similar values in the years after the transplant except for the fourth year, in which there was a decrease (see Table 1). LDL levels higher than the laboratory reference range (70–150 mg/dl) were found in 5.4% of patients in the pretransplant stage. Percentages in the subsequent 5 years were 19%, 13.8%, 12.4%, 11.7% and 13.4% respectively.

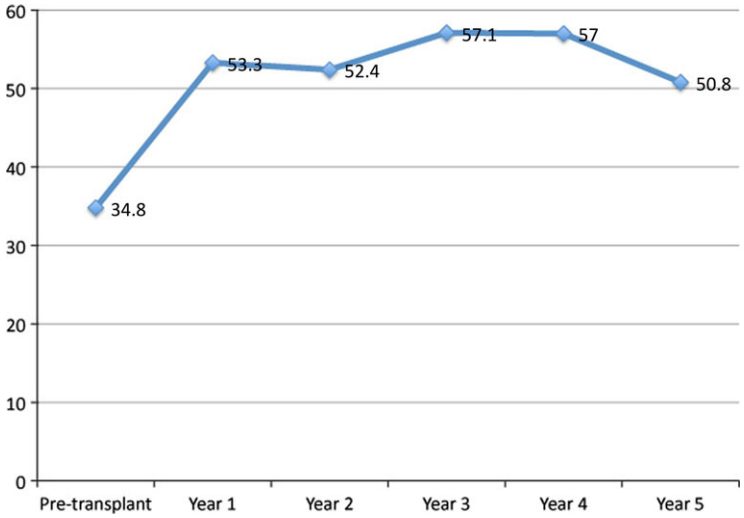

Figure 3 Evolution of the annual percentage of patients with pretransplant and posttransplant dyslipidaemia measured in the sample population

Mean triglyceride levels rose in the first year after transplant and then gradually increased until year 5 (Table 1). Levels exceeding the laboratory reference range (50–200 mg/dl) were found in 13.5% of patients in the pretransplant stage. Percentages in the following 5 years were 16.55%, 18.7%, 19.9%, 20.1% and 24.1% respectively.

As previously mentioned, dyslipidaemia was defined as a level of total cholesterol > 200 mg/dl (5.17 mmol/l) and triglycerides > 200 mg/dl (2.26 mmol/l). Based on this definition, it is evident that there was a significant increase in the percentage of patients with dyslipidaemia after kidney transplant. This is highlighted by the fact that cholesterol and triglyceride levels in subsequent years exceeded initial pretransplant levels (Figure 3).

The number of patients diagnosed with diabetes soared after transplant, a trend that continued in the following years (Figure 4). More patients were also diagnosed with hypertension (HTN) following transplant (Figure 5).

Conclusion

Kidney transplant recipients have a long history of chronic renal failure, and consequently, many of

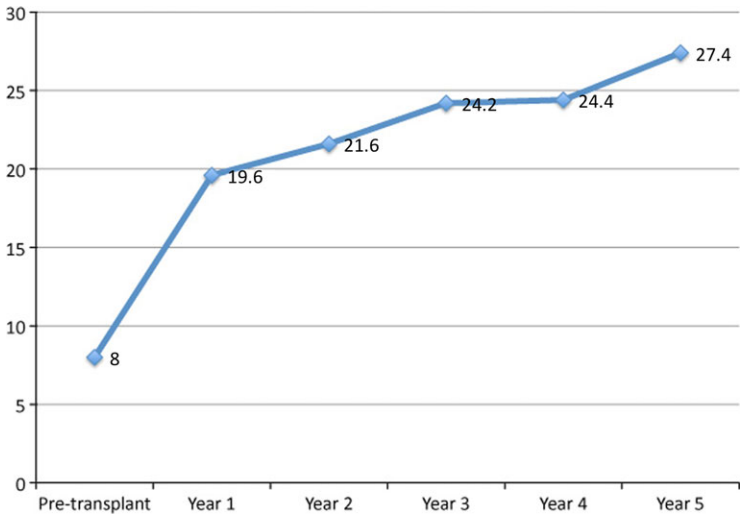

Figure 4 Evolution of the annual percentage of patients with pretransplant and posttransplant diabetes measured in the sample population

