

POST-TRANSPLANT METABOLIC SYNDROME (PTMS) AFTER LIVER TRANSPLANTATION — REVIEW OF THE LITERATURE

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Abstract. Liver transplant provides a definitive therapeutic measure for patients with chronic and acute liver diseases. Apart from the improvement of overall health, an organ transplant entails several metabolic complications. They are multi-agent and depend, among others, on the function of organ being transplanted, adverse effects of immunosuppression being applied, organ complications induced by failure of the organ being transplanted, current treatment, concomitant diseases and consequences of the acute and chronic rejection processes. Improvements in surgical techniques, peritransplant intensive care, and immunosuppressive regimens have resulted in significant improvements in short-term survival. Focus has now shifted to address long-term outcomes of liver transplantation. Therefore, this paper presents the current review of literature referring to specificity of the prevalence of metabolic syndrome and its complications in patients after liver transplantation.

Key words: metabolic syndrome, liver transplantation

Introduction

Liver transplantation is a life-saving therapy for patients with end-stage liver disease, acute liver failure, and liver tumors. The liver is currently the second most commonly transplanted major organ after the kidneys. Improvements in surgical techniques, peritransplant intensive care, and immunosuppressive regimens have resulted in significant improvements in short-term survival. Focus has now shifted to address long-term outcomes of liver transplantation.

Cardiovascular events

The liver transplant technique advance allows to treat older and higher risk patients with orthotopic liver transplantation (OLT) with good outcomes. Unfortunately, excessive weight gain, hypertension, hyperlipidemia, and diabetes are frequently observed in transplanted patients. Metabolic syndrome and its individual components

are increasingly being identified and contributing to cardiovascular complications, and late morbidity and mortality. Cardiovascular (CV) complications after OLT are the leading cause of non-graft-related deaths of recipients (Pruthi et al. 2001). Recently published meta-analysis of observational studies by Madhwal et al. showed that the 10-year risk of developing CV complications among patients after OLT was 13.6%, with 64% greater risk of experiencing them than control group. Among OLT recipients, those with metabolic syndrome were approximately 4 time more likely to have a CV event, without any significant increase in all-causes mortality (Madhwal et al. 2012). This 10-year risk of developing a cardiovascular event is consistent with a Framingham moderate- to high-risk category (Grundt et al. 1998), with indication for therapeutic lifestyle changes, although there are no practice guidelines addressing these goals. The metabolic syndrome is also common after kidney transplantation (Faenza et al. 2007) with poor outcomes and reduced graft survival. Multivariate analysis of CV risk factors after OLT showed that independent predictors of CV events were older age at transplantation, male gender, posttransplant diabetes mellitus and arterial hypertension, as well as mycophenolate mofetil (MMF). However, it is important to notice that MMF was used in this study as an adjuvant medication, and this association was indirect, related to an underlying renal insufficiency, caused by calcineurin inhibitors (cyclosporine and tacrolimus, CNI). Concomitant renal dysfunction is well established risk factor of CV events (Balamuthusamy et al. 2008). The cumulative risk of CV event at 5-year was 13,5%, and approximately 10% of patients might expect 1 or more CV events in Albeldawi et al. study. Patients with posttransplant hypertension and diabetes are twice as likely to experience CV event (Albeldawi et al. 2012).

Diabetes mellitus

Detection and management of posttransplant diabetes mellitus should be crucial parts of post-OLT care, because of its impact on graft function/outcome and cardiovascular disease morbidity and mortality. Diabetes is among the main risk factors for coronary heart disease, cerebrovascular disease, and peripheral occlusive arterial disease in transplant recipients. The mean reported incidence of posttransplant diabetes varying between 7% and 30%, and the predictors included a family history of diabetes, age >45 years, glucose intolerance prior to OLT, central obesity, metabolic syndrome, use of corticosteroid over a long period, use of tacrolimus, and hepatitis C (Pageaux et al. 2004). The prevalence of diabetes, hypertension and hyperlipidemia increased steadily from the time of transplant to 7 years after OLT, and the estimated risk for all-cause mortality, and mortality secondary to CV events, infections with multiorgan failure and allograft failure increased for each additional year of diabetes mellitus in Parekh et al. study (Parekh et al. 2012). The study of Hanouneh et al. showed that in the setting of recurrent hepatitis C after liver transplantation, diabetes mellitus and metabolic syndrome were associated with progression of graft fibrosis by univariable analysis, and metabolic syndrome with hyperinsulinemia was independently associated with progression of fibrosis beyond 1 year after OLT in multivariable analysis (Hanouneh et al. 2008). The management of diabetes in liver transplant recipients is not substantially different from its management in nontransplant patients, except that steroid reduction or withdrawal and minimizing doses of calcineurin inhibitor are beneficial (Reuben 2001).

