The Role of miRNA 33a in post liver transplantation liver steatosis

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is seen worldwide and is the most common liver disorder in Western industrialized countries. Non-alcoholic fatty liver disease (NAFLD) can occur after liver transplantation (LT), as recurrence or de novo hepatic steatosis (HS). NAFL has considered when liver biopsy shows steatosis alone, steatosis with lobular or portal inflammation, without ballooning, or steatosis with ballooning but without inflammation. Early recognition of graft steatosis and fibrosis are key issues to prevent adverse outcomes.Recent reports have highlighted the critical role of microRNAs in regulation of hepatic steatosis. MicroRNAs negatively regulate expression of a wide variety of proteins involved in lipid metabolism, and thus post-transcriptionally modify lipolysis, lipogenesis and lipoprotein turnover In addition, microRNAs are exported from liver cells and their profile in the serum correlates with the underlying mechanism of liver pathology in preclinical models of liver disease. The inhibition of these miRNAs increases insulin sensitivity, β-oxidation, and HDL circulating levels, as well as the lipid accumulation reduction in arterial plaques. Serum levels of miR-33a are significantly increased in liver transplant recipients with graft steatosis or lobular inflammation. This is the first study that described increased circulating miR-33a in patients with NAFLD. Weight loss is the most effective treatment, the management of which has already been outlined. No single drug can be recommended in patients specifically for recurrence and/or de novo NAFLD/NASH after LT.

Keywords: miRNA 33a, liver transplantation, liver steatosis

INTRODUCTION:

Nonalcoholic fatty liver disease based on recent published guidelines and reviews defined by the presence of fat accumulation in >5% of hepatocyte, is categorized into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) based on histologic findings.(Eslam M 2020) ,(AASLD 2021) ,(Dufour J et al. 2021)

NAFL has considered when liver biopsy shows steatosis alone, steatosis with lobular or portal inflammation, without ballooning, or steatosis with ballooning but without inflammation. (EASL 2016)

The diagnosis of NASH requires the presence of steatosis, ballooning and lobular inflammation. (EASL 2016)

I. Epidemiology

Prevalence — Nonalcoholic fatty liver disease (NAFLD) is seen worldwide and is the most common liver disorder in Western industrialized countries, (Tomah S et al. 2021)

Pooled prevalence of NAFLD globally is 25.24% with wide geographical variation across the world. Highest prevalence rates—mostly ultrasound based—has been reported from Middle East and South American countries (around 30%) whereas the limited number of studies from Africa reports a much lower prevalence (13%).(Mitra S et al. 2019)

Egypt, a Middle Eastern country with a population of ~100 million, with 60% of them being younger than 30 years, is considered among the highest 10 nations in prevalence of obesity. (World bank data 2019), (Tomah S et al. 2021)

The prevalence of NAFLD has risen in parallel with the aforementioned changes, with direct clinical and economic burden. Although there is scant data on the magnitude of NAFLD in Egypt, available data suggest that Egypt has one of the highest prevalence of NAFLD, affecting more than one-third of the population, compared to a global prevalence of about 25%.(Fouad Y et al.2022)

Specific studies suggest that the prevalence range of NAFLD in Egypt is approximately 47.5%, with 56.7% having fibrosis, and it was present in approximately 15.8% of children.(Tomah S et al. 2019)

Patient demographics — Most patients are diagnosed with NAFLD in their 40s or 50s. Studies vary with regard to the sex distribution of NAFLD, with some suggesting it is more common in women and others suggesting it is more common in men. (Mitra S et al. 2019)

Association with other disorders — Patients with NAFLD (particularly those with NASH) often have one or more components of the metabolic syndrome (Obesity ,Systemic hypertension ,Dyslipidemia, Insulin resistance or overt diabetes). (Ma J et al.2017) ,(Eslam M et al.2020)

Liver steatosis after liver transplantation:

Non-alcoholic fatty liver disease (NAFLD) can occur after liver transplantation (LT), as recurrence or de novo hepatic steatosis (HS).(Silva A et al.2023)

Due to high rate of Metabolic syndrome(MetS) and its individual components in the post-LT setting (mainly due to immunosuppressive medications), liver transplant recipients (LTR) have a high risk of graft steatosis and fibrosis (i.e., de novo or recurrent NAFLD). According to the data, MetS affects one out of every two LTR and accounts for up to 42% of CVD-related mortality.Therefore, early recognition of graft steatosis and fibrosis are key issues to prevent adverse outcomes. (Mikolasevic I et al.2021)

