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DYSLIPIDEMIA IN LIVER TRANSPLANT RECIPIENTS

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Liver transplant is known to be the only radical treatment for patients with end-stage liver diseases. It is known that cardiovascular diseases rank third among patients, who underwent liver transplant. Due to the current generally accepted policy of aggressive treatment of hypercholesterolemia, mortality from cardiovascular diseases has been significantly reduced in general population. Statin therapy has also demonstrated a decreasing effect on mortality among patients with chronic liver failure. Recently published research results have shown the increasing occurrence of non-communicable diseases among liver recipients, including diseases that determine cardiovascular mortality (arterial hypertension, chronic coronary syndrome, chronic heart failure, chronic kidney failure). This evidence demonstrates that in post-operative period doctors should do their best to identify not only traditional risk factors of acute transplant rejection, but also pay attention to cardiovascular risks and their timely treatment. Based on the data about a number of differences in the incidence of cardiovascular risk factors and on the specifics of confirmation and treatment of chronic coronary heart disease in liver transplant recipients in comparison with the general population, we believe that in transplant centers it is necessary to develop a specialized algorithm of dispensary follow-up of recipients (checklist) for adequate prevention of diseases of the circulatory system.

Introduction

At present, liver transplantation is the only radical method of treating patients with chronic end-stage liver diseases (CESLD). According to the clinical protocol, besides CESLD, indications for liver transplantation are a life expectancy of less than 12 months, the absence of other treatment methods, as well as the presence of chronic liver disease that significantly reduces the quality of life and working capacity of the patient, or progressive liver disease with a life expectancy shorter than in the case of liver transplantation [1]. According to the recommendations of EASL (European Association for the Study of the Liver), liver transplantation can be performed on any patient with end-stage liver damage, whose life it will prolong or improve its quality [2].

In 1 year after liver transplantation, the proportion of surviving recipients varies from 80% to 90%, and after 5 years it is 75%, which is comparable to the results of the Minsk Scientific and Practical Center for Surgery, Transplantation and Hematology: the number of surviving recipients of a liver transplant 5 years after surgery is 78% [3]. Thus, the life expectancy of liver transplant recipients is high, and among the causes of their death, according to transplant centers, chronic non-communicable diseases, in particular cardiovascular pathology, malignant neoplasms, chronic kidney disease, diabetes mellitus, come to the top after rejection and infectious complications. According to foreign sources, the proportion of deaths due to cancer, cardiovascular diseases, and kidney failure 1 year after liver transplantation is respectively 22%, 11%, and 6% [2]. Improved management tactics of liver transplant recipients in the long-term postoperative period, timely detection of diseases of the circulatory system and risk factors for their development can significantly contribute to better health outcomes.

It is known that among the causes of late mortality of patients who underwent liver transplantation, cardiovascular diseases occupy the third place [4]. Long-term use of immunosuppressive drugs in the post-transplant period, on the one hand, increases the life expectancy of patients, and on the other hand, it leads to the development of undesirable systemic and metabolic complications, including hypertension, hyperlipidemia, obesity and diabetes mellitus [5]. Thus, the administration of Tacrolimus leads to hypercholesterolemia in 44-55% of patients [6, 7]. Glucocorticosteroids, by increasing the activity of acetyl-CoA carboxylase, free fatty acid synthetase and HMG-CoA reductase, contribute to an increase in the level of atherogenic low-density lipoproteins, total cholesterol, triglycerides and reduce the level of high-density lipoproteins [8]. Cyclosporine, preventing the conversion of cholesterol into fatty acid salts and reducing the activity of lipoprotein lipase, causes hypercholesterolemia in 30% of patients and hypertriglyceridemia in 33% [9].

It is important to note that increased blood lipid levels are not characteristic of the patients with end-stage chronic liver failure. Moreover, there is a decrease in the level of total cholesterol due to a decreased synthetic function of the liver [5]. In everyday clinical practice, this usually leads to a lack of vigilance of specialist doctors regarding the correction of the lipid spectrum in the post-transplant period, which in turn accelerates the development of atherosclerosis and increases the risk of cardiovascular complications.

By now, there have been published scientific research data indicating that the use of statins by patients after liver transplantation is associated with decreased overall mortality [10]. At the same

time, the information that taking statins is safe after liver transplantation and is not associated with hepatotoxicity is quite contradictory [11]. Moreover, statins are used insufficiently in patients after liver transplantation, even if they are indicated for dyslipidemia that has already developed in the postoperative period or for a previously existing cardiovascular disease [12].

