Transpl Int (2004) 17: 617–621
DOI 10.1007/s00147-004-0765-9

ORIGINAL ARTICLE

Gabriela A. Berlakovich
Thomas Soliman
Edith Freundorfer
Thomas Windhager
Martin Bodingbauer
Peter Wamser
Hubert Hetz
Markus Peck-Radosavljevic
Ferdinand Muehlbacher

Pretransplant screening of sobriety with carbohydrate-deficient transferrin in patients suffering from alcoholic cirrhosis

Received: 5 August 2003
Revised: 12 November 2003
Accepted: 19 March 2004
Published online: 27 October 2004

G. A. Berlakovich (✉) · T. Soliman
E. Freundorfer · T. Windhager
M. Bodingbauer · P. Wamser
F. Muehlbacher
Department of Transplant Surgery,
University of Vienna,
Waehringer-Guertel 18–20,
1090 Vienna, Austria
E-mail:
gabriela.berlakovich@meduniwien.ac.at
Tel.: +43-1-404004000
Fax: +43-1-404006872

H. Hetz
Department of Anesthesiology and ICM,
University of Vienna, Vienna, Austria

M. Peck-Radosavljevic
Department of Gastroenterology and
Hepatology, University of Vienna,
Vienna, Austria

Abstract Sufficient assessment of potential candidates for orthotopic liver transplantation (OLT) is the most important factor for a low alcohol relapse rate after transplantation in patients suffering from alcoholic cirrhosis. In the current study the efficiency of pretransplant screening with carbohydrate-deficient transferrin (CDT) was analysed in patients on the waiting list for OLT. A prospective study was performed in 44 patients who had undergone OLT for alcoholic cirrhosis. All patients had had pretransplant assessment by a specialist psychologist and were found to have no problems with alcohol. Pre- and post-transplant CDT monitoring was performed. Overall, 790 CDT values were measured in the study population. The median observation period was 2.1 months before and 41.2 months after transplantation, respectively. In 35 patients (80%) pretransplant CDT values were found to be above the reference value, but only one patient suffered an alcohol relapse after transplantation. Of the nine patients (20%) who demonstrated normal CDT before transplantation, two suffered an alcohol relapse after transplantation. CDT is a very useful marker for the monitoring of an alcohol relapse in patients following OLT for alcoholic cirrhosis, as has been previously indicated. However, CDT does not appear to be useful as a pretransplant screening marker for selection of potential transplant candidates suffering from alcoholic cirrhosis.

Keywords Orthotopic liver transplantation · Alcoholic cirrhosis · Pretransplant screening

Introduction

Sufficient assessment and selection of potential candidates for orthotopic liver transplantation (OLT) are obligatory in view of the shortage of organs and a high death rate on the waiting list in most centres. All those working in the field of liver transplantation are aware of the continuing concern, often emotionally charged, regarding justification of the use of liver grafts for patients suffering from alcoholic cirrhosis [1]. Those concerns have led to the adoption of several guidelines, such as 6-month rules, 12-month rules, enrolment in alcohol rehabilitation programmes, and randomized testing of urine and blood.

Most liver transplant programmes in North America and Europe require alcoholics to attain abstinence from alcohol for 6 to 12 months as a condition of eligibility for liver transplantation [2]. This restriction is sometimes called the 6-month rule. Weinrieb et al. [3] published their concern that universal application of the 6-month rule to all patients with alcoholic liver disease does not identify the relapsed group without inappropriately discriminating against those who are going to remain abstinent. Moreover, the 6-month rule leaves the patient

who has severe disease, but who does not have time to participate effectively in rehabilitation, at a disadvantage.

Currently available biochemical indicators used as markers of chronic alcohol consumption are not applicable to patients suffering from end-stage cirrhosis, and levels of blood ethanol represent acute alcohol intake only. Randomized testing of urine has not been practicable on an outpatient basis.

So far, all attempts to identify normative prognostic parameters for alcohol relapse, after transplantation, have failed. However, further systematic assessment of all potential selection criteria has to be performed, in order for factors to be defined that are predictive of post-transplant alcohol relapse, in view of the importance of selecting those transplant candidates for whom the outcome would be best.

The purpose of this analysis was to establish whether pretransplant screening by means of CDT measurement meets a reasonable standard as a predictor of future drinking by potential candidates suffering from alcoholic cirrhosis.

