TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Metabolic syndrome and its association with fatty liver disease after orthotopic liver transplantation

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Keywords
body mass index, glycosylated hemoglobin, metabolic syndrome, obesity, risk factors.

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Conflicts of Interest
The authors of this manuscript have no conflicts of interest to disclose.

Received: 19 April 2012
Revision requested: 5 June 2012
Accepted: 14 September 2012
Published online: 5 November 2012

doi:10.1111/j.1432-2277.2012.01576.x

Summary

The metabolic syndrome (MetS) might contribute to morbidity after orthotopic liver transplantation (OLT). For this reason, we searched for MetS-associated risk factors and analyzed the link with nonalcoholic fatty liver disease (NAFLD) in OLT recipients. *De novo* MetS affected 32.9% of our cohort ($n = 170$) within 2 years after OLT. Multivariate analysis identified glycosylated hemoglobin (HbA1c) levels ≥5% [odds ratio (OR) = 3.5; 95% confidence interval (CI) = 1.56–8.13, $P = 0.003$], diabetes mellitus (OR = 4.31, CI = 1.69–10.99, $P = 0.002$), and arterial hypertension (OR = 4.59, CI = 1.46–14.49, $P = 0.009$) as independent risk factors for *de novo* MetS. MetS incidence correlated with steroid dosage after OLT (5.2 ± 2.4 mg/day vs. 7.1 ± 4.7 mg/day, $P = 0.014$), and was linked to NAFLD ($P = 0.001$) via obesity (OR = 4.67, CI = 1.55–14.1, $P = 0.006$) and dyslipidemia (OR = 4.23, CI = 1.35–13.3, $P = 0.013$) post-OLT. In conclusion, we were able to identify low threshold HbA1c as a novel risk factor for MetS after OLT and described a link of MetS with NAFLD in transplant organs. This study also indicated that steroid treatment is associated with MetS rates after OLT.

Introduction

Orthotopic liver transplantation (OLT) is the standard curative treatment of end-stage liver disease and achieves 5-year survival rates of more than 70% [1]. Hence, long-term complications after OLT have become an important medical issue. Current studies have indicated that cardiovascular events in transplant patients with stable hepatic function are a common cause of death, confirming their impact on prognosis [2–4].

Studies from the general population have conclusively shown that the metabolic syndrome (MetS) and nonalcoholic fatty liver disease (NAFLD) contribute to cardiovascular events with fatal outcome [5,6]. As components of MetS were also associated with recurrent NAFLD in patients after OLT, these factors have potential impact on patients survival after OLT [7,8]. More so, MetS rates after OLT were higher than in age-matched general population, indicating that specific factors foster the occurrence of MetS in liver transplant recipients [9]. Liver diseases with concurrent metabolic deterioration were common among OLT recipients. In particular, liver diseases associated with alcohol intake, chronic hepatitis C or nonalcoholic steatohepatitis (NASH) were frequently diagnosed among transplant recipients. The linkage of these conditions to insulin resistance and metabolic disease in nontransplant patients is well accepted [7,10–13]. Finally, modern immunosuppressive regimens, containing cyclosporine A, sirolimus or tacrolimus in addition to steroids, have further contributed to the development of metabolic pathologies after OLT. This was shown for triggering of hypercholesterinemia

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and impaired glucose tolerance by immunosupressives in different trials [14].

In this study, we retrospectively analyzed a single-center OLT cohort with the aim to identify factors, which allow risk stratification for de novo MetS upon OLT. Glycosylated hemoglobin (HbA1c) was included in this analysis, as it represents an established marker to monitor glucose homeostasis. Beside baseline variables, we searched for factors present after OLT, which might have contributed to new-onset MetS and followed the dynamics of metabolic variables leading to the diagnosis of MetS.

This study also analyzed the link between MetS and NAFLD after OLT to search for hepatic involvement in this context, as clinical data addressing this question are limited to studies from Northern America with a focus on selected transplant recipients at risk for MetS [7,15]. Therefore, histologic features of NAFLD and NASH were monitored in a nonselected European transplant cohort and risk factors were evaluated, which might prompt NAFLD after OLT.

