0041-1337/04/7710-1576/0
TRANSPLANTATION
Vol. 77, 1576–1580, No. 10, May 27, 2004

Printed in U.S.A.

REDUCED INCIDENCE OF HYPERURICEMIA, GOUT, AND RENAL FAILURE FOLLOWING LIVER TRANSPLANTATION IN COMPARISON TO HEART TRANSPLANTATION: A LONG-TERM FOLLOW-UP STUDY

OREN SHIBOLET,[1,5] ERAN ELINAV,[1] YARON ILAN,[1] RIFAAT SAFADI,[1] YAFFA ASHUR,[1] AHMED EID,[2] GIDEON ZAMIR,[2] MICHAEL FRIDLANDER,[3] TALI BDOLAH-ABRAM,[1] DANIEL SHOUVAL,[1] AND DAN ADMON[4]

Background. **Hyperuricemia and gout are common complications of heart transplantation, reaching a prevalence of 84% and 30%, respectively, in heart transplant recipients. In contrast, they are seldom reported following orthotopic liver transplantation (OLT).**

Methods. **We retrospectively evaluated 75 consecutive liver transplant recipients and 47 consecutive heart transplant recipients, followed for at least 3 years after transplantation in a single transplantation center in Jerusalem, Israel. Data was collected on demographic and clinical variables, levels of uric acid, the occurrence of gout, renal function, and variables effecting hyperuricemia, such as weight and medications.**

Results. **Clinical gout was significantly more prevalent in heart recipients than in liver recipients (25.5% and 2.6%, respectively). Hyperuricemia was present in 100% of heart recipients, with an average uric acid level of 451 μmol/l, as compared with 85.7% and 403 μmol/l for liver recipients ($P<0.001$ for both variables). Univariate analysis identified several parameters which significantly influenced the difference in hyperuricemia and gout among the two groups including age, gender, rejection episodes, hypertension, diabetes mellitus, the level of uric acid prior to transplantation, and the use of cyclosporine A, diuretics, steroids, and aspirin. Use of tacrolimus and azathioprine were associated with decreased incidence of hyperuricemia and gout. Multivariate analysis identified the type of transplantation as the only independent risk factor predicting the development of hyperuricemia and gout.**

Conclusion. **Clinical gout and hyperuricemia were significantly more prevalent in heart recipients than in liver recipients. The disparity can be explained by differences in age, gender and renal function among the groups, as well as by the use of different medication regimens.**

Hyperuricemia and gout are common complications of heart transplantation, reaching a prevalence of up to 84% and 30%, respectively, in heart transplant recipients (*1–4*). In contrast, they are seldom reported following orthotopic liver transplantation (OLT) (*5*, *6*). Recently, Neal et al. (*5*) reported a prevalence of hyperuricemia of 47% in 134 consecutive OLT recipients, with a 6% prevalence of clinical gout. The difference between the heart and liver transplantation groups has been attributed to different immunosuppression regimens, use of diuretics, and the presence of renal function impairment (*7–12*), but no direct comparison of hyperuricemia and gout between different solid organ transplantation patient groups has been previously executed.

We retrospectively compared the prevalence of hyperuricemia and clinical gout in heart and liver organ recipients, and analyzed variables affecting uric acid metabolism and excretion, such as body weight, renal function and different medication regimens.

Our results show that clinical gout and hyperuricemia are significantly less prevalent in liver recipients, a difference that can be attributed to clinical and laboratory differences between the groups, as well as to the use of different medical regimens following transplantation.

MATERIALS AND METHODS

Patients

We reviewed the patient records of 122 consecutive liver and heart recipients (47 heart recipients and 75 liver recipients), who were followed for at least 3 years after transplantation at a single transplantation center in Hadassah University Hospital, Jerusalem, Israel, between the years 1988–2002. Excluded were patients who were diagnosed with gout prior to transplantation.

Clinical Information

Data recorded included: age, sex, weight, height, underlying diseases, duration of follow-up after transplantation, concurrent illnesses such as hypertension, diabetes mellitus (NIDDM), alcohol abuse, and hypothyroidism. Episodes of gout, use of medications, and the number of rejection episodes were also recorded. Additional information was collected by telephone interviews with the patients and their attending physicians.

