THE EVOLUTION OF HYPERLIPIDAEMIA LATE AFTER RENAL TRANSPLANTATION

M L Nicholas, G P J Alexandre, C van Ypersele de Strihou

University Hospital St-Luc, University of Louvain Medical School, Brussels, Belgium

Summary

We have evaluated the incidence, long term evolution and pathogenesis of post-transplant hyperlipidaemia (HL) in 88 transplanted patients without nephrotic syndrome followed for 2 to 13 years by the same staff. Incidence of HL decreased strikingly over the years from 51% at 2 years to 25% at 10 years. This fall was due solely to the return to normal of the lipid profile in 13 patients between 2 and 8 years after transplantation. This progressive decrease should be taken into account when the frequency of posttransplantation dyslipaemia is assessed.

The incidence of hyperlipidaemia increases with age. Above 40 years, hyperlipidaemia is more frequent in females than in males. Obesity and reduced renal function are both associated with a higher incidence of dyslipaemia. No relationship was found between lipid disorders and either steroid dosage or fasting blood glucose levels. Dyslipaemia appears thus to be due to the interplay of several factors.

Normalisation of the lipid profile occurred in 13 patients without significant decrease in bodyweight, serum creatinine or prednisone dosage. At 8 years atheromatous lesions were not more frequent in dyslipaemic than in normolipidaemic subjects.

Introduction

Interest in disorders of lipid metabolism in transplanted patients stems from the known relationship between dyslipaemia and atherosclerosis on the one hand and from evidence of a high death rate from arteriosclerosis in transplanted patients [1]. Although several studies have reported an increased incidence of lipid disorders [2–11] in transplanted patients, little is known of the long term evolution of these abnormalities. We have taken advantage of a large series of patients with a long term follow-up to assess the incidence and the evolution of dyslipaemia between 2 and 12 years after transplantation.
Material and Methods

Between January 1, 1965 and January 1, 1976, 418 transplantations were performed on 380 patients. Details of immunosuppressive therapy have been already published [12].

The present study includes 88 patients, 48 males and 40 females, whose first graft survived for a least 24 months, who were followed regularly at our clinic and in whom a lipid profile was available at least every other year. A total of 412 lipid profiles were thus analysed. Patients with a nephrotic syndrome were excluded but four patients with a diabetic nephropathy are included.

The transplant originated from a cadaver in 82 cases, from a living donor in 6 cases. The patients’ ages averaged 39 years (range 7 – 65 years). Data were reviewed up to January 1978 so that the minimal potential follow-up was 2 years and the maximum 13 years. The only dietetic restrictions included a sodium restricted diet in the hypertensive patients and a limited carbohydrate intake in the four diabetic subjects.

The lipid profile was obtained after an overnight fast. Total, free and esterified cholesterol were determined by semi-automatic gas liquid chromatography [13]. Triglycerides were measured by the micromethod of Van Hendel based on the determination of glycerol after chemical hydrolysis of triglycerides [14]. Lipoprotein electrophoresis was performed in agar gel. We considered as abnormal, values in excess of 275mg/100ml for cholesterol and above 115mg/100ml for triglycerides. Dyslipaemias were classified according to Beaumont [15].

Bodyweight was expressed as the percentage of mean ideal bodyweight (IBW) for height, age and sex [16].

Results

Out of the 412 lipid profiles, 63.1% were normal, 10.2% type IIa, 13.1% type IIb, 12.1% type IV and 1.5% type V.

Frequency of Dyslipaemia After Transplantation

As demonstrated in Table I the frequency of dyslipaemic patients gradually decreases over the years from 51%, 2 years after transplantation, to 25% at 10 years. The same trend is obvious if we consider only the 39 patients with a minimum six years follow-up: 51, 36 and 31% at 2, 4 and 6 years respectively. This decrease results solely from the normalisation of 13 patients: 10 between 2 and 4 years, 2 between 4 and 6 years, 1 between 6 and 8 years. No normolipaeemic patient at 2 years becomes subsequently dyslipaemic. The value for blood lipids before and after normalisation is illustrated for the 13 patients in Figure 1.

Factors Responsible for Dyslipaemia

Age and sex The proportion of dyslipaemic patients increases with age. Two years after transplantation, it ranges from 25% in 8 patients between 10–20 years to 90% in 11 patients between 50–60 years.
TABLE I. Frequency of Dyslipaemia at Various Intervals After Transplantation

<table>
<thead>
<tr>
<th>Years after transplantation</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>88</td>
<td>60</td>
<td>39</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>% abnormal patients</td>
<td>51</td>
<td>40</td>
<td>31</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

![Blood levels of cholesterol and triglycerides in 13 patients prior to and after return to normal of their lipid profile. Normalisation occurred between 2 and 8 years after transplantation](image_url)

Figure 1. Blood levels of cholesterol and triglycerides in 13 patients prior to and after return to normal of their lipid profile. Normalisation occurred between 2 and 8 years after transplantation
The difference between patients below and above 40 years is significant (p<0.01) both at 2 and 4 years. Two years after transplantation, the frequency of dyslipaemia is not significantly different between sexes below 40 years; above 40 years, however, females are more frequently dyslipaemic (85%) than males (52%) (p<0.01).