Hyperlipidemia

After liver transplantation in adults, between 16% and 43% of recipients have increased plasma cholesterol levels and about 40% have hypertriglyceridemia. The cause of hyperlipidemia is multifactorial. Calcineurin inhibitors are associated with hypertension, hyperglycemia, and dyslipidemia, via increasing oxidative stress and lipid peroxidation.

Mammalian target of rapamycin (mTOR) inhibitors (i.e. sirolimus and everolimus), a non-nephrotoxic drugs, can also contribute independently to dyslipidemia (Hakeam et al. 2008). Hypercholesterolemia and hypertriglyceridemia secondary to sirolimus therapy are independent from concomitant tacrolimus use. Corticosteroids enhance appetite and food intake contributing to obesity, enhance hepatic secretion of very low-density lipoprotein and its conversion to low-density lipoprotein, and cause diabetes – all of which promote hyperlipidemia. Mycophenolate mofetil (MMF), as well as rarely used now azathioprine, are free from this side-effect.

Metabolic syndrome

The rate of metabolic syndrome in liver transplant recipients is more than twice that reported for the general population. 2/3 of grafted patients will develop metabolic syndrome in 5 years after liver transplantation, and 10-year risk of cardiovascular event in such a patients is 13.6% (Madhwal et al. 2012). Metabolic syndrome appeared to be associated with an increased risk of major vascular events in liver transplant population in Laryea et al. study, affecting 58% of analyzed patients (Laryea et al. 2007). Posttransplant metabolic syndrome (PTMS) was associated with cardiovascular morbidity but not mortality, and it might be predicted by pre-transplantation conditions, i.e. age, pretransplant nonalcoholic fatty liver disease, body mass index (BMI), diabetes mellitus and high triglycerides (Laish et al. 2011). Pretransplant hepatitis C virus infection was also associated with PTMS, because of its relationship to diabetes or insulin resistance (Laish et al. 2011). The rate of metabolic syndrome in liver transplant recipients was more than twice that reported for the general population in this study of Laish et al., however, cardiovascular mortality was lower than in the others papers (Laish et al. 2011). Johnston et al. found that the relative risk of death from cardiovascular disease was 2.56 in transplant recipients relative to an age-matched non-transplant population, and liver grafted patients had 64% higher risk of CV events than control group. Among all transplanted patients, these with PTMS had 4-fold higher risk of this complication (Johnston et al. 2002). As metabolic syndrome is associated with increased risk for major vascular complications, its definition after liver transplantation is based on The US National Cholesterol Education Program Adult Treatment Panel III (2001). The diagnosis requires at least three of the following:

- Central obesity: waist circumference ≥ 102 cm (male), ≥ 88 cm (female),
- Dyslipidemia: Triglycerides (TG) ≥ 1.7 mmol/L (150 mg/dl),
- Dyslipidemia: HDL-Cholesterol < 40 mg/dL (< 1 mmol/L) in men, < 50 mg/dL (< 1.3 mmol/L) in women,
- Blood pressure $\geq 130/85$ mmHg (or treated for hypertension),
- Fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dl) (NCEP 2001).

