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# Influence of perioperative sHLA I concentrations on the histological development of the liver graft

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**Abstract** Soluble HLA I (sHLA I) in human serum are ascribed an immunoregulatory role in the context of organ transplantation. Based on histological findings, the objective of the current study was to evaluate the protective influence of sHLA I in liver transplantation from the time point of reperfusion. The sHLA I concentrations in serum samples derived from the liver vein immediately after reperfusion (flush catheter) of 38 patients with liver transplantations were determined by ELISA. The postoperative histological findings of the transplant biopsies were categorized according to rejection, endothelialitis, cholestasis, and necrosis, as well as fatty degeneration. An evaluation according to Kaplan-Meier showed a lower incidence for all of these factors in liver grafts with high sHLA concentrations ($P < 0.05$). We conclude that low sHLA I concentrations during reperfusion correlate with later complications, thus indicating that sHLA I may have protective potential in liver transplantation.

**Key words** Soluble HLA I (sHLA) · Flush catheter · Rejection · Liver transplantation

## Introduction

Almost 30 years ago Van Rood described the presence of soluble HLA class I (sHLA I) in human serum [9]. It is assumed that 30 to more than 50% of the sHLA I is produced by hepatocytes [3, 5]. The functions that are ascribed to sHLA I are many-sided. As a basic function there is still the presentation of antigens which is also a function of the soluble molecules [4, 10]. Recently, the immunoregulatory role of sHLA I in the context of transplantation became clearer [2, 4, 12]. Increased concentrations of sHLA I were observed in the perioperative period as well as in periods of rejection and infection [1, 2, 12]. sHLA I seems to exert an immunosuppressive function [5, 7, 8] thereby showing a protective effect on graft function [4, 5]. This led to the hypothesis that sHLA I is able to induce graft tolerance in the recipient [4, 6, 8]. The object of the current study is to ask whether the protective influence of sHLA I is already recognizable at an early intraoperative time point in liver transplantation.

## Patients and methods

The sHLA I concentration in serum samples of 38 liver-transplanted patients [17 female (16–66 years), 21 male (12–67 years)], in 40 liver transplantations were examined. The diagnoses which led to transplantation were posthepatitic cirrhosis (B/C; $n = 8$), autoimmune cirrhosis ($n = 11$), postalcoholic cirrhosis ($n = 5$), acute liver failure ($n = 4$), retransplantations ($n = 3$), and others ($n = 9$). The determination of the sHLA I concentration was carried out on the first 200 ml asservated effluent of the flush catheter immediately after the reperfusion of the graft through a catheter which was placed in the liver vein. The sHLA I concentrations were determined by an ELISA test with the help of an ELISA kit sHLA-STAT Class I (SangStat, Menlo Park, USA).

The postoperative histological findings (103 histological findings in 38 patients, 6 histological findings in two retransplantations) of the transplant biopsies until 12 months after liver transplantation were categorized according to rejection, endothelialitis,