Despite the possibility of developing side effects in response to statins, in a prospective single-center cohort study conducted from 2011 to 2019 on the basis of Minsk Scientific and Practical Center for Surgery, Transplantation and Hematology, only a small number out of 510 liver transplant recipients developed significant side effects. Statin therapy was discontinued in 153 patients (30%). Of these, 82 patients (16%) stopped using Rosuvastatin temporarily, 15 (3%) patients stopped taking medications due to incompliance without reports of side effects. 62 patients (12%) had side effects associated with taking statins, the most frequent of which 30 (6%) were complications related to the muscular system (muscle weakness accompanied by increased creatine phosphokinase (CPK)). It should be noted that a slightly increased level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) was observed in liver transplant recipients who started statin therapy 3 months after surgery, which persisted during the first year, but these changes did not demonstrate statistical significance. None of the patients included in the study developed liver failure provoked by statin medication. The data obtained allow us to consider the administration of lipid-lowering therapy to liver transplant recipients to be a safe and effective method of medical prevention of atherosclerosis, which justifies the possibility of this therapy regimen in this group of patients in order to improve the long-term prognosis of survival [3, 24].

It should be remembered that dyslipidemia is a modifiable risk factor. Due to the current generally accepted policy of aggressive treatment of hypercholesterolemia, mortality from cardiovascular diseases has been significantly reduced in the general population [13]. Statin therapy has also demonstrated reduced mortality in patients with chronic liver failure. In patients with decompensated cirrhosis of the liver, statin administration was not associated with worsening liver failure (acute bleeding from varicose veins, ascites, spontaneous bacterial peritonitis, a new episode of hepatic encephalopathy). Nevertheless, in the dominant majority of clinical cases, the administration of statins to patients with chronic liver failure raises concerns about hepatotoxicity [14]. Indeed, in the literature you can find reports of acute liver failure that developed against the background of statin medication. These evidences are rare, as are cases of liver transplantation caused by taking this group of drugs: among 1,198 patients with acute liver failure included in a prospective study in the USA from 1998 to 2007, 133 cases were caused by taking medications, of which only 6 were caused by taking statins [15].

The insufficient administration of statins to patients after liver transplantation is also explained by the fact that after surgery, patients are almost always under the supervision of gastroenterologists, whose attention is mainly focused on maintaining adequate liver function. In this regard, there is an underestimation of cardiovascular risk and metabolic changes that require therapeutic intervention.

The AASLD (American Association for the Study of Liver Diseases) recommends measuring the level of lipids in the blood of healthy liver transplant recipients. An increase in LDL levels > 2.5 mmol/l with or without hypertriglyceridemia requires initiation of therapy with hypolipidemic drugs. If lifestyle modification and diet are ineffective, the administration of statins with the co-prescription of Ezetimibe is recommended. Despite the fact that the AASLD does not make recommendations regarding the choice of a specific statin that would be safer or more effective for liver-transplanted patients, Pravastatin is the most studied and used in patients who have undergone organ transplantation, because it is not metabolized through the cytochrome P-450 system and does not interact with immunosuppressors, unlike other statins. The EASL recommends the use of hydrophilic statins (Pravastatin and Lovastatin) for the above reasons as well as the application of the QRISK2 scale to identify patients at high risk of developing cardiovascular diseases. Besides, they note that standard scales for assessing cardiovascular risks underestimate them in those groups where there is an additional risk due to concomitant disease or treatment (autoimmune diseases, corticosteroid therapy or immunosuppressive drugs) [2, 16].

It is worth noting that cardiovascular diseases detected in the preoperative period remain with liver transplant recipients in the postoperative period and their course worsens due to the side effects of immunosuppressive drugs. Thus, initiation of lipid-lowering therapy for the prevention of cardiovascular diseases can improve both short-term and long-term outcomes in liver transplant recipients in a high-risk group. Statins, due to their pleiotropic effects, not only improve liver function, but also have a beneficial effect on the lipid spectrum, contribute to the reduction of fibrogenesis, portal hypertension, decrease the likelihood of liver cirrhosis, hepatocellular carcinoma, severe intraoperative complications, including ischemic and reperfusion injury. The probable mechanism influencing the above factors is the elimination of endothelial dysfunction in the microcirculatory system of the liver and reduced inflammation [17, 18].

Caution should be exercised when prescribing statins to patients receiving immunosuppressive therapy. Liver transplant recipients receiving cyclosporine or tacrolimus have increased statin levels due to secondary inhibition of the cytochrome P-450 enzyme, which in turn increases the risk of myositis and rhabdomyolysis [17, 19]. Thus, it is advisable to prescribe low doses of statins to this category of patients.

