Transpl Int (2000) 13 [Suppl 1]: S117–S119

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The influence of cholesterol on mortality after transplantation is age dependent

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Abstract There is still no consensus on the treatment of elevated serum cholesterol in patients with a renal transplant. In the general population treatment is age dependent. We studied the influence of serum cholesterol 1 year after transplantation in all 676 recipients of a kidney graft transplanted in Rotterdam that survived and functioned for at least 1 year. The other variables included in this analysis are: donor and recipient age and gender, original disease, race, number of HLA A and B mismatches, number of previous transplantations, postmortal or living related transplantation and transplantation year. At 1 year after transplantation the following variables were included: serum cholesterol, serum creatinine, proteinuria and hypertension. In the Cox proportional hazards analysis, serum cholesterol at 1 year after transplantation turned out to be an important, independent variable influencing patient failure. The influence was linear but there was interaction with recipient age. The negative influence of serum cholesterol on the RR for patient failure decreased with increasing recipient age. For example, the proportional increase in RR of a 20-year-old with a serum cholesterol of 12 mmol/l compared with that of a cholesterol of a patient with serum cholesterol of 6 mmol/l was 6. In a 60-year-old with a cholesterol of 12 mmol/l the proportional increase in RR was only 1.2 compared with a contemporary with a cholesterol of 6 mmol/l. Serum cholesterol levels have an independent influence on patient failure. The RR is influenced by recipient age, so that the negative effect of increasing cholesterol levels in the elderly is overruled by the RR of age and disappears.

Key words Cholesterol · Renal transplantation · Mortality

Introduction

A relationship between serum cholesterol and cardiovascular mortality has been proven for the general population [3–5, 9–11]. Apart from the serum cholesterol, elderly persons have a higher risk of cardiovascular mortality as their overall death risk is elevated. It is customary to combine the influences of age, serum cholesterol and other variables on the death risk in deciding whether to treat patients with elevated cholesterol or not [1, 6]. We wondered whether age should be included, because this would mean that the treated population was a selection of patient with a largely age-related high risk.

The population that receives renal transplants is known to have an elevated risk of cardiovascular mortality [2, 7, 8, 12]. We studied the influence of an elevated serum cholesterol level on the death risk in different age groups in our renal transplant population.

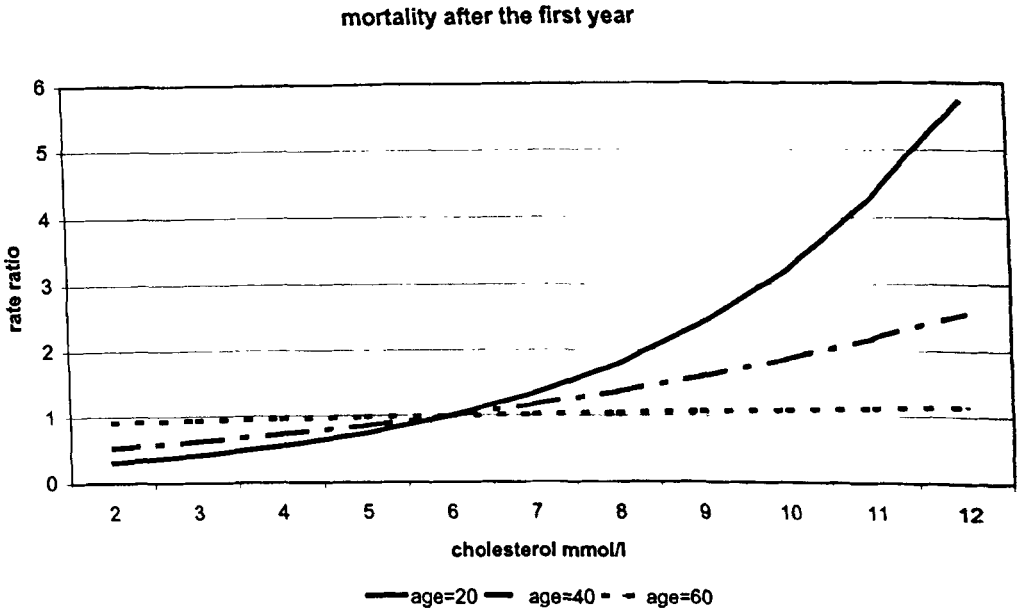

Fig. 1 Simultaneous influence of serum cholesterol and recipient age on the relative risk (RR) of death. The *solid line* is the baseline, showing the influence of cholesterol when the RR of all other variables is 1. The RR of a serum cholesterol of 6 mmol/l is set at 1, whatever the recipient age. The influence of cholesterol on the RR at different ages is calculated

Materials and methods

Patients

At the University Hospital Rotterdam-Dijkzigt, 883 kidney transplantations were carried out from the start in 1971 to January 1994. The analysis was done in January 1999, when all patients had been followed up for at least 5 years of follow-up. One year after transplantation 676 patients were still alive with a functioning graft. These patients were included in this analysis. All these patients were tested for serum cholesterol, creatinine and the presence of proteinuria and hypertension between 1 and 2 years after transplantation. Patients were not routinely treated with cholesterol-lowering medication.