Laboratory Results

Uric acid and creatinine levels, obtained during routine follow-up visits and recorded by the hospital's automated chemistry analyzer (Kodac-Vitros 950, Rochester, NY) were averaged from the beginning of follow-up to the time of transplantation, and from the time of transplantation to end of follow-up. The average number of measurements of uric acid and creatinine per patient were 350 and 460, respectively. Hyperuricemia was defined according to our laboratory

[1] Liver Unit, Division of Medicine, Hadassah University Hospital, Jerusalem, Israel.
[2] Transplantation Unit, Department of Surgery, Hadassah University Hospital, Jerusalem, Israel.
[3] Department of Nephrology, Hadassah University Hospital, Jerusalem, Israel.
[4] Department of Cardiology, Hadassah University Hospital, Jerusalem, Israel.
[5] Address correspondence to: Oren Shibolet, M.D., Liver Unit, Department of Medicine, Hadassah University Hospital, PO Box 12000, Jerusalem, 91120 Israel. E-mail: shibolet@hadassah.org.il.

Received 11 September 2003. Revision requested 28 September 2003. Accepted 19 December 2003.
DOI: 10.1097/01.TP.0000128357.49077.19

reference values as a serum urate concentration of 380 μmol/l on two or more occasions, while a high creatinine level was defined as a value above 106 μmol/l at any time.

Creatinine Clearance

Creatinine clearance was calculated using the Cockroft-Gault formula:

$$\text{Clcr (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum Cr (mg/dl)}} \times (0.85 \textit{ for women})$$

The values of creatinine were taken on the day of transplantation (or as soon as the creatinine stabilized following transplantation) and at the end of follow-up.

Body mass index

Body mass index (BMI) was calculated as: body weight (kg)/ height (m)(*2*).

Rejection Episodes

Rejection episodes were recorded from the patient files, and defined according to clinical or histological criteria (when available).

Statistical analysis

The Pearson chi-square test, as well as Fisher's exact test, were used to test the association between any two categorical variables. Association between two continuous variables was assessed by calculating the Pearson Correlation Coefficient. Comparison of continuous variables between two groups was performed by application of the two-sample *t* test, and by applying Analysis of Variance (with the Scheffe posthoc procedure) for the comparison of the groups. The logistic regression model was applied in order to test which variables simultaneously influence the development of gout and hyperuricemia.

Continuous variables are presented as Mean ± SD. All statistical tests were two-tailed, and a p-value of 5% or less was considered statistically significant.

RESULTS

Baseline characteristics.

The characteristics of the two patient groups are summarized in Table 1. There were significant differences in various baseline characteristics amongst the two groups, including male gender (87.2% of heart recipients as compared to 52.0% of liver recipients) and mean age. The follow-up period subsequent to transplantation was similar in the heart and liver groups.

Major underlying causes for heart transplantation were ischemic heart disease (70.2%), dilated cardiomyopathy (12.8%), and valvular heart disease (10.6%). For liver transplantation, major underlying causes were viral hepatitis (49.4%), cryptogenic cirrhosis (27%) and cholestatic liver disease (16.9%).

Clinical gout, manifesting as recurrent bouts of inflammatory monoarthritis, was significantly more prevalent in the heart transplant patients, noted in 12 out of the 47 patients (25.5%), as compared to only 2 clinical gout cases among the 75 liver recipients (2.6%, $P<0.001$). Hyperuricemia occurred in 100% of heart recipients as compared to 85.7% in the liver recipients ($P=0.007$, Figure 1). Average posttransplantation uric acid levels were 451.3±13.5 μmol/l in the heart recipient group, as compared with 403.0±8.1 μmol/l in the liver recipient group ($P=0.003$, Figure 2).

Average pretransplantation uric acid levels were 460.79±79 μmol/l in the heart transplantation group, as compared with 398.36±73.6 μmol/l in the liver group ($P=0.007$), which suggests that the pretransplantation uric acid load was higher in the heart recipients than in the liver transplantation group.