All patients on immunosuppressive therapy should start statin therapy with the minimum effective doses and gradually titrate the dose, carefully monitoring the appearance of side effects. If the use of hypolipidemic drugs is ineffective, it is recommended to consider making changes to immunosuppressive therapy or using new innovative methods of treatment in order to influence the lipid spectrum. The change of cyclosporine to Tacrolimus in liver transplant recipients with dyslipidemia leads to a decrease in total cholesterol without provoking rejection reactions [19, 23]. Withdrawal of prednisone at the earliest possible time after liver transplantation also reduces hypercholesterolemia [20]. In patients suffering from severe dyslipidemia, the prescription of Sirolimus should be avoided due to its hyperlipidemic effect [6].

In a retrospective cohort study, Lovastatin did not show an increased risk of adverse effects from the hepatic system in 93 out of 106 patients with liver damage. Another prospective, randomized, double-blind, placebo-controlled, multicenter study demonstrated that the administration of Pravastatin in high dosages in patients with liver diseases is safe. After 36 weeks of treatment, ALT levels in patients from the group taking Pravastatin were lower than in patients from the control group [21]. In most cases, the benefits of statins exceeded the potential risks of their administration [22].

The implementation of the results of scientific research, the success of transplant surgery, the creation of effective modern drugs for immunosuppressive therapy have allowed increasing the survival rate of liver transplant recipients in the long-term postoperative period. As a result of a significant decrease in mortality rates, their absolute number in our country has increased to 540 people within ten years since 2008. The incidence of coronary heart disease (CHD) in liver transplant recipients 5 years after the intervention reaches 42%, according to a prospective single-center cohort study conducted from 2011 to 2019 on the basis of Minsk Scientific and Practical Center for Surgery, Transplantation and Hematology. Taking into account the above, improving the management tactics of liver transplant recipients in the long-term postoperative period, timely detection of circulatory system diseases and risk factors for their development, correction of arterial hypertension and dyslipidemia using innovative facilities of modern cardiology are urgent tasks of the healthcare system that require scientific research aimed at determining an effective and safe method of medical prevention of coronary heart disease and its complications.

The results of scientific studies published in the open press in recent years indicate an increased incidence of chronic non-communicable diseases in liver transplant recipients, including conditions that determine cardiovascular mortality (arterial hypertension, coronary heart disease, chronic heart failure, chronic kidney disease) [24]. This substantiates the conclusions that in the postoperative period, practitioners should make efforts to identify not only traditional risk factors for acute transplant rejection, but also cardiovascular risk factors for their timely correction.

The scientific literature describes the specific features of the diagnosis and treatment of cardiovascular pathology in liver transplant recipients. For example, pharmacotherapy of arterial hypertension and dyslipidemia in this category of patients should be carried out taking into account the unfavorable interaction of immunosuppressors prescribed to almost all patients from the group of calcineurin inhibitors with non-dihydropyridine calcium antagonists (Diltiazem, Verapamil), since they increase the level of both cyclosporine and tacrolimus [24]. The same enzyme participates in the metabolism of most statins as in the metabolism of calcineurin inhibitors, namely CYP3A4; this increases the risk of statin-associated myopathy and other toxic effects, which requires careful clinical and laboratory monitoring. Pravastatin and Fluvastatin are not metabolized by the enzyme CYP3A4, so they are preferred in many transplant centers. These medicines are not registered on the territory of the Republic of Belarus and cannot be used to correct dyslipidemia in liver transplant recipients. This entails the need to develop new methods of medical prevention of diseases associated with atherosclerosis, the prevalence of which in the cohort of transplanted patients increases annually. Herewith, the innovative achievements of modern cardiology, the capabilities of the national health system and the availability of lipid-lowering drugs must be taken into account.

Conclusion

The currently known patterns of the pathogenesis and course of chronic non-infectious diseases in liver transplant recipients are important to consider when developing individual preventive programs to reduce the risk of circulatory system diseases, both in primary prevention and in the case of treatment of existing conditions, the incidence of which increases with increasing period after transplantation and the age of recipients (secondary prevention).

