Complications after liver transplantation

- special consideration to renal function impairment, biliary complications and new-onset diabetes mellitus–

Doctoral thesis

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Introduction

In end-stage liver disease the only life-saving procedure for the patients is liver transplantation. Due to the better outcomes and survival results, short and long-term complications of other organ systems come to the field of view. The literature suggests, that HCV infection, recurrent diseases (HCC, PSC), de novo malignancy and hypertony all have a negative effect on long term results. This study analyses the topic of biliary complications, kidney impairement and new-onset diabetes mellitus (NODAT) after orthotopic liver transplantation (OLT) that are also well known risk factors. **Biliary complications (BCs) are common after OLT and significantly affect morbidity and mortality.** We have to follow and evaluate the risk factors in our liver transplant programme, to achieve successful management. Only the reduction of these can reduce the incidence of biliary complications and improve mortality. **In liver cirrhosis the renal function decreases as well.** Its most frequent cause is hepatorenal syndrome, but primer kidney failure, diabetes mellitus and some diseases underlying endstage liver failure (like HCV infection) can also play an important role. After OLT several further factors (total cross-clamping of vena cava inferior, polytransfusion, immunsuppressive therapy) also impair the renal function. The early recognition of kidney impairment and the evaluation of

potential loss of function is necessary. Sensitive markers in the prediction of post OLT renal function are usefull. **NODAT can be also a serious complication with a prevalence of 20-25% after OLT.** Diabetogenic effect of HCV infection and the immunosuppressive therapy is well known, but f.e. elder age, high body mass index (BMI), positive family history, the preoperative non-recognized blood sugar imbalance are also risk factors. The exact endocrinologic backround is not completely understood yet, the incretin-insulin axis and the dipeptidyl-peptidase-4 (DPP-4) activity may play an important role. The use of DPP-4 inhibitors is not the part of the therapic protocol of NODAT after liver transplantation.

Objective

- Analyse the incidence of the different types of biliary complications after OLT in Hungary
- Evaluate the main risk factors, therapic methods and patient survival in our program
- Follow the changes in kidney function during the first postoperative year
- Evaluate the cystatin C, as a sensitive marker of kidney impairement
- Organize a pre-and postoperative OGTT screening and blood serum sample collection
- Analyse the endocrinological backround of NODAT after OLT through the measurement of DPP-4, GIP and GLP-1

Patients and methods

Biliary complications were retrospectively analysed (n=519). Different groups were formed and the following BCs were evaluated: biliary leakage (BL), biliary necrosis (BN), non-anastomotic biliary stricture (NAS), anastomotic biliary stricture (AS) and ischaemic type biliary lesion (ITBL). The control group included those patients who did not have any biliary complication. Early biliary complication was diagnosed within the first 3 postoperative months; late complication was diagnosed after the 3rd months in the postoperative period.

In the topic of kidney impairement retrospective data-analysis was performed after n=321 primer OLT. Two preoperative groups were created according to preop GFR (above 60ml/min=Group1 and under 60ml/min=Group2). After the postoperative first year patients were devided in four groups according to their renal function. Group A = preop and postop GFR above 60ml/min. Group B = GFR preop above, but postop under 60ml/min. Group C = GFR preop under, but postop above 60ml/min. Group D= both preop and postop GFR under 60 ml/min. Risk factors, survivals were analysed. For cystain C analysis serum samples were collected. The predictive function was statisticaly tested with ROC analysis.