Methods

Patient cohort and data acquisition

Patients with a minimum follow-up of 2 years receiving OLT between 2004 and 2010 were retrospectively analyzed at our transplant unit at Mainz University, Germany. Patients with missing documentation of study endpoints ($n = 38$) were excluded from analysis. Following these exclusion criteria, a total of 170 OLT patients were enrolled.

Patients were followed during routine outpatient visits, which were scheduled 6, 12, and 24 months after OLT. Patients were allowed to have a small meal prior to their visits, but were instructed to postpone the intake of immunosuppressive medication after routine blood sample acquisition. Patient data and laboratory parameters were derived from visit files, laboratory, and interventional reports. Standard immunosuppression included a combination therapy of mycomofetil-phenolate (250–1000 mg, b.i.d.) and tacrolimus or cyclosporine A (serum-level adapted). Steroids (methylprednisolone) were applied intravenously within the first week post-OLT, followed by tapering of oral methylprednisolone from 100 to 5 mg within 3 months. Methylprednisolone was stopped at 6 months post-OLT. Patients receiving immunosuppression during a trial assessing steroid avoidance [16,17] were grouped into the steroid-reduced treatment group. Following these trial, a shortened steroid regimen for 120 days after OLT was introduced as standard procedure in our transplant center.

Histologic findings derived from pathology reports were based on fine-needle biopsies obtained within a median of 368 days after OLT in 129 patients. Biopsies obtained within 6 months after OLT were excluded from analysis to avoid time course or indication dependent sampling bias as indicated by previous studies [18]. Mixed (micro and macrovesicular) lipid accumulations affecting hepatocytes in more than 5% were defined as hepatic steatosis. Hepatic steatosis was further graded into mild (<33%), moderate (33–66%), and severe cases (>66%). Reported histological features of steatohepatitis were documented in addition to hepatic steatosis. Clinical, laboratory, histological, and patient variables were transferred to a SQL-data bank system and were analyzed using computed algorithms. Informed consent was given by each patient. The study followed the ethical guidelines of the Declaration of Helsinki and was approved by the local ethics committee.

Definition of the metabolic syndrome

Metabolic syndrome was defined by modified adult treatment panel III criteria (ATP-III) [19], including obesity, dyslipidemia, hypertension, and diabetes mellitus (Table 1). Obesity was identified by a body mass index (BMI) ≥30 kg/m^2. Although waist circumference is superior compared with BMI in predicting cardiovascular risk in the general population, it does not show advantages over BMI for diagnosis of MetS [20]. Especially in this cohort, waist circumference was not used as variable for obesity because of its limited availability during retrospective analysis, and because of deviations resulting from ascites. BMI was identified before hepatic decompensation from patient files to reduce this bias at baseline. Dyslipidemia was defined by serum triacylglycerol (TAG) levels ≥150 mg/dl and high-density lipoprotein (HDL) concentrations <40 mg/dl for male and <50 mg/dl for female patients, respectively. Hypertension was confirmed using repeated Riva-Rocci measurements (>130/85 mmHg) or by a documented antihypertensive medication. Monotherapy with diuretics was not considered as antihypertensive treatment. Diabetes mellitus was defined by occasional serum glucose levels ≥200 mg/dl [21], as fasting status was not entirely assured in the outpatient setting. Documented antidiabetic treatment also accounted for diagnosis of diabetes mellitus.

Table 1. Modified adult treatment panel (ATP)-III criteria of the metabolic syndrome.