Even 44,5% [16] to 58% (Hanouneh et al. 2008) transplant recipients might be affected with PTMS, and patients with metabolic syndrome had a significantly higher average age, BMI post-OLT, fasting glucose, high-density lipoprotein levels, and serum triglycerides (Laryea et al. 2007). The novel study of Sprinzel et al. showed that de novo metabolic syndrome affected 32.9% of analyzed population within 2 years after OLT (Sprinzel et al. 2013). The component of PTMS, i.e. hypertension, hyperlipidemia, high glucose, enlarged waist circumference and insulin resistance was seen in 53%, 51%, 37%, 32% and 41% of patients, respectively. The prevalence of metabolic syndrome after liver transplantation was found to be significantly higher than that estimated in the general population and PTMS appeared to be associated with an increased risk of major vascular events after OLT (Laryea et al. 2007). The rates of hypertension, dyslipidemia, and diabetes were also more common in pediatric liver transplant recipients than in general children population, and these conditions might lead to significant long-term

morbidity (Rothbaum et al. 2012). Metabolic syndrome was also an important risk factor for graft failure, especially secondary to hepatitis C recurrence, malignancy, infections and renal failure in liver transplant recipients (Charlton 2009). On the other hand, patients who developed chronic kidney disease after OLT, were a 4-fold increased risk of death (Tinti et al. 2012), and hypertension, and dyslipidemia were associated with a faster rate of decline in renal function after OLT (Leithead et al. 2012).

Strategies to reduce the development of PTMS after liver transplantation should include lifestyle modifications involving alterations in diet and increased physical activity. Mediterranean diet rich in omega-3 fatty acids, fruit, vegetables, and dietary fiber, is recommended. Additional measures that may be potentially beneficial include also the optimal control of blood glucose, and the use of tacrolimus instead of cyclosporine (Pagadala et al. 2009).

Weight

Disorders related to PTMS are frequent in patients after liver transplantation, and are related to both pre-OLT conditions and to weight gain. The pretransplant risk factors include a higher age at OLT, male gender, a history of smoking, the pretransplant BMI, pretransplant diabetes, the etiology of the underlying disease (hepatitis C, NAFLD/cryptogenic cirrhosis, alcohol), as well as an increased donor BMI, and marital status (Pagadala et al. 2009). Weight control, due to its association with insulin resistance, seems to be mandatory after OLT to prevent risk factors of premature atherosclerosis (Bianchi et al. 2008). In the study of Wawrzynowicz-Syczewska et al. mean weight gain and BMI change were the highest within the first six months after OLTx and men gained more weight than women, especially in the first half-year after OLTx. The only clear predictive factor of overweight and obesity was the baseline weight; dietary mistakes and lack of physical activity might play a major role in the weight increase after OLT (Wawrzynowicz-Syczewska et al. 2009). The impact of metabolic changes on PTMS development after liver transplantation is showed in Table 1.

Table 1. The metabolic changes in PTMS development

Feature	Role
Hepatic steatosis	Increased absolute hepatic free fatty acids (FFA) uptake, increased esterification of hepatic FFA to from triglycerides (TG), increased FFA synthesis from cytosolic substrates
Decreased apoB-100 synthesis	Decreased export of FFA and TG from the liver
Decreased hydrolysis of TG	Diminished hepatic TG and FFA export
Increased oxidative stress	Increased beta oxidation of mitochondrial long-chain fatty acids
Mitochondrial dysfunction	
Increased leptin and decreased adiponectin circulation	
Tumor necrosis factor alpha	Down-regulation of insulin-induced phosphorylation of insulin-receptor substrate-1 Reduction of the expression of the insulin-dependent glucose-transport molecule Glut 4
Genetic polymorphism of adiponutrin or patatin-like phospholipase domain containing protein 3 (PNPLA3)	Fatty liver development with advanced fibrosis

Arterial hypertension

Arterial hypertension is one of the most frequent complications of solid organ transplantation; about 70–90% of transplanted patients have high blood pressure or require antihypertensive therapy. Hypertension was observed during the first weeks to months in 50% to 75% of the liver transplant recipients, and more than 50% of them

developed hypertension by 1 year. Abnormal blood pressure is a potent non-immunological risk factor directly related to patient and graft survival. In liver and heart transplantation, hypertension is mainly due to impaired kidney function, profound by the use of CNI (Textor et al. 2000). The number of patients with hypertension rises as well as the severity of the disease with time after OLT. Within 10 years of follow up, the percentage of all OLT recipients on a double or triple antihypertensive drug regimen almost double from 12% to 23% (Guckelberger 2009). Steroids medication should be minimized or completely withdrawn, and the conversion of a calcineurin-based regimen to mycophenolate or sirolimus-based immunosuppression may be considered (Mells and Neuberger 2009). However, only MMF is a drug free of metabolic side effects, but monotherapy with MMF is not recommended due to increased risk of graft rejection.