NODAT was alaysed in the period between 2012 and 2014. On the waiting list 49 non-diabetic patients were enrolled

(group-A) and 21 patients after OLT (group-B). Seven patients were monitored continuously both before and after OLT. OGTT was performed. After at least 12 hour fasting period in the morning time (8:00AM-9:00AM) blood sample was taken. Patients took a 75g glucose solution. Second sample was taken after 120 minutes. The evaluated parameters were: BMI, blood sugar, cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), CRP, insulin, DPP-4 and incretine hormone levels. Insulin sensitivity and beta-cell function were assessed using a HOMA2 calculator program. The diagnostic criterium (according to 120 minutes blood sugar test) was the following: NGT (<7,8 mmol/l), IGT (7,8-11,0 mmol/l) and DM (> 11,1 mmol/l). The determination of DPP-4 enzyme activity was measured kinetically on ELISA reader. For GIP and GLP-1 additional blood samples were collected in special tubes containing spray-dried K_2EDTA anticoagulant and DPP-4 enzyme inhibitor. Both GIP and GLP-1 levels were quantified with competitive enzyme-linked immunoassay (ELISA) method. The exact concentration values have been calculated with the four-parameter logistic curve fit model. Concentrations were given in ng/ml.

Results

Biliary complication after OLT was found in 27% of patients (N=141). In 74 cases (52,5%) BC occured within 3 month. Leakage and necrosis were diagnosed only in the early postoperative period, while ITBL and VBDS were found as late complications. Bile duct strictures occured both within and after the 3rd postoperative month. The most frequent BC type was bile duct stricture, stenosis 17,7%. It was followed by biliary leakage 10,4% and necrosis 5,4%. ITBL 1,3% and VBDS 1,3% showed a sporadic incidence. Compared to the initial period (1995-2000), decreasing tendency of BN and stenosis was observed, however, the incidence of biliary leakage were stable during the study period. Longer cold ischamic time did not effect statistically the incidence of biliary complications. Warm ischaemic time above 65 minutes significantly increased the developement of BN. Necrosis significantly reduced graft and patient survival (59%, 51%, 51% vs 81%, 75%, 70%, p=0,007). Seventy-four percent of the biliary interventions were radiological, mainly percutan transhepatic drainage. In 40 cases more than four biliary interventions were performed. The rate of retransplantation was 30% after non- anastomotic strictures.

According to my results, independently of the preoperative kidney function, 71% of patients had a reduce in the GFR

level at the first year after OLT. In this group of patients, NODAT was more often diagnosed (21,6% vs 12,7%; p=0,087) At 50% of the recipients with impaired preoperative renal function improvement in their postoperative GFR was detected. This could be explained with the reversibility of the HRS. Impaired preoperative renal function (GFR<60 ml/min) increased the occurence of postoperative complications (bleeding, infection, sepsis) and the patient survival was significant worse (p<0,018). In the long-term survival of patients in group D compared to the other patients a large-scale decrease was observed. After the analysis of collected blood serum samples the findings show that cystatin C is a sensitive marker of kidney function and has a predictive value for kidney impairment after OLT. We also calculated a cutoff point that can be used in clinical practice.

Thirteen patients on the waiting list (group-A; n=49) had by our OGTT newly diagnosed DM (26,5%). In 11 cases IGT was found (22,5%), while NGT in 25 cases. Despite DM or IGT 67% of the patients had the fasting blood sugar level in the normal range. The mean values of the calculated HOMA2-IR levels and the prevalence of HCV were significant higher in case of DM and IGT. Regarding the postoperative results, six patients of the group-B had NODAT (28,6%), 9 had IGT (42,8%) and in 6 cases NGT was diagnosed. Fasting DPP-4

activities were not differ in the postoperative groups, but in case of HCV infection (n=9) were higher compared to patients with all other indications for OLT (15,5 ± 5,2 vs 8,7 ± 3,5; p=0,008). The patients followed both before and after OLT (n=7) mainly had a decrease in glycaemic status postoperatively. In these patients rather decrease in beta-cell function was more characterizing. Evaluating the parameters characterizing glucose metabolism in case of IGT and NODAT the fasting insulin and c-peptide levels were also greater compared to results of patients with NGT ($p<0,001$ and $p=0,029$ respectively). After oral glucose load we did not remark any significant difference in insulin or c-peptide levels between the groups of patients with variant glucose metabolism status. GIP and GLP-1 incretin hormone levels were similar in all three groups both before and after OGTT and there were no statistically differences between HCV vs non-HCV patients.