Modified ATP-III criteria (metabolic syndrome defined by ≥3 of 5 criteria)
Body mass index ≥30 kg/m^2
Serum triacylglycerol ≥150 mg/dl or lipid lowering therapy
Serum high-density lipoprotein <40 mg/dl (male)/<50 mg/dl (female)
Blood pressure ≥130/85 mmHg or antihypertensive therapy
Serum glucose ≥200 mg/dl or antidiabetic therapy

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Statistical analysis

SPSS (17.0) software was employed to perform statistical analysis. MetS 2 years after OLT and NAFLD after OLT were defined as primary test variables for statistical exploration. Patients with MetS prior to OLT were excluded from statistical exploration of risk factors associated with MetS occurrence. Continuous variables are shown as mean values and corresponding variances as standard deviation. Normal distribution was confirmed using Shapiro–Wilk test. Variables with uneven distribution were analyzed using Mann–Whitney *U*-test or Wilcoxon test for independent or connected variables, respectively. Variables, which were identified in >90% of the study population and were associated with MetS using univariate analysis ($P < 0.01$), were included for further multivariate analysis using log-regression. Log-regression was based on a step-wise variable inclusion, resembling an inclusion level of 0.05 and exclusion level of 0.1. Significant associations were assumed at a *P*-level below 0.05.

Results

Patient characteristics

Patients ($n = 170$) covering the inclusion criteria defined above were 54.9 ± 10 years old and showed a model of end-stage liver disease score of 18.4 ± 9.4 at time of OLT. OLT recipients were predominantly male patients (68.2%) and nearly all patients received a deceased donor OLT (98.2%) because of pathologies resulting in end-stage liver disease (97.1%). A comprehensive list of OLT-indications is given in Table 2.

Table 2. Indications for orthotopic liver transplantation (OLT). Indications rates refer to 170 patients with complete follow up for 2 years post-OLT. Patients with primary liver cancer without underlying hepatic comorbidity were included into the hepatocellular carcinoma subgroup. OLT indications with a frequency ≤3 were summarized as other indications.

OLT indication	*N* (%)
Alcoholic cirrhosis	49 (28.8)
Hepatitis C	49 (28.8)
Hepatitis B	21 (12.4)
Cryptogenic cirrhosis	11 (6.5)
Primary biliary cirrhosis	9 (5.3)
Hemochromatosis	5 (2.9)
Hepatocellular carcinoma	5 (2.9)
Miscellaneous toxic	5 (2.9)
Primary sclerosing cholangitis	4 (2.4)
Other indications	12 (7.1)

Metabolic syndrome after OLT

On the basis of chart reviews and laboratory parameters, we identified patients with MetS prior to OLT in 14.7% ($n = 25/170$). During the first 6 months after OLT, we observed a rapid increase in MetS rates among the OLT recipients, which was followed by a stable MetS rate during subsequent years after OLT. MetS prevalence rates reached 45.3% ($n = 77/170$) 2 years after OLT, which was threefold higher than prior to OLT ($P < 0.001$) (Fig. 1). Diabetes mellitus, obesity, and arterial hypertension were the most frequent factors contributing to the ATP-III-based definition of MetS at baseline. Whereas the most common MetS factors after OLT were diabetes mellitus, arterial hypertension, and elevated TAG serum levels.

MetS defining variables after OLT

Deteriorated lipid metabolism corresponded with occurrence of MetS after OLT and TAG levels increased from 104.6 ± 71.2 mg/dl at baseline to 178.9 ± 133.4 mg/dl, 2 years after OLT. The same trend was observed for low-density lipoprotein (LDL) as well as total serum-cholesterin serum levels. Whereas, HDL serum concentrations did not change substantially between baseline (42.0 ± 21.8 mg/dl) and 2 years post-OLT (43.9 ± 14.1 mg/dl). Patients with MetS received statin-based lipid lowering therapy in 32.5% ($n = 26/77$) after confirmation of hypercholesterinemia.

Blood pressure altered similar to the lipid profiles after OLT. Herein, systolic blood pressure increased from 116.6 ± 17.5 mmHg to 131.7 ± 19.9 mmHg within 2 years after OLT, which was paralleled by an elevation of diastolic blood pressure values (Fig. 2). In contrast, BMI values passed through a transient decrease from 26.2 ± 4.3 kg/m^2 to 23.8 ± 4.0 kg/m^2 during the first 6 months after OLT and reached pretransplant OLT levels (26.2 ± 4.6 kg/m^2) at end of follow up (Fig. 2). Albeit, diabetes mellitus was a major contributor to MetS after OLT, glucose serum levels showed a decline from 119 ± 45.0 mg/dl to 110.5 ± 40.0 mg/dl. Latter, glucose reduction could be attributed to antidiabetic treatment administered in 40.2% ($n = 31/77$) of patients with MetS. Despite these therapeutic efforts, HbA1c levels showed a persistent increase throughout this study starting with 5.1 ± 1.22% at baseline and reaching 5.7 ± 0.93% 2 years after OLT (Fig. 2).