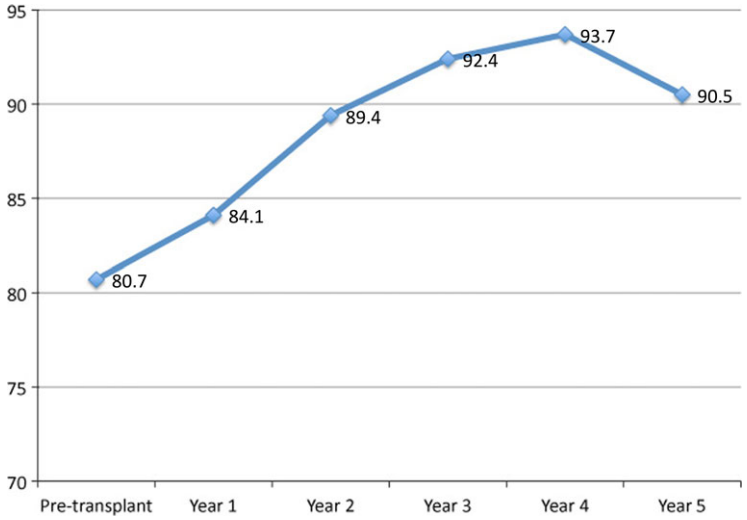

Figure 5 Evolution of the annual percentage of patients with pretransplant and posttransplant hypertension measured in the sample population

them suffer from lipid disorders prior to receiving the transplant (11,12). However, lipid metabolism does not return to normal when renal function is recovered after transplant (13). For this reason, posttransplant dyslipidaemia is a relatively common metabolic change, especially in the first year after transplant. This is of great clinical interest, not only because of the increased incidence of posttransplant cardiovascular events but also because of the possible contribution of dyslipidaemia to the development of chronic kidney disease in the graft (14).

According to our study, in the first year after transplant, the total cholesterol levels of the patients increased from 18% to 49%, and then decreased slightly over the subsequent 4 years. Nevertheless, they still remained fairly high compared with the pretransplant stage. As a result, HDL and LDL levels increased. The rise in high-density lipoproteins following transplant may be related to excessive HDL production because of the elimination of uraemic toxins by the transplanted kidney and also because of chronic corticosteroid use (15). As pointed out in various studies, the increase in HDL levels in kidney transplant recipients does not protect them against atherogenic complications (16,17). Although this phenomenon has still not been satisfactorily explained, it may be related to changes in HDL quality, a decrease in the HDL-2 fraction, as well as intensive LDL oxidation (18).

Previous studies have primarily focused on increased serum cholesterol (19,20). Our data reflect a progressive rise in triglyceride levels and dyslipidaemia after kidney transplant. Dyslipidaemia was found to affect a significant percentage of patients (Figure 3). Conditioning factors included the duration of renal failure prior to transplant, diet, lipid-lowering treatment and genetic predisposition (21).

Most research indicates that there is an increase in BMI following kidney transplant (22–25), a finding that coincides with the results obtained in this study (Figure 2). This is accompanied by progressively higher triglyceride levels, which is an aggravating factor for the onset of diabetes (Figure 4), and of cardiovascular disease and hypertension (Figure 5).

The evaluation and treatment of posttransplantation dyslipidaemia should be multifactorial and include general prevention measures such as the following: weight reduction (when needed), moderate exercise, a lipid-lowering diet, drug treatment and the optimisation of immunosuppressive therapy. In all cases, patients should follow a diet low in saturated fats and cholesterol. Unlike in the general population, a lipid-lowering diet has a discrete effect on the reduction in total cholesterol and LDL (26). Nevertheless, it is always advisable, especially when the patient also suffers from hypertriglyceridaemia.

In conclusion, kidney transplants significantly increase hyperlipidaemia, which is associated with a typical pattern of lipid alterations, characterised by higher levels of total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides. Patients are thus at a greater risk of diabetes, hypertension and cardiovascular disease, despite statin therapy. More effective treatment will be needed to decrease hyperlipidaemia and cardiovascular events, as well as to increase graft survival.

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