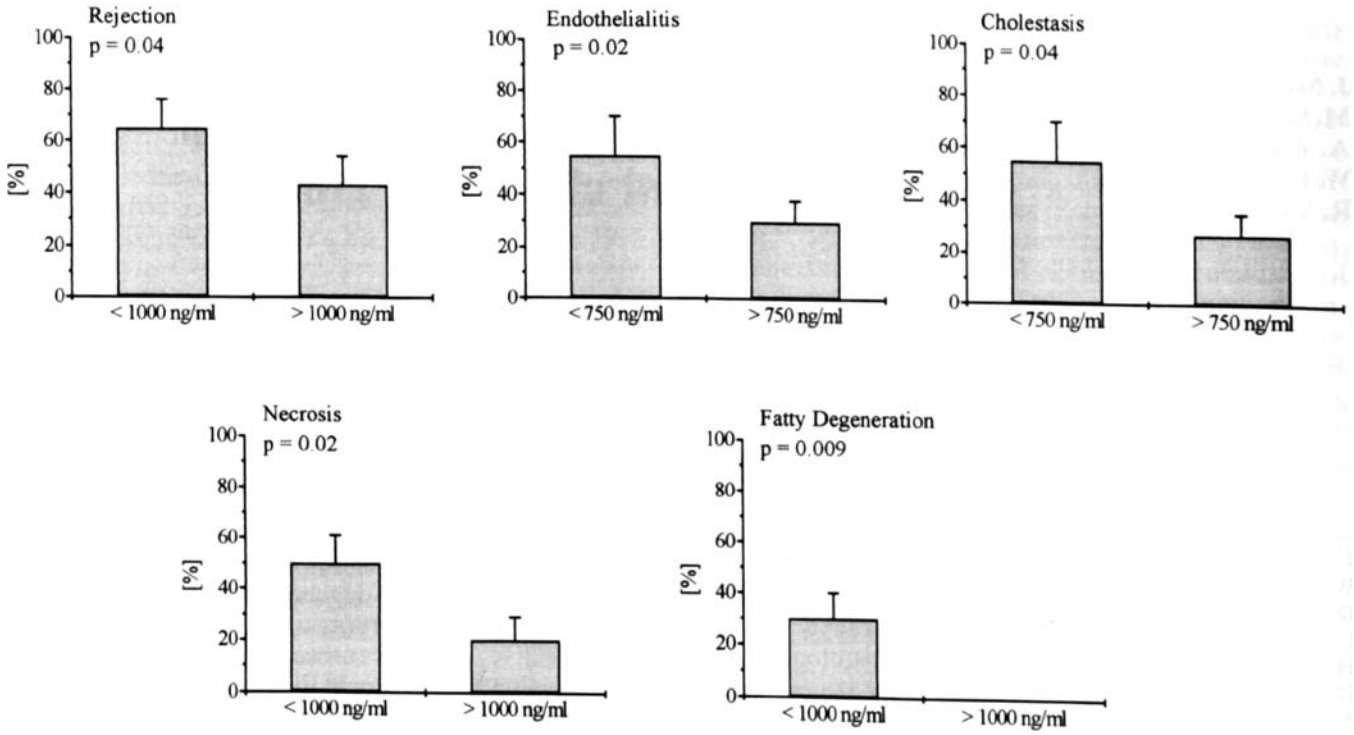


**Fig. 1** Impact of soluble sHLA I concentrations (ng/ml) in the serum of the flush catheter on the different complications after liver transplantation

cholestasis, and necrosis, as well as fatty degeneration, and evaluated according to Kaplan-Meier. These findings were derived from biopsies of the donor liver and were implemented at suspicion of reduction or failure of graft function or at suspicion of graft rejection. The criteria were divided into different degrees of severity from to the findings of the pathologists: rejection (grade 0–4), endothelialitis (grade 0–2), cholestasis (grade 0–3), necrosis (grade 0–3), and fatty degeneration (grade 0–3). A division by the Banff classification was not obligatory at the beginning of the study. Significance was estimated by the Wilcoxon/Kruskal-Wallis test and the log-rank test. The results were expressed in mean ± SD.

## Results

The mean of the sHLA I concentrations measured in this study (1098 ± 565 ng/ml) was almost 300 ng/ml above the normal values (820 ± 750 ng/ml; SangStat). We observed that sHLA I concentrations above 1000 ng/ml in the flush catheter were followed by the evidence of histologically detectable rejection after 1 year of 43% compared to 65% with an sHLA concentration at a lower level (Fig. 1; $P = 0.04$). Fifty-five percent of the patients with concentrations of less than 750 ng/ml showed endothelialitis, whereas only 30% with higher concentrations were affected ($P = 0.02$). Twenty-seven percent of the patients with an sHLA I level above 750 ng/ml developed cholestasis within the 1st year. Fifty-five percent of the patients with a lower concentration developed cholestasis ($P = 0.04$). With respect to necrosis, patients with an sHLA I level above 1000 ng/ml showed an occurrence rate of 20% compared to 50% of the patients with lower concentrations ($P = 0.02$). Fatty degeneration of liver grafts was detectable in 30% of patients with low sHLA I concentrations, whereas in patients with a high sHLA I level no fatty degeneration occurred ($P = 0.009$).

## Discussion

The results of the current study point out that the recipients with an sHLA I concentration above the cut-off value showed more seldom rejection, endothelialitis, and cholestasis which could indicate a reduction of the risk. The risk of developing a necrosis of the graft seems to be considerably higher if the recipient shows an sHLA I concentration lower than 1000 ng/ml in the serum of the flush catheter. With regard to this, the sHLA I concentration appears to be a marker for risk estimation of the development of graft necrosis similar to rejection. Based on these observations, the assumption that the height of the sHLA I concentration in the serum is essentially determined by cell death has to be disproved [5, 11]. The reason for non-fatty degeneration of the grafts with an sHLA I concentration above 1000 ng/ml could be that fatty degenerated livers are

not able to produce sHLA I in such high amounts. That fact becomes evident already at this early time point.

It could be observed that high sHLA I concentrations present at the time of graft reperfusion correlated with a lower extent of undesired histological changes in later biopsies. These findings also support the hypothesis that the release of sHLA I has a marked impact in clinical liver transplantation. The observations of the current study are based on a small number of transplantations and biopsies were taken only at clinical suspicion of relevant changes in the graft. Nevertheless, it has to be stated that, in this study, an increased concentration of sHLA I in the serum of the flush catheter above 750 or 1000 ng/ml shows a correlation to the histological development of the liver graft, especially to the criteria of rejection, endothelialitis, cholestasis, necrosis, and fatty degeneration. This led us to the conclusion that sHLA I seems to have a protective effect against rejection and inflammatory reaction after liver transplantation.

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