Risk factors of metabolic syndrome after OLT

Risk factor assessment for MetS included analysis of organ donor and transplant recipient variables. Donor variables, such as donor age, body weight, and variables of MetS, did not show any correlation with MetS after OLT. Also, liver graft steatosis, quantified during routine

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biopsy prior to transplantation, was not related with MetS after OLT (Table 3).

Recipient variables, such as diabetes mellitus and arterial hypertension, showed a correlation with MetS incidence after OLT in univariate analysis. HbA1c levels were also associated with MetS, particularly, when exceeding 5.0%. Beside alcoholic cirrhosis, other OLT indications did not have any impact on new onset of MetS and neither hepatitis C-related disease nor cryptogenic cirrhosis influenced MetS incidence after OLT (Table 3).

Immunosuppressive regimens influenced the occurrence of MetS after OLT and steroid treatment seemed to be linked with MetS. In this cohort, we were able to monitor patients, who had participated in previous prospective studies [17] investigating steroid-sparing or steroid-reduced regimens. This analysis confirmed a trend toward lower MetS rates in patients receiving steroid treatment for <120 days after OLT, compared with patients under steroid administration for more than 120 days post-OLT (42.6% vs. 57.4%, $P = 0.205$) In addition, daily steroid dosage was higher among patients with occurring MetS after OLT compared with unaffected OLT recipients (5.2 ± 2.4 mg/day vs. 7.1 ± 4.7 mg/day, $P = 0.014$). In contrast, dosage or serum levels of alternative immunosuppressive compounds were not associated with MetS rates (Table 4).

After multivariate analysis, diabetes mellitus and HbA1c levels ≥5% at baseline maintained the strongest correlation with MetS incidence after OLT and were associated with a more than threefold increased risk of MetS

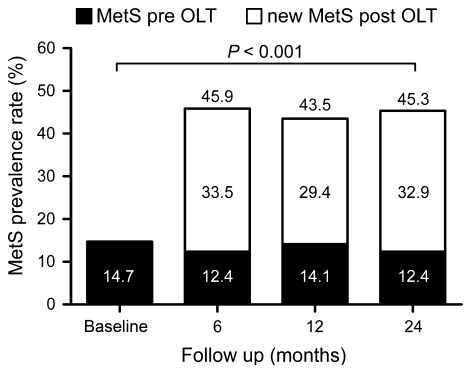

Figure 1 Prevalence of metabolic syndrome (MetS) after orthotopic liver transplantation (OLT). MetS was identified according to the modified adult treatment panel III definitions. Black bars represent MetS prevalence rates at baseline prior to OLT. White bars show MetS incidence rates during follow up after OLT. Numbers, located above the columns, indicate total MetS rates.