The average posttransplantation creatinine levels and creatinine clearance were 152±7.8 μmol/l and 61.9±3.9 cc/min, respectively, in the heart transplant group, as compared with 115±4.9 μmol/l and 83.9±4 cc/min in the liver transplant group ($P<0.05$ for both parameters, Figures 3 and 4).

Several clinical and laboratory factors, known to affect uric acid levels and the incidence of clinical gout, were notably different among the two groups, as shown in Table 2. Medication regimens differed markedly among the groups. Cyclosporine, steroids, azathioprine, diuretics, and aspirin were used more frequently in heart recipients (95%, 100%, 66%, 83%, and 83%, respectively) than in liver recipients (35%, 59.2%, 5.2%, 13% and 15.6%, respectively, $P<0.001$ for all medications). In contrast, tacrolimus was used more often by liver recipients (64.9%) than heart recipients (4.3%). Allopurinol for the treatment of gout was used in 8 heart recipients (17%) as compared with 2 liver recipients ($P<0.001$).

Acute rejection episodes occurred in 58.6% of the heart transplantation group, as compared with only 35.1% in the liver transplantation group ($P<0.004$). Non-insulin dependent diabetes mellitus (NIDDM), hypertension, and hypothyroidism were more prevalent in the heart transplantation group (38.3%, 57.4% and 4.3%, respectively) than in the liver transplantation group (14.3% and 40.3% and 1.3%, respectively.). However, these differences reached statistical significance only for NIDDM ($P<0.004$).

No significant difference was noted between the two groups in respect to body mass index, consumption of alcohol, or the use of mycophenolate mofetil as part of the immunosuppressive regimen.

TABLE 1. Patient characteristics

	Liver Transplantation	Heart Transplantation	p Value
Patients (n)	75	47	
Mean age (y) (range)	48 (20–69)	57 (23–78)	<0.001
Gender (male/female)	39/36	41/6	<0.001
Mean follow-up (mo) (range)	98.4 (40–225)	105.6 (37–225)	0.304
Background medical conditions			
Diabetes mellitus (%)	14.3	38.3	0.004
Hypertension (%)	40.3	57.4	0.067
Hypothyroidism (%)	1.3	4.3	0.557
Alcohol abuse (%)	1.3	2.1	0.722

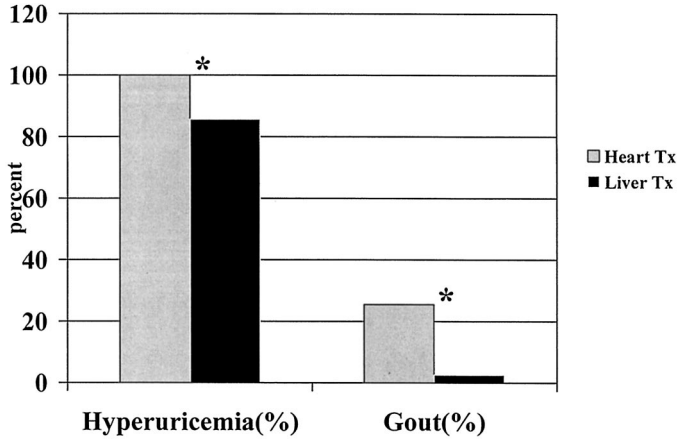

FIGURE 1. Prevalence of hyperuricemia and gout. *, P < 0.005.

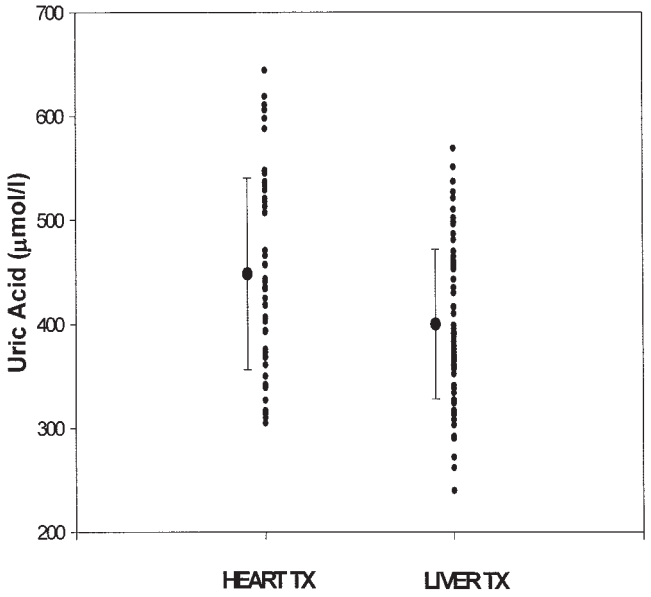

FIGURE 2. Posttransplant uric acid levels.