**Obesity** Ideal bodyweight (IBW) was calculated in 66 patients. Obesity was defined as a bodyweight above 110% of IBW. As shown in Table II the frequency of dyslipaemia is higher in obese subjects but this difference reaches statistical significance only at 4 years (p<0.01). No significant relationship was observed between triglyceride levels and bodyweight. In 35 patients bodyweight changed during follow-up by more than 10% of IBW. Seventeen patients were initially normolipaemic and remained so despite an increase in bodyweight. Eighteen patients were dyslipaemic: among the 15 who gained weight 6 became normolipaemic whereas among the 3 who lost weight 1 became normolipaemic; normalisation in the latter patient was already present when weight loss was only 4% of IBW. Interestingly, normalisation of serum lipids observed during follow-up in 13 patients, was associated with a weight gain >10% of IBW in 6, <10% in 6 and a weight loss <10% in the last patient.

**TABLE II. Effect of Obesity on the Frequency of Dyslipaemia After Transplantation**

<table>
<thead>
<tr>
<th>ideal body weight</th>
<th>at 24 months</th>
<th></th>
<th>at 48 months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;110%</td>
<td>&gt;110%</td>
<td>X²</td>
<td>&lt;110</td>
</tr>
<tr>
<td>% of total patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(47)</td>
<td>(19)</td>
<td>N.S.</td>
<td>25</td>
</tr>
<tr>
<td>% of males</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(26)</td>
<td>(6)</td>
<td>N.S.</td>
<td>33</td>
</tr>
<tr>
<td>% of females</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(21)</td>
<td>(13)</td>
<td>N.S.</td>
<td>16</td>
</tr>
</tbody>
</table>

( ) number of patients

**Steroids** Mean steroid dosage was virtually identical in the normo- and in the dyslipaemic groups (11.8 versus 13.3mg/d at 2 years and 9.6 versus 10.8mg at 4 years respectively). Normalisation of lipid profile occurred in 13 patients while steroid dosage remained identical (10 cases at 10mg/d) or decreased only moderately (3 cases from 20, 17.5 and 12.5mg/d to 10mg/d respectively).

**Renal function** Frequency of dyslipaemia is higher in the patients with an abnormal (serum creatinine ranging from 1.3 to 3.2mg/100ml) than in patients with a normal renal function (creatinine ≤1.2mg/100ml): 59 versus 43% at 2
years and 53 versus 23% at 4 years respectively. This difference is significant (p<0.05) only at 4 years.

The return to normal of the lipid profile observed in 13 patients was associated with a fall in serum creatinine in only 3 patients (1.7, 0.3 and 0.3 mg/100ml respectively). In the 10 others, serum creatinine rose or fell by less than 0.2mg/100ml.

**Blood glucose level** Blood glucose obtained simultaneously with the lipid profile was always normal even in the four diabetic patients given insulin. It is noteworthy that 2 of the latter patients remained constantly normolipaemic whereas the 2 others became normal 3 and 4 years after transplantation.

**Long Term Consequences of Dyslipaemia**

The long term effect of the lipid profile on vascular or bone disease was evaluated in 15 of the 20 patients whose follow-up exceeded 8 years. Nine of them remained constantly normolipaemic whereas 6 were constantly dyslipaemic. The 5 patients who became normolipaemic during follow-up are not included. As shown in Table III the incidence of vascular or bone disorders is not significantly different in the 2 groups.

**TABLE III. Frequency of Associated Disorders in Constantly Normo- and Dyslipaemic Patients Followed for at Least 8 Years After Transplantation**

<table>
<thead>
<tr>
<th></th>
<th>number</th>
<th>hypertension</th>
<th>arteritis</th>
<th>angina pectoris</th>
<th>cardiovascular disease</th>
<th>osteonecrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>normolipaemic</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>dyslipaemic</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion**