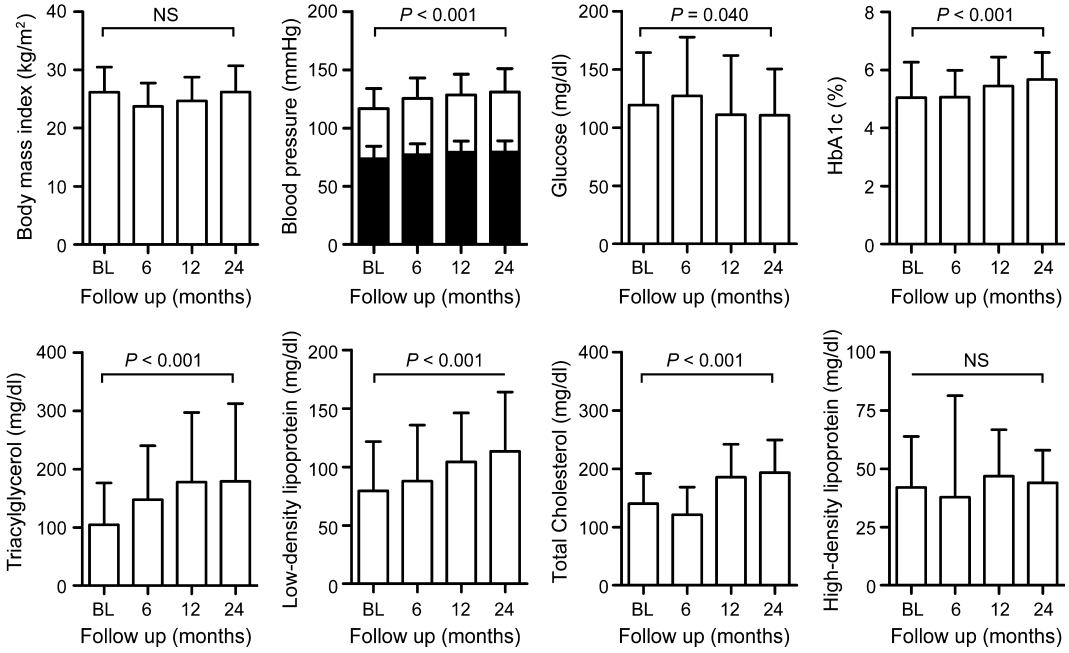

Figure 2 Kinetics of metabolic factors after orthotopic liver transplantation (OLT). Metabolic variables (mean ± SD) were assessed in the entire cohort ($n = 170$) at baseline (BL) and during follow up 6, 12, and 24 months after OLT, respectively. *P* values refer to differences between BL and follow up levels 2 years after OLT. Glucose and lipid levels are derived from serum samples. Glycosylated hemoglobin (HbA1c) was detected in full blood samples. Blood pressure measurements are depicted for systolic (white bars) and diastolic (black bars) values. Statistics as outlined above were performed for systolic blood pressure measurements.

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Table 3. Donor and patient variables. Risk factors were documented at baseline before orthotopic liver transplantation (OLT). *P* values refer to univariate analysis for differences between patients with new onset metabolic syndrome (MetS) versus patients without MetS after OLT. Graft steatosis accounts for the proportion (%) of hepatocytes affected by macrovesicular or mixed steatosis as indicated. Risk factors rates are depicted in absolute numbers and percent in parentheses. Continuous variables are presented in mean values and corresponding SD. OLT indications with a frequency ≤3 were summarized among other indications.

Donor variables	No MetS (n = 88)	MetS (n = 57)	*P*
Age (years)	49.2 ± 17.9	49.9 ± 14.3	0.729
Gender (male/female)	43/45	31/26	0.516
Hypertension	24 (27.9)	15 (26.3)	1.000
Body mass index (kg/m^2)	25.5 ± 3.4	26.1 ± 4.0	0.841
Diabetes mellitus	8 (11.8)	4 (8.3)	0.759
History of alcohol abuse	8 (10.0)	6 (11.8)	0.777
History of smoking	30 (35.7)	17 (32.1)	0.714
Graft steatosis (macro)	6.2 ± 6.0	4.89 ± 4.4	0.332
Mixed graft steatosis (%)	16.6 ± 17.0	16.4 ± 13.7	0.753
Recipient variables			
Age (years)	52.7 ± 11.4	56.8 ± 7.8	0.277
Gender (m/f)	56/32	40/17	0.474
OLT indications			
Alcoholic cirrhosis	17 (19.3)	20 (35.1)	0.033
Hepatitis C	28 (31.8)	15 (26.3)	0.479
Hepatitis B	13 (14.8)	6 (10.5)	0.459
Cryptogenic cirrhosis	5 (5.7)	5 (8.8)	0.515
Primary biliary cirrhosis	6 (6.8)	3 (5.3)	0.705
Hemochromatosis	2 (2.3)	1 (1.8)	1.000
Toxic miscellaneous	5 (5.7)	0 (0.0)	0.157
Hepatocellular carcinoma	4 (4.5)	1 (1.8)	0.648
Primary sclerosing cholangitis	1 (1.1)	3 (5.3)	0.300
Others indications	7 (8.0)	3 (5.3)	0.740
Comorbidities before OLT			
Body mass index (≥30 kg/m^2)	9 (10.2)	13 (22.8)	0.057
Hypertension	7 (8.0)	14 (24.6)	0.008
Diabetes mellitus	14 (15.9)	25 (43.9)	<0.0001
HbA1c (%)	4.6 ± 0.8	5.3 ± 1.2	<0.0001
HbA1c (≥5.0%)	23 (27.7)	34 (63.0)	<0.0001
Dyslipidemia	28 (31.8)	17 (29.8)	0.856
Drug history	8 (9.1)	4 (7.0)	0.765
Nicotin history	30 (34.1)	24 (42.1)	0.381
CMV infection	17 (19.3)	12 (21.1)	0.834