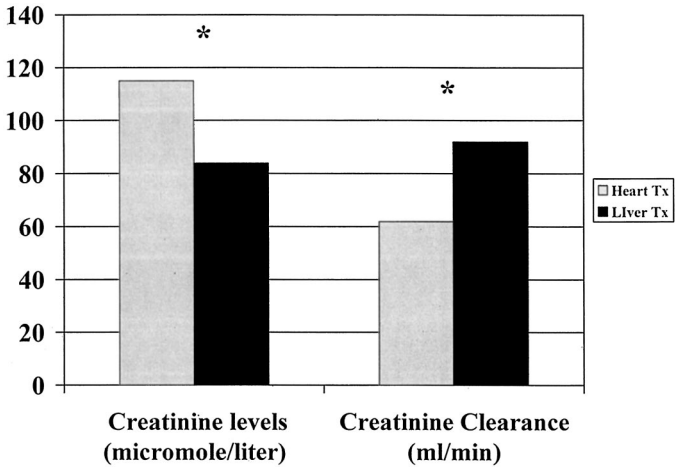

FIGURE 3. Serum creatinine levels and creatinine clearance. *, P < 0.005.

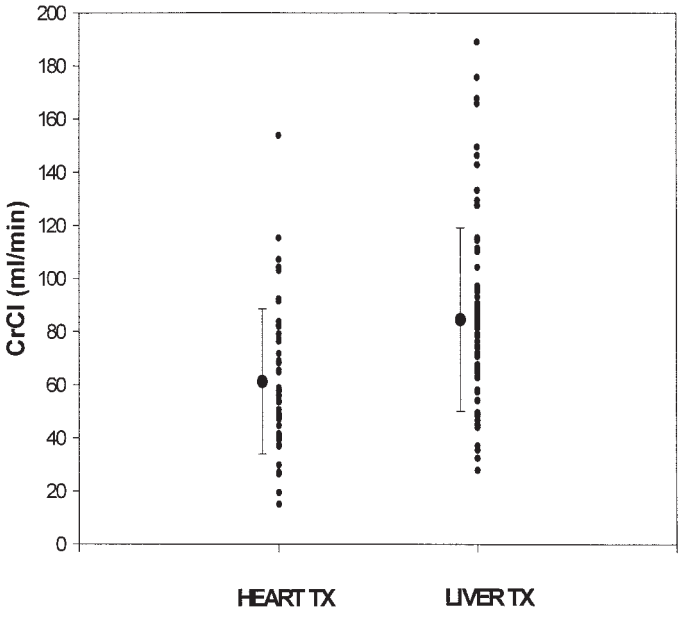

FIGURE 4. Posttransplant creatinine clearance.

The following parameters were shown to be independent risk factors for hyperuricemia and gout by univariate analysis: age, gender, number of rejection episodes, NIDDM, hypertension, pretransplantation uric acid, pre- and posttransplantation blood creatinine and creatinine clearance, and the use of cyclosporine, diuretics, steroids and aspirin.

Using a multivariate analysis model, the only significant risk factor found to be independently correlated to the development of gout was the type of transplantation ($P<0.009$).

DISCUSSION

We compared the prevalence of clinical gout and hyperuricemia in two groups of solid organ recipients (heart and liver). Studies have shown that gout and hyperuricemia usually develop within 2.5 years after solid organ transplantation. Therefore, only patients who were followed for at least 3 years were included in the study.

The results show that gout and hyperuricemia were significantly more prevalent in heart recipients than in liver recipients. Only 2 cases of gout were found among 75 liver recipients, as compared with 12 cases of gout among 47 heart recipients. Hyperuricemia occurred in 100% of heart recipients as compared with 85.7% in liver recipients; both of these results were statistically significant.