Material and methods

Study population

From 1996 to 2000, in 44 patients suffering from alcoholic cirrhosis a prospective study was undertaken at the Department of Transplant Surgery, University of Vienna. In the study population pretransplant assessment and pretransplant outpatient follow-up was performed at our hospital exclusively. All of the patients received a primary liver graft as they were found to be suitable candidates for transplantation, especially when no contraindications concerning their alcohol history were defined by the specialist psychologist.

The pretransplant assessment was performed by a multidisciplinary team of hepatologists, surgeons, anaesthetists and a specialist psychologist. Both the pretransplant assessment of drinking behaviour and the repeated post-transplant examinations were performed by the psychologist, and the psychological assessment was defined as gold standard.

A fixed period of abstinence from alcohol was not required. Potential candidates whose abstinence was regarded by the specialist psychologist as being stable were accepted on the active waiting list. The waiting period for a liver often exceeds 6 months, and, therefore, the patient's progress can be followed, and when indicated, support and treatment offered. Patients without stable abstinence were sent for addiction treatment. If successful, the patient was listed; if not, transplantation was not indicated.

Patient follow-up

Patients on the active waiting list had pretransplant routine outpatient check-ups every 4 to 6 weeks, when they were personally interviewed by a member of the transplant team and by the psychologist. Additionally, appointments with the psychologist were arranged if indicated. The psychologist employed standardized questionnaires [4] and semi-structured interviews in order to classify drinking patterns and coping structures, as well as severity of somatic, psychological and social deterioration. The course between the visits was recorded retrospectively at the interview [5]. Alcohol relapse was defined as any exposure to alcohol at all. For the purposes of this study the quantity of alcohol was not considered reliable.

A complete laboratory investigation was carried out at each visit. For the purpose of this study, checks of serum alcohol and CDT levels were made, before transplantation, during each visit.

CDT measurement

The method that was used for quantitative measurement of CDT is a commercially available double antibody radioimmunoassay (Pharmacia Diagnostics AB, Uppsala, Sweden). The reference value amounts to less than 20 U/l for men and less than 26 U/l for women. CDT values were measured serially on a prospective basis. During alcohol abstinence, the CDT value normalizes, with a half-life of 17 days [6].

Statistical analysis

Numerical data were expressed as the mean ± SE and were compared by Student's *t*-test. The patient survival rate was calculated by the Kaplan–Meier method. Results were considered statistically significant when the alpha error was < 0.05. Sensitivity was defined as the proportion of alcoholic patients who had relapsed, with a pretransplant elevated CDT value, whereas specificity was the proportion of alcoholic patients who were abstinent, with pretransplant normal serum CDT values.

Results

Patient characteristics

The mean age of the study group at the time of OLT was 51.5 ± 6.9 years, with a range of 38.0 to 68.3 years. Men (73%) predominated in the sample. In 35 patients (80%) the indication for transplantation was alcoholic cirrhosis alone; four patients suffered from additional virus-in-

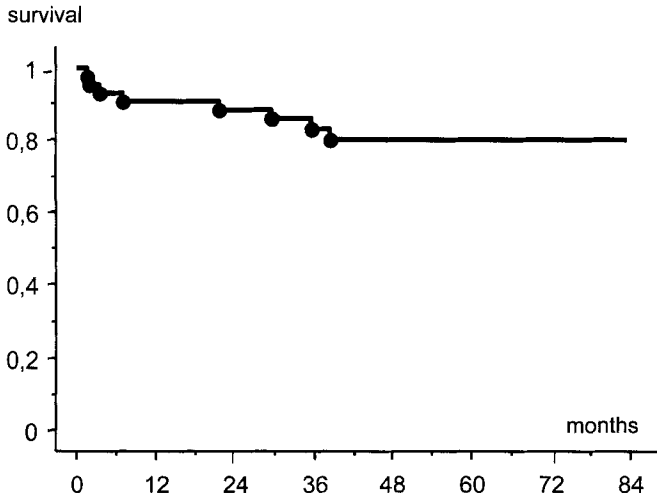

Fig. 1 Probability of overall patient survival ($n=44$)

duced cirrhosis, two patients from another type of cirrhosis as well, and three patients had a hepatoma in alcoholic cirrhosis. Fifty-nine percent of the patients that received a transplant were classified as having a Child's score of C, and 41% scored a B.

Mean follow-up time, pretransplant, was 2.9 ± 2.8 months, with a range of 0.2 to 11.7 months, and posttransplant, 43.5 ± 19.6 months (3.6 to 84.3 months). Overall actual patient survival was 91% and 83% at 1 year and 3 years, respectively (Fig. 1).

