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# Endotoxemia is Associated with Renal Dysfunction in Liver Transplantation Recipients during the First Postoperative Week

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**Abstract:** The effect of endotoxemia on renal function was studied in 76 orthotopic liver transplant patients. In the preoperative period, a high preoperative serum creatinine level ( $>2.0$  mg/dl) was significantly associated with postoperative endotoxemia. The serum total bilirubin level was significantly greater in the patients with high serum creatinine levels than in those with lower serum creatinine levels ( $<2.0$  mg/dl). On the 7th postoperative day (POD), the serum creatinine level was significantly associated with an increased plasma endotoxin level. The serum total bilirubin and AST levels did not differ significantly between the patients with high and those with low serum creatinine levels. Based upon these data postoperative endotoxemia is suspected as being the principal cause of early postoperative renal dysfunction. A synergistic effect on renal function between cyclosporine and endotoxin may be important in the pathogenesis of the renal dysfunction seen after successful liver transplantation.

## Introduction

In human orthotopic liver transplantation (OLTx), patients are exposed to a wide variety of nephrotoxic insults during the perioperative period before and immediately after OLTx (1). In the preoperative period, the most common form of renal dysfunction seen in potential transplant candidates is functional in nature and is often referred to as the hepatorenal syndrome (2). During the transplant procedure and postoperatively, a panoply of renal insults can occur ranging from prerenal conditions such as hypotension or intrinsic renal insults such as occur with the use of nephrotoxic agents such as cyclosporine, aminoglycoside antibiotics and intravenous contrast agents (3).

Endotoxin is known to be nephrotoxic. Moreover, endotoxemia is often seen in patients with advanced particularly chronic liver disease (4). Endotoxin has been reported to be a major factor contributing to the development of functional renal dysfunction associated with liver disease (5).

Recent studies have shown that endotoxemia occurs during the operative and immediate postoperative periods of a liver transplant and is particularly evident during the anhepatic phase of the transplant procedure in both animal (6) and human transplantation (7).

A possible role for endotoxemia in the development of the early renal dysfunction seen following orthotopic liver transplantation is herein proposed based upon clinical observations at a large transplant center.

## Materials and methods

From March 15 to August 15, 1988, 81 patients who underwent orthotopic liver transplantation were selected for inclusion in this study. 76 of these 81 patients survived greater than 7 days and were studied in detail. The selection of the patients for inclusion in this study from the larger pool of patients seen at the University of Pittsburgh was based solely on the availability of one of the investigators (IY).

The serum creatinine level was measured immediately preoperatively and on the morning of the 7th postoperative day. Additionally, the serum total bilirubin and aspartate aminotransferase (AST) levels were measured at these same two time points.

For all patients, a standard cyclosporine-prednisone immunosuppression regimen was used. The cyclosporine dose was adjusted daily according to the whole blood cyclosporine level measured by the TDX Assay System (8).

Plasma endotoxin was assayed using platelet poor blood obtained from a peripheral vein utilizing sterile technique and a venipuncture or an indwelling venous catheter. The plasma was separated immediately and stored at minus 80°C until being assayed. The specific endotoxin assay utilized was the limulus coagulation assay which has been described elsewhere (6).

**Statistical Analysis:** The student t-test was used to determine differences between groups. A p value  $<0.05$  was considered to be significant.

## Results

The age of the 76 patients studied ranged from 18 to 66 years (mean 44). The male to female ratio was 43:33. The specific liver disease indications for orthotopic liver transplantation in these 76 patients are shown in **Table 1**.

TABLE 1. INDICATION OF LIVER TRANSPLANT IN 76 PATIENTS.

DIAGNOSIS	Number of Patients
Postnecrotic Cirrhosis	38
Cholestatic Disease	15
Fulminant Hepatic Failure	3
Malignancy	6
Budd-Chiari syndrome	2
Primary Graft Failure	12
<b>TOTAL</b>	<b>76</b>

TABLE 3. PREOPERATIVE LABORATORY VALUES OBTAINED IN 76 PATIENTS CATEGORIZED INTO THE LOW AND HIGH SERUM CREATININE GROUPS EXCLUDING THE 4 PATIENTS ON HEMODIALYSIS.

Laboratory Test	Serum Creatinine	
	low (< 2.0 mg/dl) (n=66)	high (>2.0 mg/dl) (n=6)
Plasma Endotoxin (Pg/ml)	*8.7 ± 2.9	23.3 ± 5.9
Total Bilirubin (mg/dl)	* **8.0 ± 1.8	**17.2 ± 3.3
AST (IU/L)	206.9 ± 44.2	130.3 ± 34.3

\* statistically significant difference

\*\*excluding 4 on hemodialysis.

The largest single disease indication was postnecrotic cirrhosis (35 patients, 46%). Cholestatic liver disease was second; primary graft failure and malignancy were the third and fourth most frequent disease indications for OLTx. This distribution in disease indications did not differ from that seen at the University of Pittsburgh in general. The preoperative creatinine level in the group of patients undergoing retransplantation (3.2±0.9, n=12) was greater than that of the patients undergoing primary OLTx (1.3±0.2, n=64), (P <0.05). Patients with cholestatic liver disease had the lowest preoperative creatinine of all the liver disease groups (0.8±0.7, n=15) (Table 2). The preoperative plasma endotoxin level in the group of patients undergoing retransplantation was significantly greater than that seen in any of the other disease groups (p<0.01) (Table 2).