after OLT. A weaker association with MetS after OLT was identified for baseline arterial hypertension. Obesity and alcoholic liver cirrhosis at baseline failed to reach a significant correlation for *de novo* MetS after OLT (Table 5).

Histological features of fatty liver disease after OLT

Mixed vesicular steatosis was observed with a rate of 34.1% (n = 44/129) in patients receiving liver biopsy about 1 year after OLT. Hepatic steatosis was graded into mild, moderate, and severe cases, which accounted for 28 (16.5%), 12 (7.1%), and 5 (2.9%) patients after OLT, respectively. Steatosis was accompanied with steatohepatitis in 5.4% (n = 7/129) among patients with histological follow up. Higher serum-ALT levels (49.5 ± 31.8 vs. 53.2 ± 36.3) were indicative for an active fatty liver disease in these cases. Consistent with a dysregulated lipid metabolism, NAFLD patients showed higher serum-TAG levels (132 ± 66.5 mg/dl vs.197.5 ± 157.4 mg/dl, P = 0.002) and reduced serum HDL concentrations (54.4 ± 23.7 mg/ml vs. 41.1 ± 13.1 mg/dl, P < 0.0001) compared with patients without metabolic deterioration. Elevated uric acid (5.9 ± 2.0 mg/dl vs. 7.4 ± 1.8 mg/dl, P = 0.001) and higher BMI (23.7 ± 3.4 kg/m^2 vs. 25.8 ± 5.7 kg/m^2, P = 0.003) were additional features in patients with NAFLD after OLT.

As the laboratory signatures in patients with NAFLD and MetS were similar in both groups, we searched for a correlation between MetS and NAFLD occurrence post-OLT. During this analysis, we confirmed a link between MetS and hepatic pathology, as NAFLD rates were higher among patients who developed MetS within 1 year (23.0% vs. 50.0%, P = 0.001) or within 2 years (25.4% vs. 45.8%, P = 0.015) after OLT compared with patients without metabolic changes. Following this observation,

Table 4. Immunosuppressive drug regimens. Immunosuppressive regimens were documented within the initial 6 months after orthotopic liver transplantation. Therapeutic serum levels and total daily dosage is given for each immunosuppressive compound. Individual variables represent mean values and corresponding standard deviations.

	n	No MetS	MetS	*P*
Therapeutic serum level (ng/ml)				
Tacrolimus	100	5.4 ± 2.8	5.8 ± 3.0	0.835
Sirolimus	5	6.4 ± 2.4	2.5 ± 1.2	0.400
Cyclosporine A	31	78.3 ± 76.8	82.7 ± 67.8	0.862
Daily dose of therapeutic regimen (mg/day)				
Tacrolimus	99	5.0 ± 3.0	4.9 ± 2.7	0.894
Cyclosporine A	38	193.9 ± 56.6	206.1 ± 77.1	0.745
Sirolimus	6	3.2 ± 1.6	2.3 ± 1.5	1.000
Steroid	108	5.2 ± 2.4	7.1 ± 4.7	0.046

Table 5. Risk factors for new onset of metabolic syndrome. Multivariate analysis of selected risk factors associated with metabolic syndrome after orthotopic liver transplantation. Obesity was defined as body mass index ≥30 kg/m^2. Odds ratio and corresponding 95% confidence interval (CI) was obtained using logistic regression.