Immunosuppression

Initially azathioprine (AZA) was given as primary immunosuppressive in a dose of 2–3 mg/kg body weight. From July 1983 onwards cyclosporin (CsA) was used as the primary immunosuppressant and was given on the basis of 12-h trough levels. Steroids were given on the day of transplantation and were gradually tapered to a maintenance dose of 10 mg of prednisone daily 6 months after transplantation. No patient received triple drug therapy on a routine basis.

Statistical analysis

"Patient survival" was censored for graft failure. There were no exclusions for technical or nonimmunological failures. Potential associations with survival were analysed by means of the Cox proportional hazards regression model. The variables included in the study were cholesterol, creatinine, proteinuria and hypertension at 1 year after transplantation, and also recipient and donor age and gender, HLA mismatches on A and B, recipient race, original disease and transplantation period. HLA-DR mismatches were excluded from this analysis because they were not available in transplants before 1983. Variables were selected by backward elimination using likelihood ratio tests. For categorical variables indicator coding was used with the first category as reference. For categorical variables the rate ratio (RR) of a category versus the reference was equal to e^B, where B is the regression coefficient for that category. Both donor and recipient age were analysed as continuous variables measured in years. As a reference value, the rate ratio (RR) of a 20-year-old (both recipient and donor) was set at 1. Among the 1-year-variables, cholesterol was analysed as a continuous variable, and the RR of a cholesterol of 6 mmol/l was set at 1. Creatinine was also analysed as a continuous variable, the RR of 75 μmol/l being 1. The RR of each continuous variable is per unit of the variable considered. Because the influence of AZA and CsA on survival appeared not to satisfy the proportional hazards assumption we chose to stratify for immunosuppressive medication. The analyses were performed with SPSS for Windows version 7.52.

Results

In the observed population of 676 patients, 220 received AZA and 456 CsA as the primary immunosuppressant. For each of 18 patients one or more variables were missing (2.7%).

Cox proportional hazards analysis showed that serum cholesterol was an independent covariate influencing the RR for patient death. Because there was an interaction with recipient age, the effect of both variables on the hazard rate was considered. The simultaneous risk is defined as a continuous function of serum cholesterol for three ages (20, 40 and 60 years). It is expressed relatively to a cholesterol level of 6 mmol/l in a contemporary with a renal transplant. Figure 1 shows the influence of the interaction of cholesterol and recipient age as a RR relative to the rate in a contemporary with a

cholesterol of 6 mmol/l. As the proportional increase in the RR is highest in the youngest recipients, the negative influence of a high serum cholesterol is largest in the youngest patients.

Discussion

Results from studies in the general population on the influence of serum cholesterol on the chances of death have led to a general consensus concerning the treatment of persons with elevated serum cholesterol levels [1, 6]. In The Netherlands it is customary to treat "uncomplicated" patients with serum cholesterol levels above 8 mmol/l with cholesterol-lowering medication. Below this value treatment is dependent upon six variables: cholesterol/HDL ratio, age, gender, diabetes, smoking habits and hypertension. It is remarkable that in this scoring system the frequency with which treatment is considered to be indicated increases with age. This is because the risk is calculated by means of the equation coefficients of all six variables mentioned. The calculated risk is the 10-year chance of a cardiovascular event. However, this risk increases with age, independent of any other risk factor. Moreover, age cannot be treated. Thus, it is questionable whether this variable should have such a heavy weighting. More interesting is the question as to whether the risks of the other variables add to that of increasing age. Apart from the age-related risk, does an equally elevated serum cholesterol result in the same risk at different ages? Is smoking as dangerous for an elderly person as for a young person? The population we studied is not a general population, but as cardiovascular disease is such a prominent cause of death it is an interesting population for the study of influences [2, 7, 8, 12].

In this retrospective study concerning 658 kidney transplants Cox regression analysis has shown that serum cholesterol is a serious risk factor for patient death, but the effect is different at different ages. The largest proportional increase in RR is found in the youngest age groups, so that the influence of high serum cholesterol on the risk of death is largest for the young recipients (Fig. 1). The RR of elderly persons is not influenced by serum cholesterol levels, so that although their death risk is larger than that of young patients the serum cholesterol level does not add to this effect. Our conclusion for this patient population is that treatment of elevated cholesterol levels in the hope of preventing patient death seems to be indicated especially in the young and middle-aged.

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