Conclusions:

- The incidence of biliary complications in Hungary are similar to the international results
- The main risk factors are infections, acut rejection, and hepatic artery impairement
- More than 70% of the biliary interventions were radiological, mainly percutan transhepatic drainage
- Management of the duration of WIT under 65 minutes is necessary in reducing biliary complications
- From the waiting list 25% of the patients have impaired kidney function, which significantly decreases patient survival after OLT
- Independently of the preoperative kidney function, 71% of patients had a reduce in the GFR at the first postoperative year
- Preoperative cystatin C is a predictive marker of postoperative renal function and our cutoff point can be effectively used in the clinical practice
- Preoperative OGTT should be part of the diagnostic procedure of NODAT. HOMA2-index can be an effective method for pre-and postOLT screening of glucose homeostasis

- DPP-4 activity is stronger associated to HCV infection than to the type of glucose homeostasis imbalance
- Incretin hormones are present after OLT, even in case of NODAT
- DPP-4 inhibitors can be effective in the therapy of NODAT after liver transplantation, especially in HCV infected patients.

List of publications:

Connecting to doctoral thesis: [1-5]:

1. Nemes B, Zadori G, Gelley F, Gaman G, Gorog D, Doros A, Sarvary E. (2010) Can a cutoff value for cystatin C in the operative setting be determined to predict kidney function after liver transplantation? Transplant Proc. 42(6):2323-2326.
2. Gaman G, Gelley F, Doros A, Zadori G, Gorog D, Fehervari I, Kobori L, Nemes B. (2013) Biliary complications after orthotopic liver transplantation: the Hungarian experience. Transplant Proc. 45(10):3695-3697.
3. Gámán G, Gelley F, Gerlei Z, Dabasi E, Görög D, Fehérvári I, Kóbori L, Lengyel G, Zádori G, Fazakas J, Doros A, Sárváry E, Nemes B. (2013) Veseérintettség májátültetés során. Orv Hetil. 154(26):1018-1025.
4. Gaman G, Sarvary E, Gelley F, Doros A, Gorog D, Fehervari I, Kobori L, Wagner L, Nemes B. (2014) New-onset diabetes mellitus and the analysis of dipeptidyl-peptidase-4 after liver transplantation. Transplant Proc. 46(6):2177-2180.

5. Gaman G, Sarvary E, Gelley F, Doros A, Gorog D, Fehervari I, Kobori L, Wagner L, Mathe Z, Nemes B. (2015) Analysis of Incretin Hormones After Orthotopic Liver Transplantation. Transplant Proc. 47(7):2207-2209.

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6. Nemes B, Gaman G, Doros A. (2015) Biliary complications after liver transplantation. Expert Rev Gastroenterol Hepatol. 9(4):447-466.
7. Gelley F, Gámán G, Gerlei Z, Zádori G, Görög D, Kóbori L, Fehérvári I, Schuller J, Szőnyi L, Nagy P, Doros A, Fazakas J, Lengyel G, Schaff Z, Kiss A, Sárváry E, Nemes B. (2013) Hepatitis C-vírus-fertőzés kiújulása májátültetés után. Mi változott az elmúlt 10 évben? Orv Hetil. 154(27):1058-1066.
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9. Nemes B, Gaman G, Sarvary E, Doros A, Gorog D, Fehervari I, Kobori L. (2013) Retransplantations in

the Hungarian liver transplant program. Transplant Proc. 45(10):3688-3690.

10. Gelley F, Zadori G, Gorog D, Kobori L, Fehervari I, Gaman G, Gerlei Z, Nagy P, Sarvary E, Nemes B. (2014) Recurrence of primary sclerosing cholangitis after liver transplantation - The Hungarian experience. Interv Med Appl Sci. 6(1):16-18.
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