The possibility of contacting the attending physician of the transplant center in case of any deterioration of the condition is a generally accepted rule for monitoring liver transplant recipients in the long-term postoperative period. On the other hand, real clinical practice has shown that recipients, especially from areas remote from the republican center, still quite often visit outpatient clinics at their place of residence for symptoms of various diseases (increased blood pressure (BP), shortness of breath, rhythm disturbances, pain syndrome of various genesis). At the same time, in the primary documentation of a number of regions studied by us, despite the active visits of many patients to the district general practitioner, data on body mass index, blood pressure dynamics and glomerular filtration rate, waist circumference, smoking, lipid profile are extremely rare, cardiovascular disease is not always adequately veri-

fied, detailed formulations of the diagnoses are often lacking. As part of a retrospective study, it can be assumed that in addition to an increased number of cardiovascular risk factors, the cause of a significant increase in the incidence of coronary heart diseases is the inadequate diagnosis of cardiovascular pathology in patients with severe liver damage before transplantation.

Extreme restriction of physical activity of patients before transplantation masks the clinical manifestations of reduced coronary reserve, even in conditions of atherosclerotic lesions of coronary vessels. In addition, attention is drawn to the almost complete non-use of CHD verification methods, which gives scientific and practical relevance for planning a prospective study of the prevalence of this pathology among liver transplant recipients with the introduction of a "roadmap" of screening and in-depth examination, as well as the development and implementation of a method of medical prevention of coronary heart disease in the long-term postoperative period. In connection with the above, it seems appropriate to focus the attention of internists on the targeted detection of dyslipidemia in patients after liver transplantation. Considering that the main share of comorbidity among liver-transplanted individuals is hypertension (65%), special attention in daily clinical practice should be paid to the identification and correction of lipid metabolism disorders, the addition of which to the syndrome of high blood pressure results in the development and rapid progression of chronic CHD in liver transplant recipients.

Based on the data on a number of differences in the incidence of cardiovascular risk factors, on the specific features of confirmation and treatment of chronic coronary heart disease in liver transplant recipients in comparison with the general population, we believe that in transplant centers it is necessary to develop a specialized algorithm of dispensary follow-up of recipients (checklist) for adequate prevention of diseases of the circulatory system. The World Health Organization Global Action Plan for the Prevention and Control of Non-communicable Diseases for 2013–2020 suggests that "A strengthened health system directed towards addressing noncommunicable diseases should aim to improve health promotion, prevention, early detection, treatment and sustained management of people with or at high risk for cardiovascular disease, cancer, chronic respiratory disease, diabetes and other noncommunicable diseases, in order to prevent complications, reduce the need for hospitalization and costly high-technology interventions and premature deaths." That is the goal medical practitioners should pursue at all stages of providing medical care to this category of patients, provided the significantly reduced risks of rejection and improvement in the survival of recipients after liver transplantation.