During the observation period, one patient died in the group with alcohol relapse (not alcohol related) and eight patients died in the group without relapse. Infection was the most significant contributing cause of death and was involved in three of the nine patients who died (33%).

In the study population ($n=44$), 68 CDT measurements were performed before transplantation, prospectively (mean 1.5 ± 0.9 per patient), and 675 measurements (mean 15.3 ± 8.2 per recipient) after transplantation.

Although all patients were assessed with stable abstinence in the pretransplant psychological examinations, 35 patients (80%) showed significantly elevated CDT levels pretransplant (group 1) with an average CDT value of 32.5 ± 11.4 U/l ($P < 0.0001$). Of these, two recipients demonstrated elevated CDT values after transplantation (Fig. 2). One patient suffered an alcohol relapse as diagnosed by the psychologist, and the other showed false positive CDT values. All other recipients from group 1 had normal levels after transplantation, although one suffered an alcohol relapse (false negative).

On the other hand, nine patients (20%) showed pretransplant CDT values (16.9 ± 2.0 U/l) within the target range (group 2). Seven recipients remained within the normal range after transplantation, and none of them suffered an alcohol relapse. The other two recipients demonstrated elevated CDT values that were true positives, as both recipients suffered an alcohol relapse.

Of 44 patients, four recipients (9%) suffered a posttransplant alcohol relapse during the observation period. The mean time to alcohol relapse was 14.3 ± 13.8 months (range 2.4 to 37.4 months), and the median was 8.7 months.

In patients who suffered an alcohol relapse, excluding the false-negative patient, the mean CDT value after transplantation was 36.3 ± 5.2 U/l following diagnosis of alcohol relapse and, therefore, was significantly ($P < 0.0058$) above the reference value. The mean CDT value in patients without drinking episodes, excluding one patient who was a false positive, was calculated to

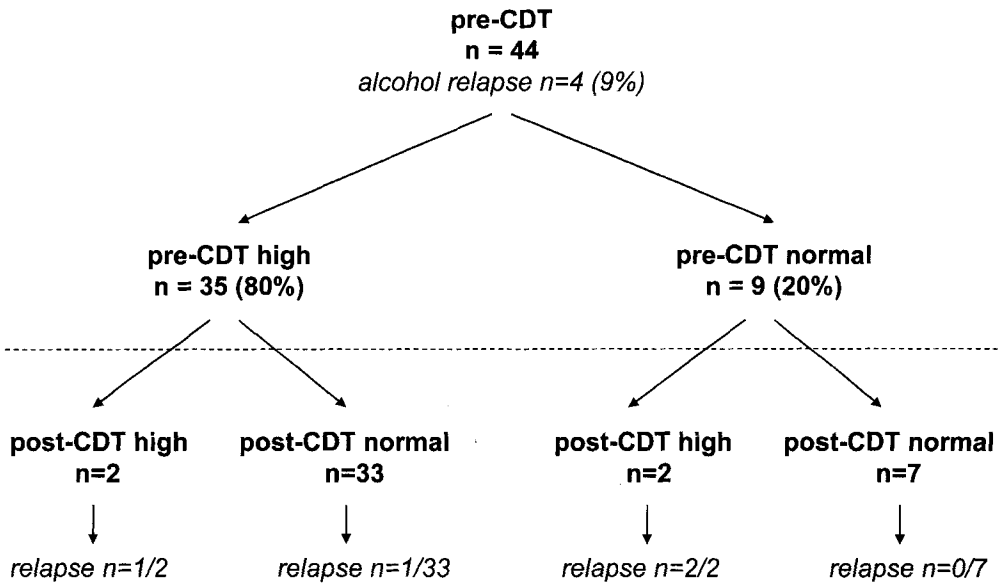

Fig. 2 Pretransplant CDT levels in comparison with posttransplant CDT course and sobriety

be 12.6 ± 2.9 U/l and, therefore, was significantly below the reference value ($P < 0.0001$). The difference in mean CDT values between patients with and without alcohol relapse showed statistical significance ($P < 0.0005$).

The efficiency of pretransplant CDT screening was examined by comparison of pretransplant CDT levels with post-transplant alcohol relapse as assessed by the specialist psychologist. Of the patients who suffered an alcohol relapse, two had true positive CDT levels before transplantation and two were false negatives before transplantation (Table 1). Of the patients who suffered no alcohol relapse, 33 showed false positive CDT screening before transplantation and only seven were true negatives before transplantation. Hence, a sensitivity of 50% and specificity of 17% were obtained. The proportion of true positive test results among all the positive test results (positive predictive value) amounted to 6% and the negative predictive value to 78%.