Sixty-six of the 76 patients studied, survived at least 7 days postoperatively and had a preoperative serum creatinine <2.0 mg/dl. They were defined as being the low serum creatinine group. Four of 10 patients whose preop-

TABLE 2. PREOPERATIVE CREATININE AND ENDOTOXIN LEVELS FOR THE VARIOUS LIVER GROUPS.

LIVER DISEASE	n	CREATININE (mg/dl)	ENDOTOXIN (pg/ml)
Postnecrotic Cirrhosis	38	1.5 ± 0.2	9.9 ± 1.8
Cholestatic Disease	15	0.8± 0.1	12.3 ± 3.0
Others Budd-Chiari syndrome, Malignancy	11	1.4 ± 0.6*	8.0 ± 2.8*
Primary Graft Failure	12	3.2 ± 0.9	36.9 ± 6.7

\*statistically significant (P&lt;0.01)

TABLE 4. POSTOPERATIVE LABORATORY VALUES OBTAINED IN 76 PATIENTS CATEGORIZED INTO THE 7TH POSTOPERATIVE DAY IN 66 SURVIVING RECIPIENTS WHO HAD LOW SERUM CREATININE LEVEL PRIOR TO OLTx., EXCLUDING 2 PATIENTS ON HEMODIALYSIS.

Laboratory Test	Serum Creatinine	
	low (< 2.0 mg/dl) (n=47)	high (>2.0 mg/dl) (n=17)
Plasma Endotoxin (Pg/ml)	*14.4 ± 2.1	43.6 ± 17.4
Total Bilirubin (mg/dl)	6.5 ± 1.2	6.9 ± 1.2
AST (IU/L)	928.6 ± 180.5	1132.1 ± 241.8

\*statistically significant difference

erative creatinine was >2.0 mg/dl) defining them as being in the high serum creatinine group required hemodialysis both before and after OLTx. The immediate preoperative plasma endotoxin, serum bilirubin and AST levels in the patients with high and low preoperative serum creatinine levels excluding the 4 patients on hemodialysis are shown in Table 3. The preoperative plasma endotoxin and serum bilirubin levels were significantly higher in the high creatinine group (p<0.01).

On the 7th postoperative day (POD), 47 of the 66 patients who had had a low serum creatinine (<2.0 mg/dl) and two of 19 patients whose postoperative creatinine was high (>2.0 mg/dl) required hemodialysis. Plasma endotoxin, serum bilirubin and AST levels obtained on the 7th POD in the patients with high and low postoperative serum creatinine levels excluding the 2 patients on hemodialysis are shown in Table 4. A statistically significant greater plasma endotoxin level was seen in the high creatinine group (p<0.05). No significant differences were noted between the two groups for either the serum bilirubin

bin or the AST level obtained on the 7th POD.

The serum cyclosporine level on the 7th POD was  $1132.8 \pm 148.0$  ng/ml and  $1140.6 \pm 165.6$  ng/ml in those with high and low serum creatinine levels, respectively.

## Discussion

Endotoxin is a lipopolysaccharide derived from the wall of gram negative bacteria. The presence of this material in the systemic circulation is known to be associated with a wide array of adverse biological responses in various organs (9). In a recent report, plasma endotoxin levels, measurable in systemic blood, were shown to be elevated following liver transplantation. More importantly, markedly elevated endotoxin levels in systemic blood has been reported to be associated with an increased rate of graft failure (7) as well as an increased morbidity and mortality (10).

The kidney is known to be one of the target organs for endotoxin (11). The pathophysiological features of endotoxin induced renal dysfunction are thought to occur secondarily to a reduced renal perfusion occurring as a consequence of the vasoconstrictor effects of endotoxin. These dysfunctions are manifested as a reduction in the glomerular filtration rate and to a lesser degree tubular injury (12).

Experimental studies have shown that endotoxin directly damages vascular endothelial cells. This injury could be the most important mechanism underlying endotoxin induced renal injury (13).

Cyclosporine which is used as the principal immunosuppressive agent following liver transplantation is also known to be nephrotoxic. Various mechanisms for cyclosporine-induced acute renal failure have been postulated.

Recently intracapillary glomerular thrombosis has been recognized as one of the specific findings in acute cyclosporine-induced renal injury (14). In animal studies, the pathophysiological consequences of such an injury have been shown to include an increased renal vascular resistance (15), resulting in a reduction in renal perfusion accompanied by a reduction in the glomerular filtration rate (16). Similar findings have been reported in the clinical setting associated with endotoxemia (17-18).

Another interesting feature of cyclosporine-induced renal dysfunction is its association with the hemolytic uremic syndrome (19-20). The hemolytic uremic syndrome can be produced experimentally by administering endotoxin to pregnant rats (21). Subsequent studies have shown that cyclosporine acts synergistically with endotoxin to produce a state of circulatory collapse and that the effects of endotoxin on the kidney are additive to the effects of hypovolemia (22). Cosio et al has shown that cyclosporine treated animals do not develop significant renal damage after a single dose of endotoxin, while clear cut renal damage occurs when endotoxin is given

repeatedly suggesting that a Schwartzman's reaction may be the underlying mechanism further renal dysfunction under this set of circumstances (23).

The results of the present study suggest that endotoxemia may be responsible for some of the renal dysfunction seen both pre- and postoperatively in a liver transplant population. In the preoperative period, liver dysfunction per se is the underlying mechanism for the endotoxemia and associated renal dysfunction. Postoperatively, endotoxemia possibly coupled with cyclosporine appears to be an important factor associated with the presence of clinically significant renal dysfunction.

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