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a common form of chronic liver disease, progressing to advanced fibrosis in about 30% of patients. According to the 2011 United Network for Organ Sharing registry database for liver transplant recipients, NAFLD is the fourth most common cause of OLT, due to rising prevalence of obesity and diabetes mellitus. NAFLD in the posttransplant setting may represent either recurrent or the novo disease (Lim et al. 2007; Seo et al. 2007). *De novo* fatty liver occurs in ~20%, and *de novo* steatohepatitis in ~10%. However, studies providing detailed histological criteria, have found that the recurrent steatosis is often mild (<50%) and usually develops within a period of 6 months, whereas >50% steatosis is seen after 1 year after OLT. Steatohepatitis after OLT is almost always preceded by steatosis, however, progression is seen in minority of patients (Contos et al. 2001). The rate of steatosis and steatohepatitis were 20% and 32%, respectively, and fibrosis developed in 2 of 5 patients with posttransplant nonalcoholic steatohepatitis (NASH), and it was not seen in patients without posttransplant steatosis (Ong et al. 2001). Patil and Yerian in 2012 showed that NAFLD recurrence was common, advanced fibrosis was rare, and graft and patients survival rates were comparable to the other indication to OLT (Patil and Yerian 2012). However, NAFLD patients are in increased risk for postoperative cardiovascular events, independently of traditional cardiac risk factors (Vanwagner et al. 2012). Treatment should be directed at managing obesity and complication of metabolic syndrome, with steroid minimization in immunosuppression (Charlton 2009). However, it is important to notice that recurrent NAFLD and NASH can occur despite normal liver enzymes, and features of metabolic syndrome, as associated with disease recurrence, should point to such a possibility (Malik et al. 2009). The frequencies of PTMS components are summarized in Table 2.

Table 2. The frequency of metabolic syndrome and its feature before and after OLT (%)

Feature	Frequency before OLT	Frequency after OLT
Diabetes mellitus	15	30–40
Arterial hypertension	15	60–70
Obesity	*	~60
Hyperlipidemia	unusual	50–70
PTMS	unusual	44–58
Frank steatohepatitis	*	60

* No clear data available.

Immunosuppressive therapy

Immunosuppressive agents may contribute to increased CV complications risk, e.g. cyclosporine is associated with new-onset hypertension and dyslipidemia, tacrolimus leads to posttransplant diabetes mellitus and, to a lesser extent, to hypertension and dyslipidemia, and sirolimus accelerates hypercholesterolemia and hypertriglyceridemia. Mycophenolate mofetil in general has a better safety profile with respect to metabolic risk, whereas corticosteroids induce hypertension, insulin resistance, hypercholesterolemia and weight gain (Miller 2002). Calcineurin inhibitors induce hypertension causing changes in vascular tone, particularly in the kidney, leading to diminished glomerular filtration and enhanced sodium retention. Disturbances of endothelial function stimulate of endothelin and impair nitric oxide synthesis. Increased vasoconstriction leads to arterial hypertension, with its complication, including disturbances in circadian rhythm, left ventricular hypertrophy, and acceleration of atherosclerotic and renal injury (Textor et al. 2000; Hryniewiecka et al. 2011). These give the possibility for early intervention with modification of immunosuppressive regimens and early initiation of statins, as showed by Soveri et al. and Charlton (Charlton 2009; Soveri et al. 2009). Additional measures that may potentially beneficial include also the optimal control of blood glucose, and the use of tacrolimus instead of cyclosporine (Pagadala et al. 2009). Cyclosporine increases circulation levels of low-density lipoprotein, and tacrolimus appears less likely to cause hypercholesterolemia (Reuben 2001). Data regarding the impact of immunosuppressive agents on metabolic syndrome are summarized in Table 3.