Discussion

Alcoholic liver disease became the commonest indication for liver transplantation in Europe between January 1988 and June 2000 [7]. However, this indication for transplantation remains controversial. The greatest concerns are related to abstinence before and after transplantation. This could result in graft loss or patient death due to non-compliance with immunosuppressive therapy and/or a direct hepatotoxic effect of alcohol on the graft. There is no doubt that a small proportion of patients return to a damaging pattern of drinking, but the number of grafts lost through a return to drinking is small [8]. Patient and graft survival are comparable to those for other indications [7, 9].

In order for treatment to be managed optimally and the most effective use made of the scarce availability of donor livers, patient selection and assessment are important.

Most centres in Europe and North America have adopted a rule that requires 6 months' abstinence before patients are accepted for listing, although relatively few centres follow their own guidance in all instances [8, 10, 11, 12]. Pretransplant abstinence does not reliably predict post-transplant abstinence or compliance [10, 12, 13, 14, 15, 16, 17].

Compared with other biological markers the most important advantage of CDT was the independence from the severity of the liver disease [18]. According to this observation, CDT was identified as a very useful marker for the monitoring of an alcohol relapse in patients following OLT for alcoholic cirrhosis, as has been previously indicated [19]. Moreover, we demonstrated that CDT values were independent of additional events such as rejection episodes or severe infection.

The purpose of this study was to determine the efficacy of CDT as a pretransplant screening marker for the identification of those potential candidates for OLT who are at risk of alcohol relapse after transplantation. The study population was followed, before transplantation, from 0.2 to 11.7 months, according to time spent on the waiting list. Thus, one to five pretransplant CDT measurements per patient were available. Post-transplant follow-up was correspondingly longer (median 41.2 months), with a median of 18.0 CDT measurements per patient needed to detect potential alcohol relapse.

All the patients in the study population were accepted on the active waiting list by the specialist psychologist. Assessments were made in accordance with the suggestions published by the European Association for the Study of the Liver (EASL) and the European Liver Transplant Association (ELTA) [8]. Although all these patients' abstinence was stable, 80% demonstrated significantly increased CDT values before transplantation. This discrepancy between the current gold standard (specialist psychologist) and the new method (pretransplant CDT measurement) implied that pretransplant CDT values were not reliable as screening markers for assessment and patient selection. This result was also confirmed by the low alcohol relapse rate of 9% after transplantation.

These results suggest that an elevated CDT value may not accurately represent alcohol consumption in patients with advanced liver disease. Concerns over the impact of the severity of liver disease have been also voiced by other authors [20, 21]. For example, Heinemann et al. [20] found an unacceptable, low specificity rate in patients awaiting liver transplantation, in both alcoholic and non-alcoholic liver disease. Therefore, the authors concluded that CDT does not appear to be useful for assessing patients before OLT, and CDT was no longer implemented in the determination of whether an OLT should be implemented.

The comparison of the different methods [22] of CDT measurement offered advantages of the newer %CDT assay over the conventional CDTect method, which has been used in our analysis. Nevertheless, sensitivity was poor in patients suffering from advanced liver disease, and elevated CDT value may not accurately represent alcohol consumption.

Table 1 Efficacy of pretransplant CDT in comparison with post-transplant diagnosis of alcohol relapse. Sensitivity % = (2/2+2)×100 = 50%; sensitivity % = (7/7+33)×100 = 50%

$n = 44$	Psychological diagnosis	
	Relapse	No relapse
Pre-CDT +	2	33
pre-CDT −	2	7

Several hypotheses have been proposed as to the mechanism for the development of CDT, including interference by ethanol with transferrin glycosylation, CDT secretion, or CDT elimination [6]. With the loss of functioning hepatocytes in cirrhosis, normal cellular activity is diminished, potentially affecting one or several of these mechanisms.

In conclusion, CDT could not be regarded as being reliable as a pretransplant screening marker for the selection of potential transplant candidates suffering from alcoholic cirrhosis. In fact, there are no normative factors that may identify those at risk of non-compliance. The EASL and the ELTA organized a workshop to draw up guidelines to clarify the role of liver transplantation in the management of the treatment of patients with alcoholic cirrhosis [8]: patients should be assessed, and if transplanted, followed by a multidisciplinary team, including a clinician experienced in addiction.