The present study demonstrates that in patients whose graft functioned for at least two years, the frequency of dyslipaemia falls progressively from 51% 2 years after transplantation to 25% after 10 years. This decrease does not result from the progressive elimination of dyslipaemic patients: it is also observed in a group of 39 patients whose follow-up extends for at least 6 years. It is due to the normalisation of the lipid profile in 13 patients between 2 and 8 years after transplantation. Interestingly, a similar fall in the incidence of hypertriglyceridaemia has been reported by Thomas and Lee [17] between 1 and 13 years after transplantation. Unfortunately, the number of patients included at each time interval is not given and it is not clear whether this fall results from the death of
dyslipaemic patients or from the return to normal of the lipid profile. Stähelin et al [8] have also observed a fall in the frequency of dyslipaemia from 83% 4 to 12 months after transplantation to 68% at 13 to 36 months and 61% at 37 to 48 months. Here again it is not clear whether this decrease is due to the return of the lipid profile to normal values in some patients. The fact that the incidence of hyperlipaemia decreases progressively over the years might explain to some extent the great variation in the prevalence of dyslipaemia reported in transplanted subjects [2–10]. Indeed, most studies include patients with very different length of follow-up. Interestingly, Beaumont et al [4] report a 22% incidence of lipid disorders in a group of 37 patients whose mean follow-up reached 43 months whereas Ponticelli [10] notes a 54% incidence in a group of 26 patients whose mean follow-up lasted only 17 months.

Obviously, factors other than the delay after transplantation influence the prevalence of lipid disorders. Our data suggest that both age and sex should be taken into account. Although age has already been recognised as a factor [4,8] sex had not yet been identified.

Several causes are probably implicated in the maintenance of dyslipaemia. Steroid dosage incriminated early after transplantation when large amounts are given [6,7,11] does not appear to play an important role late after transplantation. By contrast the level of renal function appears to be of some importance as already reported by Ibels [11].

Obesity is also a causal factor: the prevalence of dyslipaemia is higher in overweight patients. This finding confirms that of others [7]. The role of dietary habits does not seem to be a critical factor since preliminary observations have shown that although the caloric intake of our patients was excessive, it was virtually identical in normo- and dyslipaemic subjects.

The thirteen patients who normalised their lipid profile provided us with an opportunity to assess the factors that might have played a role in the onset of dyslipaemia. Interestingly, changes in body weight, renal function or steroid dosage were only rarely observed: one patient lost weight, another had a fall in serum creatinine and three had a small decrease in steroid dosage. We have thus no good explanation to account for the improvement in the 8 other patients.

Finally, it is of interest to note that over a period of 8 years the incidence of vascular disease does not appear to be higher in the constantly dyslipaemic subjects than in the patients whose lipid profile had always been normal. This lack of difference, despite a similar mean age, may be due to the small size of the sample. Alternatively, it may reflect the fact that more sophisticated methods with quantification of the individual lipoproteins should be employed to assess the relationship between vascular disease and disorders of lipid metabolism [18–20].

Acknowledgment

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References

1. Ibels, LS, Stewart, JH, Mahony, JF, Neale, FC and Shiell, AGR (1977) *Quart. J. Med.*, **46**, 197

Open Discussion

PARSONS (London) I am very interested in this study because it does make a difference to the survival rate of the transplanted patient. And I wonder whether you have any observations on the morbidity which results from these dyslipidaemias. Do you see in those with an abnormal pattern over the years an increased prevalence of ischaemic heart disease, cerebral vascular accidents or hypertension?

VAN YPERSELE Well, may I show a further slide? We have followed for 8 years at least, 9 patients who are constantly normolipaemic throughout follow-up and 6 patients who remained constantly dyslipaemic. We have excluded five patients who became normal during follow-up. The incidence of angina pectoris, arteritis, cardiovascular disease is virtually the same in both groups. It is also the same for osteonecrosis in the aetiology of which lipids have also been implicated. This lack of effect may be due to the small number of subjects. Alternatively it is possible that it is due to the fact that we have not done a very sophisticated analysis of blood lipids which should include lipoprotein determinations, such as HDL.

TOURKANTONIS (Salonica) In our material we find that the majority of the patients belong to type IV lipidaemia (=40%) and no change appears two years
after transplantation. Has the type of lipidaemia a geographical distribution and
does the amelioration of lipidaemia (after transplantation) depend on the type
of lipidaemia?

VAN YPERSELE To the first part of your comment: I think that most studies
on the incidence of dyslipidaemia after transplantation, have reported, contrary
to dialysis patients, a higher frequency of type II, that is associated with an in-
creased cholesterol levels, than type IV associated with an increased triglyceride
level. Among our 13 patients whose lipid profiles changed, 9 had a type II dyslip-
idaemia.

YUSUKE TSUKAMOTO (Japan) You reported hypertriglyceridaemia for the
patients whose triglyceride level was above 115mg/dl. But this 115mg/dl is lower
than the control value which was investigated by other workers including me.
What is the serum triglyceride level of control subjects?

VAN YPERSELE It depends on the method used for triglycerides. With our
method upper limit of normal was 115.

TSUKAMOTO What was the control which you investigated?

NICHOLAS Well, students and people working at the post office.