Only two studies assessing the occurrence of gout and hyperuricemia in liver recipients have been previously published, neither of which was comparative and controlled. The study by Neal et al.(*5*) measured the two highest uric acid levels following transplantation, thereby tilting results towards hyperuricemia; the study by Bismuth et al.(*6*) included uric acid levels collected on arbitrary dates and was therefore also subject to bias. Although the two studies varied in their assessment of the prevalence of hyperuricemia, their reported prevalence of clinical gout was similarly low.

In the present study, we included the average uric acid and creatinine levels as calculated from all blood tests drawn since the time the patient presented to our center, which resulted in a large number of results collected per patient

TABLE 2. Clinical and laboratory factors

	Liver Tx	Heart Tx	p Value
Post-Tx average serum uric acid levels (μmol/L)	403	451	0.003
Hyperuricemia (%)	85.7	100	0.007
Gout (%)	2.6	25.5	<0.001
Body mass index (kg/meter^2)	26.3	27.3	0.189
Acute rejection episodes	35.1	58.6	0.004
Post-Tx average serum Creatinine levels (μmol/L)	115	152	<0.001
Post-Tx average Creatinine Clearance (ml/min)	83.9	61.9	<0.001
Pre-Tx average serum Uric acid levels (μmol/L)	398.3	460.7	0.007
Medication (% treated with the drug)			
Cyclosporin A	35.1	95.9	<0.001
Tacrolimus	64.9	4.1	<0.001
Steroids	59.2	100	<0.001
Azathioprine	5.2	66.0	<0.001
Mycophenolate mofetil	11.7	4.3	0.204
Diuretics	13	83	<0.001
Aspirin	15.6	83	<0.001
Allopurinol	2.8	17.0	<0.001

Tx, transplantation.

during the 9 years of follow-up. This made any transient changes in uric acid and creatinine levels negligible. We calculated the creatinine clearance using the Cockroft-Gault formula, which was previously shown to correlate well with creatinine clearance assessed in more elaborate methods.

The two groups markedly differed in their baseline characteristics. Heart recipients were older than the liver recipients and were predominantly male, reflecting the general ischemic heart disease (IHD) population. Both male gender and age are known risk factors for development of gout and hyperuricemia.

Heart recipients had a higher level of pretransplantation uric acid levels, suggesting that these patients may have a higher pretransplantation uric acid load. The change in uric acid levels before and after transplantation were insignificant in the heart and liver recipients (data not shown), suggesting that the act of transplantation itself had no effect on the patients' uric acid levels.

Average posttransplantation creatinine levels were higher, and calculated creatinine clearance reduced in the heart recipient population as compared to liver transplant recipients. Renal excretion is the main route of uric acid clearance, and reduced renal function might contribute to the higher occurrence of gout and hyperuricemia in this patient group. In addition, heart recipients suffered more from hypertension and diabetes mellitus than liver recipients, a feature that may also have contributed to the higher levels of hyperuricemia, either directly or via their effect on renal function.

There was a major difference in the medication profile between the two groups, with heart transplant recipients using significantly more diuretics and cyclosporine. Suggested mechanisms for cyclosporin-induced hyperuricemia include a decrease in glomerular filtration rate (GFR) or increased proximal tubular reabsorption of uric acid (*13*)

In contrast, liver recipients used more tacrolimus, which is reported to resolve clinical gout when substituted for cyclosporine in renal transplant recipients (*14*, *15*). The effect of both calcineurin inhibitors on renal function is reported to be similar. All of the heart recipients were treated with steroids and most were treated with aspirin; the former is known to prevent gout, while the latter (especially in low doses) is known to exacerbate it.

These marked differences in medication regimens reflect the patients' underlying illnesses, different spectrums of posttransplant complications and physician preferences, and may have a substantial cumulative impact on the uric acid levels in both patient groups.

Another difference between the groups was the higher incidence of rejection episodes among the heart recipients. The treatment of acute rejection with high dose corticosteroids can ameliorate gout. Therefore, the incidence of gout in the heart recipients might have been underestimated.

Several other factors known to be associated with a higher incidence of gout and hyperuricemia, such as obesity and alcohol consumption, were not different among the groups.