The association of miRNA with liver steatosis:

miRNAs are a class of short non-coding RNAs transcribed by RNA polymerase II that possess approximately 19 to 25 nucleotides and function as post-transcriptional regulators of gene expression.(Treiber T et al.2019)

Recent reports have highlighted the critical role of microRNAs in regulation of hepatic

steatosis. MicroRNAs negatively regulate expression of a wide variety of proteins involved in lipid metabolism, and thus post-transcriptionally modify lipolysis, lipogenesis and lipoprotein turnover In addition, microRNAs are exported from liver cells and their profile in the serum correlates with the underlying mechanism of liver pathology in preclinical models of liver disease.(Erhartova D et al.2019)

miR-33a and miR33b are co-transcribed with the SREBP1 and SREBP2, which are regulators of *de novo* lipogenesis and cholesterol biosynthesis. They are also related to repression of the ATP binding cassette transporter member 1 of human transporter sub-family (ABCA1), which is essential for HDL synthesis through the regulation of ApoA1 and cholesterol binding . Therefore, they contribute to the modulation of fatty acid metabolism pathways, cholesterol, and insulin synthesis. The inhibition of these miRNAs increases insulin sensitivity, β-oxidation, and HDL circulating levels, as well as the lipid accumulation reduction in arterial plaques, which is why they are proposed as potential therapeutic targets not only for NAFLD but also for metabolic syndrome management.(López-Sánchez GN et al.2021)

Erhartova D et al. STUDY has shown that serum levels of miR-33a are significantly increased in liver transplant recipients with graft steatosis or lobular inflammation. this is the first study that described increased circulating miR-33a in patients with NAFLD, and these novel findings are consistent with the current understanding of the role of miR-33a in lipid metabolism.(Erhartova D et al.2019)

Elevation of serum level of miR-33a in patients with liver graft steatosis is consistent with the known role of miR-33a in lipid metabolism. First, miR-33 is encoded by an intronic sequence within genetic loci encoding SREBP-1 and SREBP-2, two transcription factors critically involved in regulation of fatty acid and cholesterol homeostasis.Second, expression of miR-33, along with expression of SREBP-1 and -2, is upregulated by insulin resistance, which has a causal role in pathogenesis of NAFLD.Third, suppression of miR-33a by genetic approaches or by therapeutic RNA in preclinical models of NAFLD resulted in the development of liver steatosis or in major changes of plasma lipoprotein profile.(Agbu P et al.2021)

Although Erhartova D et al. findings suggest that the high level of serum miR-33 may reflect increased expression of SREBP-1 and -2 driving an increased lipid and cholesterol synthesis, it could not be completely rule out the possibility that increased miR-33 reflects insulin resistance rather than increased lipogenesis. Similarly, it could not be attributed the increased levels of miR-33 in the serum solely to its release from liver cells as miR-33 (and SREBP-1) are expressed in all tissues metabolizing lipids or cholesterol, albeit to a lesser degree compared to hepatocytes .Although it was identified miR-33a as independent predictor of liver graft steatosis and inflammation. (Erhartova D et al.2019)

Treatment of Post-transplant Recurrent or De Novo NAFLD

Weight loss is the most effective treatment, the management of which has already been outlined. No single drug can be

recommended in patients specifically for recurrence and/or de novo NAFLD/NASH after LT. Recommendations are extrapolated from the non-LT NASH population from the medications; however, this is complicated by the potential for drug-drug interactions and adverse risk profiles (MS, cardiovascular risk, and malignancies). Dietary and lifestyle recommendations should mirror recommendations in nontransplant NASH patients.(Horn P et al.2021)

Exercise offers a synergistic effect in hepatic fat mobilization when paired with calorie restriction. (Kalogirou MS et al.2022)

Immunosuppression

Immunosuppressant therapy is vital in improving allograft survival and outcomes but, unfortunately, they are accompanied by multiple side effects, including altered metabolic homeostasis. Among the immunosuppressants, corticosteroids early tapering regimens are recommended. CNIs are linked to hypertension, diabetes, and hyperlipidemia, as discussed previously and dose reduction should be considered in patients with these comorbidities.The mTOR inhibitors are associated with significant hyperlipidemia, and an alternate immunosuppressant should be considered when hyperlipidemia remains uncontrolled.(Burra P et al.2020) , (cotter T et al.2020)

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