	Odds ratio (CI)	*P*
Diabetes mellitus	4.31 (1.69–10.99)	0.002
HbA1c (≥5.0%)	3.5 (1.56–8.13)	0.003
Hypertension	4.59 (1.46–14.49)	0.009
Obesity	2.43 (0.82–7.14)	0.108
Alcoholic cirrhosis	1.57 (0.64–3.89)	0.324

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we further investigated, which MetS components were associated with NAFLD in particular. Univariate analysis identified an association between obesity ($P = 0.001$) and dyslipidemia ($P = 0.001$) with NAFLD after OLT, which was also confirmed in multivariate exploration (Table 6).

Interestingly, analysis did not indicate a link between arterial hypertension and diabetes mellitus with NAFLD development in this cohort. NAFLD was also not associated with diagnosis of hepatitis C at baseline or with confirmed HCV reinfection after OLT, which included 29 cases of HCV-genotype 1 and 10 cases of HCV-genotype 3 infections, respectively.

Whether NAFLD was an indicator of a more severe metabolic imbalance among patients with MetS, was explored using a comparative analysis among MetS patients with or without additional NAFLD. In this respect, patients with MetS and NAFLD showed higher BMI compared with patients without NAFLD (26.7 ± 3.8 kg/m^2 vs. 23.5 ± 3.6 kg/m^2, $P = 0.009$). BMI was further increased in presence of NASH (28.9 ± 2.7 kg/m^2). These differences were eventually mirrored by higher obesity rates among MetS patients in presence of NAFLD (5.3% vs. 36.8%, $P = 0.042$) at end of follow up. Interestingly, the frequency of dyslipidemia, hypertension, and diabetes mellitus, were not significantly affected by NAFLD in MetS patients.

Discussion

Metabolic syndrome is a common long-term complication after OLT, which potentially contributes to cardiovascular morbidity and overall mortality in these patients. Previous studies have identified MetS rates between 19% and 58%, which were dependent on regional MetS prevalence rates of the investigated populations [22–24]. In this retrospective cohort of 170 patients, we were able to confirm new onset of MetS after OLT in 32.9%, leading to a total MetS prevalence of 45.3% after OLT, which is consistent with reports focusing on MetS prevalence rates in European and northern American OLT cohorts [22,25].

Table 6. Factors associated with nonalcoholic fatty liver disease (NAFLD) after orthotopic liver transplantation (OLT). Multivariate analysis of selected risk factors associated with NAFLD after OLT in patients with complete histological assessment ($n = 129$). Obesity was defined as body mass index ≥30 kg/m^2. Dyslipidemia accounts for serum triacylglycerol levels ≥150 mg/dl and high-density lipoprotein concentrations <40 mg/dl for male and <50 mg/dl for female patients, respectively. Odds ratio and corresponding 95% confidence interval (CI) was obtained using logistic regression.

	Odds ratio (CI)	*P*
Dyslipidemia	4.23 (1.35–13.3)	0.013
Obesity	4.67 (1.55–14.1)	0.006
MetS	1.56 (0.63–3.85)	0.335

We found that changes in the lipid metabolism and body weight contributed strongly to MetS after OLT, albeit, a transient reduction in total serum cholesterol, and BMI was observed within the first 6 months after OLT. These finding could be attributed to an enhanced lipid turnover and body fluid recompensation during hepatic recovery, but might also be explained by a postinterventional catabolic phase.

Diabetes mellitus at baseline was confirmed as a risk factor for MetS occurrence using multivariate analysis [23,25]. In addition, we identified a correlation between MetS occurrence and pre-OLT HbA1c levels at an unexpected low threshold of ≥5%. In contrast to our observation, higher HbA1c thresholds of more than 6.5% have been defined in general population to identify diabetes mellitus [26]. We attribute this to an overall reduction in HbA1c levels in this specific patient population showing an enhanced hemoglobin turnover caused by portal hypertension, as HbA1c elimination is coupled to erythrocyte sequestration [27]. Therefore, we propose that HbA1c thresholds should be adjusted for metabolic risk stratification in patients with end-stage liver disease and portal hypertension, but larger prospective trials are mandatory to validate these findings.