Table 3. The impact of commonly used medication after OLT on PTMS development

Agent	Effect
Calcineurin inhibitors (cyclosporine, tacrolimus)	mitochondrial inhibition impaired beta cell insulin production dyslipidaemia hypertension renal insufficiency
Corticosteroids	insulin resistance hypertension dyslipidaemia
mTOR inhibitors (sirolimus)	dyslipidaemia

Physical activity

One of the important elements of positive health preservation is to take up physical activity, being also a preventive measure with respect to many diseases: ischaemic heart disease, arterial hypertension, diabetes mellitus, lipid disorders, osteoporosis, overweight or obesity. Physical activity is a useful prophylactic tool of both mental and physical health, reducing number of cardiovascular events, risk of arterial hypertension, diabetes mellitus, dyslipidemia, osteoporosis and weight gain. However, the number of studies regarding physical activity and metabolic syndrome is scanty. Reduced aerobic capacity (decreased peak oxygen consumption [VO_2] during symptom-limited cardiopulmonary exercise testing) is frequently present in cirrhosis and peak VO_2 during cardiopulmonary exercise testing may predict short-term outcome after hepatic transplantation. The study of Epstein et al. showed that 6 patients (10.2% of analyzed cohort), who died within 100 days of liver transplantation, had reduced aerobic capacity (peak VO_2 <60% predicted and VO_2 at anaerobic threshold [VO_2 -AT] <50% predicted

peak VO_2) compared to survivors. Using a multiple logistic regression model controlling for duration and severity of liver disease and time to transplantation, reduced aerobic capacity was independently associated with 100-day mortality, and reduced aerobic capacity during cardiopulmonary exercise testing was associated with decreased short-term survival after hepatic transplantation (Epstein et al. 2004).

Exercise training resulted in significant improvements on the physical condition of liver transplanted Familial Amyloidotic Polyneuropathy (FAP) patients in Tomas et al. study (Tomas et al. 2013). The exercise training program improved body composition, isometric quadriceps muscle strength, functional capacity, fatigue, and levels of physical activity before and after a 6-month period of combined exercise training in FAP female patient (49 years of age; body mass index = 18.8 kg/m²), who underwent a liver transplantation 133 months before assessment, with improvement of quality of life (Tomas et al. 2011). On the other hand, pediatric kidney and liver transplant recipients have significantly reduced cardiorespiratory fitness (CRF), muscle strength, and physical activity and approximately 44% of both groups had percent fat greater than the upper criterion value of the Healthy Fitness Zone (HFZ) (Krasnoff et al. 2006).

Conclusion

The survival rates after liver transplantation have improved in recent decades, but cardiovascular disease has become a source of major concern in long term follow up. The rate of metabolic syndrome in liver transplant recipient is more than twice that reported for the general population, and significant independent predictors of PTMS are age, pretransplant nonalcoholic fatty liver disease, BMI, diabetes mellitus and triglycerides. PTMS is associated with the higher risk of CV events. The number of cardiovascular events correlate well with the increased prevalence of cardiovascular risk factors. Up to 20% of all deaths of long-term survivors after OLT have been attributed to cardiovascular disease, giving the reason for PTMS screening and management. Lifestyle changes, e.g. diet, weight control, treatment of comorbidities and regularly taken up physical activity is one of the effective types of metabolic syndrome treatment.

References

- Albeldawi M., Aggarwal A., Madhwal S., Cywinski J., Lopez R., Eghtesad B., Zein N.N. Cumulative risk of cardiovascular events after orthotopic liver transplantation. *Liver Transpl.* 2012; 18: 370–375.
- Balamuthusamy S., Srinivasan L., Verma M., Adigopula S., Jalandhara N., Hathiwala S., Smith E. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. *Am Heart J.* 2008; 155: 791–805.
- Bianchi G., Marchesini G., Marzocchi R., Pinna A.D., Zoli M. Metabolic syndrome in liver transplantation: relation to etiology and immunosuppression. *Liver Transpl.* 2008; 14: 1648–1654.
- Charlton M. Obesity, hyperlipidemia, and metabolic syndrome. *Liver Transpl.* 2009; 15 Suppl 2: 83–89.
- Contos M.J., Cales W., Sterling R.K., Luketic V.A., Shiffman M.L., Mills A.S., Fisher R.A., Ham J., Sanyal A.J. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl.* 2001; 7: 363–373.
- Epstein S.K., Freeman R.B., Khayat A., Unterborn J.N., Pratt D.S., Kaplan M.M. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. *Liver Transpl.* 2004; 10: 418–424.
- Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* 2001; 285: 2486–2497.
- Faenza A., Fuga G., Nardo B., Donati G., Cianciolo G., Scolari M.P., Stefoni S. Metabolic syndrome after kidney transplantation. *Transplant Proc.* 2007; 39: 1843–1846.