Our study has several limitations. It is retrospective and as such may be subject to confounders, although we attempted to assess all possible causes affecting hyperuricemia. Also, the two groups markedly differ in age, gender, background illnesses, and medication profiles. This limits the validity of the multivariate analysis, because the two groups may not be comparable. However, both groups share many similarities including vigorous pre- and posttransplantation evaluation and follow-up, immunosuppressive treatment, and a variety of posttransplantation complications. Another limitation is the lack of information concerning the dietary habits of our patients, regarding the consumption of food containing high levels of uric acid or purines. However, it is unlikely that the patients markedly differed in their diet, since to the best of our knowledge none of our patients were instructed to avoid such foods, and no such recommendation can be found in the transplantation literature. In addition, our results are based on the practice of transplantation teams in a single transplantation center and as such may not be applicable to different centers where drug regimens may be different.

In view of the fact that hyperuricemia was not associated with clinical disease in liver recipients, we deem that no specific treatment or dietary recommendations to control uric acid levels are needed in this group. In contrast, in view of the high incidence of hyperuricemia and gout in heart recipients, we

suggest that a diet low in uric acid and purines, or even pharmacological hypouricemic therapy, should be considered, commencing at the time of enrollment for transplantation.

Our results conclude that the incidence of gout and hyperuricemia is significantly lower in liver recipients than in heart recipients. This may result from liver recipients' younger age, higher prevalence of female gender, and relative infrequency of diabetes, hypertension and renal failure. Medication regimens such as infrequent use of diuretics, cyclosporine and aspirin, and increased use of tacrolimus may also play a part in this phenomenon. The type of transplantation was the only variable independently associated with the risk of developing hyperuricemia and gout following solid organ transplantation.

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0041-1337/04/7710-1580/0
TRANSPLANTATION
Vol. 77, 1580–1588, No. 10, May 27, 2004
Printed in U.S.A.

HUMAN IMMUNE RESPONSES TO PORCINE ENDOGENOUS RETROVIRUS-DERIVED PEPTIDES PRESENTED NATURALLY IN THE CONTEXT OF PORCINE AND HUMAN MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I MOLECULES: IMPLICATIONS IN XENOTRANSPLANTATION OF PORCINE ORGANS

SABARINATHAN RAMACHANDRAN,[1] ANDRÉS JARAMILLO,[1] XIAO-CHUN XU,[1] BRICE W. MCKANE,[1] WILLIAM C. CHAPMAN,[1] AND T. MOHANAKUMAR[1,2,3]

Background. **Porcine endogenous retroviruses (PERV) have been shown to infect human cells, raising concerns regarding safety of xenotransplantation. In patients exposed to porcine tissues, no PERV infection has been observed. This study was designed to develop human CD8$^+$ cytotoxic T lymphocytes (CTL) against PERV-derived peptides presented in the context of human leukocyte antigen (HLA) or swine leukocyte antigen (SLA) class I molecules and to define dominant epitopes contributed by PERV.**

Methods. **Human CD8$^+$ CTL were generated against porcine aortic endothelial cells (PAEC). Peptides presented on SLA class I molecules were acid eluted and fractionated by reverse-phase high-performance liquid chromatography. Peptide fractions that restored lysis of acid-stripped PAEC were sequenced by tandem mass spectrometry. Human CD8$^+$ CTL were generated against PERV envelope-derived peptides and PERV-infected human cells to identify immunodominant PERV-derived epitopes.**

Results. **We identified two peptides derived from retroviral transactivating regulatory protein (AHQD-**

This work was supported by National Institutes of Health grant HL57796.

[1] Department of Surgery Washington University School of Medicine, St. Louis, MO.
[2] Department Pathology and Immunology, Washington University School of Medicine, St. Louis, MO.
[3] Address correspondence to: T. Mohanakumar, Ph.D., Department of Surgery, Washington University School of Medicine, Box 8109-3328.CSRB, 660 South Euclid Avenue, St. Louis, MO 63110. Email: kumart@msnotes.wustl.edu.

Received 9 October 2003.
Revision requested 30 October 2003. Accepted 24 November 2003.
DOI: 10.1097/01.TP.0000122220.61309.1D