References

1. Beresford TP, Turcotte J, Merion R, Burtch G, Blow FC, Campell D, et al. A rational approach to liver transplantation for the alcoholic patient. Psychosomatics 1990; 31:241.
2. Everhart JE, Beresford TP. Liver transplantation for alcoholic liver disease: a survey of transplantation programs in the United States. Liver Transpl Surg 1997; 3:220.
3. Weinrieb RM, Van Horn DHA, McLellan AT, Lucey MR. Interpreting the significance of drinking by alcohol-dependent liver transplant patients: fostering candor is the key to recovery. Liver Transpl 2000; 6:769.
4. American Psychiatric Association: diagnostic and statistical manual of mental disorders, 3rd edn. American Psychiatric Association, Washington DC, 1980.
5. Ades J, Badawy A, Barrias JA, Besson J, Borg S, Chick J, et al. Guidelines on evaluation of treatment of alcohol dependence. Alcoholism 1994; 30:S5.
6. Stibler H, Hultcrantz R. Carbohydrate-deficient transferrin in serum in patients with liver disease. Alcohol Clin Exp Res 1987; 11:468.
7. European Liver Transplant Registry (http://www.eltr.com)
8. Neuberger J, Schulz KH, Day C, Fleig W, Berlakovich GA, Berenguer M, et al. Transplantation for alcoholic liver disease. J Hepatol 2002; 36:130.
9. Berlakovich GA, Steininger R, Herbst F, Barlan M, Mittlböck M, Mühlbacher F. Efficacy of liver transplantation for alcoholic cirrhosis with respect to recidivism and compliance. Transplantation 1994; 58:560.
10. Osorio RW, Ascher NL, Avery M, Bachetti P, Roberts JP, Lake JR. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. Hepatology 1994; 20:105.
11. Bird GL, O'Grady JG, Harvey FA, Calne RY, Williams R. Liver transplantation in patients with alcoholic cirrhosis: selection criteria and rates of survival and relapse. BMJ 1990; 301:15.
12. Kumar S, Stauber RE, Gavaler JS, Basista MH, Dindzans VJ, Schade RR, et al. Orthotopic liver transplantation for alcoholic liver disease. Hepatology 1990; 11:159.
13. Gledhill J, Burroughs A, Rolles K, Davidson B, Blizard B, Lloyd G. Psychiatric and social outcomes following liver transplantation for alcoholic liver disease: a controlled study. J Psychosom Res 1999; 46:359.
14. Neuberger J, Tang H. Relapse after transplantation: European studies. Liver Transpl Surg 1997; 3:275.
15. Foster P, Fabrega F, Karademir S, Sankary HN, Mital D, Williams JW. Recidivation of abstinence from ethanol in alcoholic recipients following liver transplantation. Hepatology 1997; 25:1469.
16. Gerhardt TC, Goldstein RM, Urschel HC, Tripp LE, Levy MF, Husberg BS, et al. Alcohol use following liver transplantation for alcoholic cirrhosis. Transplantation 1996; 62:1060.
17. DiMartini A, Jain A, Irish W, Fitzgerald MG, Fung J. Outcome of liver transplantation in critically ill patients with alcoholic cirrhosis. Transplantation 1998; 66:298.
18. Bell H, Tallaksen C, Sjaheim T, Weberg R, Raknerud N, Orjasaeter H, et al. Serum carbohydrate deficient transferrin as a marker of alcohol consumption in patients with chronic liver disease. Alcohol Clin Exp Res 1993; 17:246.
19. Berlakovich GA, Windhager T, Freundorfer E, Lesch OM, Steininger R, Muehlbacher F. Carbohydrate deficient transferrin for detection of alcohol relapse after orthotopic liver transplantation for alcoholic cirrhosis. Transplantation 1999; 67: 1231.
20. Heinemann A, Sterneck M, Kuhlencordt R, Rogiers X, Schulz KH, Queen B, et al. Carbohydrate-deficient transferrin: diagnostic efficiency among patients with end-stage liver disease. Alcohol Clin Exp Res 1998; 22:1806.
21. Anton RF. Carbohydrate-deficient transferrin for detection and monitoring of sustained heavy drinking. What have we learned? Where do we go from here? Alcohol 2001; 25:185.
22. Anttila P, Järvi K, Latvala J, Blake JE, Niemelä O. Diagnostic characteristics of different carbohydrate-deficient transferrin methods in the detection of problem drinking: effects of liver disease and alcohol consumption. Alcohol Alcohol 2003; 38:415.