- Grundy S.M., Balady G.J., Criqui M.H., Fletcher G., Greenland P., Hiratzka L.F., Houston-Miller N., Kris-Etherton P., Krumholz H.M., LaRosa J., Ockene I.S., Pearson T.A., Reed J., Washington R., Smith S.C., Jr. Primary prevention of coronary heart disease: guidance from Framingham: a statement for healthcare professionals from the AHA Task Force on Risk Reduction. *American Heart Association. Circulation.* 1998; 97: 1876–1887.
- Guckelberger O. Long-term medical comorbidities and their management: hypertension/cardiovascular disease. *Liver Transpl.* 2009; 15 Suppl 2: 75–78.
- Hakeam H.A., Al-Jedai A.H., Raza S.M., Hamawi K. Sirolimus induced dyslipidemia in tacrolimus based vs. tacrolimus free immunosuppressive regimens in renal transplant recipients. *Ann Transplant.* 2008; 13: 46–53.
- Hanouneh I.A., Feldstein A.E., McCullough A.J., Miller C., Aucejo F., Yerian L., Lopez R., Zein N.N. The significance of metabolic syndrome in the setting of recurrent hepatitis C after liver transplantation. *Liver Transpl.* 2008; 14: 1287–1293.
- Hryniewiecka E., Zegarska J., Paczek L. Arterial hypertension in liver transplant recipients. *Transplant Proc.* 2011; 43: 3029–3034.
- Johnston S.D., Morris J.K., Cramb R., Gunson B.K., Neuberger J. Cardiovascular morbidity and mortality after orthotopic liver transplantation. *Transplantation.* 2002; 73: 901–906.
- Krasnoff J.B., Mathias R., Rosenthal P., Painter P.L. The comprehensive assessment of physical fitness in children following kidney and liver transplantation. *Transplantation.* 2006; 82: 211–217.
- Laish I., Braun M., Mor E., Sulkes J., Harif Y., Ben A.Z. Metabolic syndrome in liver transplant recipients: prevalence, risk factors, and association with cardiovascular events. *Liver Transpl.* 2011; 17: 15–22.
- Laryea M., Watt K.D., Molinari M., Walsh M.J., McAlister V.C., Marotta P.J., Nashan B., Peltekian K.M. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. *Liver Transpl.* 2007; 13: 1109–1114.
- Leithead J.A., Ferguson J.W., Hayes P.C. Modifiable patient factors are associated with the late decline in renal function following liver transplantation. *Clin Transplant.* 2012; 26: E316–E323.
- Lim L.G., Cheng C.L., Wee A., Lim S.G., Lee Y.M., Sutudja D.S., Da C.M., Prabhakaran K., Wai C.T. Prevalence and clinical associations of posttransplant fatty liver disease. *Liver Int.* 2007; 27: 76–80.
- Madhwal S., Atreja A., Albeldawi M., Lopez R., Post A., Costa M.A. Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. *Liver Transpl.* 2012; 18: 1140–1146.
- Malik S.M., Devera M.E., Fontes P., Shaikh O., Sasatomi E., Ahmad J. Recurrent disease following liver transplantation for nonalcoholic steatohepatitis cirrhosis. *Liver Transpl.* 2009; 15: 1843–1851.
- Mells G., Neuberger J. Long-term care of the liver allograft recipient. *Semin Liver Dis.* 2009; 29: 102–120.
- Miller L.W. Cardiovascular toxicities of immunosuppressive agents. *Am J Transplant.* 2002; 2: 807–818.
- Ong J., Younossi Z.M., Reddy V., Price L.L., Gramlich T., Mayes J., Boparai N. Cryptogenic cirrhosis and posttransplantation nonalcoholic fatty liver disease. *Liver Transpl.* 2001; 7: 797–801.
- Pagadala M., Dasarathy S., Egtesad B., McCullough A.J. Posttransplant metabolic syndrome: an epidemic waiting to happen. *Liver Transpl.* 2009; 15: 1662–1670.
- Pageaux G.P., Calmus Y., Boillot O., Ducerf C., Vanlemmens C., Boudjema K., Samuel D. Steroid withdrawal at day 14 after liver transplantation: a double-blind, placebo-controlled study. *Liver Transpl.* 2004; 10: 1454–1460.
- Parekh J., Corley D.A., Feng S. Diabetes, hypertension and hyperlipidemia: prevalence over time and impact on long-term survival after liver transplantation. *Am J Transplant.* 2012; 12: 2181–2187.
- Patil D.T., Yerian L.M. Evolution of nonalcoholic fatty liver disease recurrence after liver transplantation. *Liver Transpl.* 2012; 18: 1147–1153.
- Pruthi J., Medkiff K.A., Esrason K.T., Donovan J.A., Yoshida E.M., Erb S.R., Steinbrecher U.P., Fong T.L. Analysis of causes of death in liver transplant recipients who survived more than 3 years. *Liver Transpl.* 2001; 7: 811–815.
- Reuben A. Long-term management of the liver transplant patient: diabetes, hyperlipidemia, and obesity. *Liver Transpl.* 2001; 7: S13–S21.
- Rothbaum P.E., Lau A., Rhee S., Roberts J.P., Rosenthal P. Posttransplant metabolic syndrome in children and adolescents after liver transplantation: a systematic review. *Liver Transpl.* 2012; 18: 1009–1028.
- Seo S., Maganti K., Khehra M., Ramsamooj R., Tsodikov A., Bowlus C., McVicar J., Zern M., Torok N. De novo nonalcoholic fatty liver disease after liver transplantation. *Liver Transpl.* 2007; 13: 844–847.
- Soveri I., Abedini S., Holdaas H., Jardine A., Eriksson N., Fellstrom B. Metabolic syndrome and cardiovascular risk in renal transplant recipients: effects of statin treatment. *Clin Transplant.* 2009; 23: 914–920.