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REFERENCES

1. *Klinicheskij protokol transplantacii pecheni* [Clinical protocol for liver transplantation]: Prilozhenie 6 k prikazu Ministerstva zdravoohraneniya Respubliki Belarus 05.01.2010 № 6. (in Russian).
2. EASL clinical practice guidelines. Liver transplantation. *J Hepatol*, 2016, vol. 64(2), pp. 433-485. doi: 10.1016/j.jhep.2015.10.006.
3. Grigorenko E.A., Rummo O.O., Mitkovskaya N.P. Prognosticheskaya ocenka posttransplantacionnoj vyzhivaemosti recipientov transplantatov pecheni [Prognostic assessment of posttransplantation survival of liver transpant recipients]. *Neotlozhnaya kardiologiya i kardiovaskulyarnye riski*, 2017, vol. 1, no. 1, pp. 72–77. (in Russian).
4. Watt K.D.S., Pedersen R.A., Kremers W.K., Heimbach J.K., Charlton M.R. Evolution of Causes and Risk Factors for Mortality Post-Liver Transplant: Results of the NIDDK Long-Term Follow-Up Study: Long-Term Mortality Post-Liver Transplant. *Am J Transplant*, 2010, vol. 10, no. 6, pp. 1420–1427.
5. Desai S., Hong J.C., Saab S. Cardiovascular risk factors following orthotopic liver transplantation: predisposing factors, incidence and management. *Liver Int*, 2009, vol. 30, no. 7, pp. 948-957. doi: 10.1111/j.1478-3231.2010.02274.x.
6. Trotter J.F., Wachs M.E., Trouillot T.E., Bak T., Kugelmas M., Kam I., Everson G. Dyslipidemia during sirolimus therapy in liver transplant recipients occurs with concomitant cyclosporine but not tacrolimus. *Liver Transpl*, 2001, vol. 7(5), pp. 401–408.
7. Neff G.W., Montalbanoa M., Tzakisa A.G. Ten years of sirolimus therapy in orthotopic liver transplant recipients. *Transplant Proc*, 2003, vol. 35(3Suppl), pp. 209s–216s.
8. Mells G., Neuberger J. Reducing the risks of cardiovascular disease in liver allograft recipients. *Transplantation*, 2007, vol. 83(9), pp. 1141–1150.
9. Kobashigawa J.A., Kasiske B.L. Hyperlipidemia in solid organ transplantation. *Transplantation*, 1997, vol. 63(3), pp. 331–338.
10. Patel S.S., Rodriguez V.A., Siddiqui M.B., Faridnia M., Lin F.P., Chandrakumaran A., Laurenzano J., Clinton J., Kowlgi G.N., Kirkman D., Sima A.P., Liptrap E., Bhati C., Siddiqui M.S. The impact of coronary artery disease and statins on survival after liver transplantation. *Liver Transpl*, 2019, vol. 25(10), pp. 1514–1523.
11. Chou R., Dana T., Blazina I., Daeges M., Jeanne T.L. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US preventive services task force. *JAMA*, 2016, vol. 316(19), pp. 2008-2024. doi: 10.1001/jama.2015.15629.
12. Athyros V.G., Tziomalos K., Gossios T.D., Griva T., Anagnostis P., Kargiotis K., Pagourelias E.D., Theocharidou E., Karagiannis A., Mikhailidis D.P. et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet*, 2010, vol. 376(9756), pp. 1916–1922.
13. Blais P., Lin M., Kramer J.R., El-Serag H.B., Kanwal F. Statins are underutilized in patients with nonalcoholic fatty liver disease and dyslipidemia. *Dig Dis Sci*, 2016, vol. 61(6), pp. 1714–1720.
14. De Luca L., Kalafateli M., Bianchi S., Alasaker N., Buzzetti E., Rodríguez-Perálvarez M., Thorburn D., O'Beirne J., Patch D., Leandro G., Westbrook R., Tsochatzis E.A. Cardiovascular morbidity and mortality is increased post liver transplantation even in recipients with no preexisting risk factors. *Liver Int*, 2019, vol. 39(8), pp. 1557–1565.
15. VanWagner L.B., Harinstein M.E., Runo J.R., Darling C., Serper M., Hall S., Kobashigawa J.A., Hammel L.L. Multidisciplinary approach to cardiac and pulmonary vascular disease risk assessment in liver transplantation: an evaluation of the evidence and consensus recommendations. *Am J Transplant*, 2018, vol. 18(1), pp. 30–42.
16. Mohanty A., Tate J.P., Garcia-Tsao G. Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis. *Gastroenterology*, 2016, vol. 150(2), pp. 430–440.
17. Omar M.A., Wilson J.P., Cox T.S. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother*, 2001, vol. 35(9), pp. 1096–1107.
18. Charlton M. Obesity, hyperlipidemia, and metabolic syndrome. *Liver Transpl*, 2009, vol. 15, Suppl 2, pp. s83-s89. doi: 10.1002/lt.21914.
19. Roy A., Kneteman N., Lilly L., Marotta P., Peltekian K., Scudamore C., Tchervenkov J. Tacrolimus as intervention in the treatment of hyperlipidemia after liver transplant. *Transplantation*, 2006, vol. 82(4), pp. 494–500.
20. Stegall M.D., Everson G.T., Schroter G., Karrer F., Bilir B., Sternberg T., Shrestha R., Wachs M., Kam I. Prednisolone withdrawal late after adult liver transplantation reduces diabetes, hypertension, and hypercholesterolaemia without causing graft loss. *Hepatology*, 1997, vol. 25(1), pp. 173-177. doi: 10.1002/hep.510250132.
21. Lewis J.H., Mortensen M.E., Zweig S., Fusco M.J., Medoff J.R., Belder R. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. *Hepatology*, 2007, vol. 46(5), pp. 1453–1463.
22. Björnsson E.S. Hepatotoxicity of statins and other lipid-lowering agents. *Liver Int*, 2017, vol. 37(2), pp. 173–178.
23. Neal D.A., Gimson A.E., Gibbs P., Alexander G.J. Beneficial effects of converting liver transplant recipients from cyclosporine to tacrolimus on blood pressure, serum lipids, and weight. *Liver Transpl*, 2001, vol. 7(6), pp. 533–539.
24. Grigorenko E.A., Mitkovskaya N.P., Roudenok V.V., Rummo O.O. Coronary artery calcification in liver transplant recipients. *Vestnik Avitsenny*, 2020, vol. 22, no. 2, pp. 246–252.

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