Beside this, arterial hypertension at baseline was the only independent predictor for the occurrence of MetS, whereas factors, such as patient age, obesity, and transplant indications, did not correlate with MetS incidence. In this cohort, patients were rarely assigned to have cryptogenic cirrhosis ($n = 13$) or NASH-associated cirrhosis ($n = 1$) at baseline because alcohol-related comorbidity was frequently observed due to a high per capita ethanol consumption in our region [28]. Hence, we speculate that patients with NASH-related liver disease at risk to develop MetS were underestimated in this study.

Steroid doses were associated with occurrence of MetS, indicating that steroid sparing regimens could reduce the risk of MetS after OLT. Early steroid withdrawal lowered MetS rates, but this effect missed significance level. We hypothesize that shortened steroid application did not translate into reduction in cumulative steroid doses, and therefore failed to substantially reduce MetS after OLT. Other immunosuppressive compounds completely missed a correlation with MetS, and we believe that adapted drug regimens following diagnosis of MetS or related findings, such as diabetes, hypertension or dyslipidemia, explain this missing link.

Histological features of fatty liver disease confirmed the relevance of MetS for hepatic pathology after OLT. Given that only a small proportion of liver grafts have shown relevant steatosis during organ donation, a dynamic hepatic

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lipid accumulation could be assumed in patients developing MetS after OLT. A previous report has confirmed the dynamic process of NAFLD recurrence, which nicely parallels the changes in MetS prevalence observed in our cohort over time [18]. In this context, our approach to assess NAFLD 1 year after OLT gives a cross-sectional estimation of NAFLD prevalence, as the majority of recurrent NAFLD manifests within 7–12 months after OLT. Hence, NAFLD rates observed in our cohort match with rates of 33–39% derived from other selected cohorts [18,29]. Screening by liver biopsy also identified mild NAFLD stages, which are usually missed by standard ultrasound screening [30]. Given that mild NAFLD is not associated with relevant morbidity subsequent transition into NASH needs to be evaluated during long-term follow up to identify its clinical relevance after OLT.

In contrast to previous reports, which were focusing on specific OLT-indication subgroups [12,13,18,29], our data reflect NAFLD rates from nonselected OLT patients. This also included patients with recurrent hepatitis C, which are at risk to develop virus-related liver steatosis [31]. However, steatosis rates of about 55% observed during chronic hepatitis C do not match with lower steatosis rates (∼10–30%) observed during the first year of HCV re-infection post-OLT [32,33]. Hence, we speculate that NAFLD rates early after OLT are primarily affected by general accelerators, such as dyslipidemia and obesity.

In conclusion, we were able to identify pre-OLT HbA1c ≥5% as novel indicator to stratify patients awaiting OLT at risk to develop post-OLT MetS. This approach will allow to initiate MetS prevention in risk populations and to adopt the immunosuppressive treatment, particularly by aiming for a fast-dose tapering of steroids after OLT. In addition, we were able to link MetS with NAFLD and could identify dyslipidemia and obesity as indicative factors for NAFLD development within 1 year after OLT. Hence, life style interventions should primarily aim for weight reduction and lipid normalization via increased physical activity or specific medical treatments, respectively.

Authorship

MFS: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript. AW: acquisition, analysis and interpretation of data. NL, HT, SK, MH-L, JS and TZ: acquisition of data. TH: acquisition and interpretation of histological data. PRG, GO: Study concept, providing institutional infrastructure and manuscript revision. MSch: Study concept and design, interpretation of data and manuscript revision.

Funding

The authors have declared no funding.

Acknowledgements

Data presented in this publication are partially derived from the doctoral thesis of N. Lohse and H. Tönissen. We thank Dr. K. Sprinzl for critical reading of this manuscript.

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