- Sprinzl M.F., Weinmann A., Lohse N., Tonissen H., Koch S., Schattenberg J., Hoppe-Lotichius M., Zimmermann T., Galle P.R., Hansen T., Otto G, Schuchmann M. Metabolic syndrome and its association with fatty liver disease after orthotopic liver transplantation. *Transpl Int.* 2013; 26: 67–74.
- Textor S.C., Taler S.J., Canzanello V.J., Schwartz L., Augustine J.E. Posttransplantation hypertension related to calcineurin inhibitors. *Liver Transpl.* 2000; 6: 521–530.
- Tinti F., Mitterhofer A.P., Muiesan P. Liver transplantation: role of immunosuppression, renal dysfunction and cardiovascular risk factors. *Minerva Chir.* 2012; 67: 1–13.
- Tomas M.T., Santa-Clara H., Bruno P.M., Monteiro E., Carrolo M., Barroso E., Sardinha L.B., Fernhall B. The Impact of Exercise Training on Liver Transplanted Familial Amyloidotic Polyneuropathy (FAP) Patients. *Transplantation.* 2013; 95: 372–377.
- Tomas M.T., Santa-Clara H., Monteiro E., Barroso E., Sardinha L.B. Effects of an exercise training program in physical condition after liver transplantation in familial amyloidotic polyneuropathy: a case report. *Transplant Proc.* 2011; 43: 257–258.
- Vanwagner L.B., Bhawe M., Te H.S., Feinglass J., Alvarez L., Rinella M.E. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. *Hepatology.* 2012; 56: 1741–1750.
- Wawrzynowicz-Syczewska M., Karpinska E., Jurczyk K., Laurans L., Boron-Kaczmarek A. Risk factors and dynamics of weight gain in patients after liver transplantation. *Ann Transplant.* 2009; 14: 45–50.

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