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New-onset Diabetes Mellitus: Predictive Factors and Impact on the Outcome of Patients Undergoing Liver Transplantation

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Abstract: Liver transplantation (LT) for hepatocellular carcinoma (HCC) is the treatment of choice for patients with tumor characteristics within the Milan criteria associated with Child B or C cirrhosis. LT provides the best cure for both the tumor and the cirrhosis.

There have been several emerging reports that new-onset diabetes mellitus (NODM) after transplantation (NODAT) is one of the most negative predictive factors for low survival rate and related co-morbidities.

Little is known about the onset of NODM in post-transplant patients and, overall, whether the pathogenesis of NODM differs from that known for the general population. Principally, it is still unknown whether NODAT is related to the primary hepatic disease, the surgical procedures, immunosuppressive treatments, or is it due to the donor liver.

This review will focus on the identification of factors, in the setting of LT, which may lead to the development of NODM. Early prevention of these factors may abate the incidence of NODM and positively impact survival rate, and thus ameliorate the worsening of cardiovascular risk factors which usually occur after LT.

Keywords: Liver transplantation, metabolic syndrome, new-onset diabetes mellitus, HCV, immunosuppressive therapy, nonalcoholic steatohepatitis, insulin resistance, liver surgery.

INTRODUCTION

Liver transplantation (LT) is increasingly becoming a health burden due to the cost and associated co-morbidities. LT for hepatocellular carcinoma (HCC) is the treatment of choice for patients with tumor characteristics that fall within the Milan criteria associated with Child B or C cirrhosis. LT provides the best cure for both the tumor and the cirrhosis [1]. New-onset diabetes mellitus (NODM) is the most serious metabolic-complication after LT, nevertheless liver transplant recipients are not always routinely assessed for diabetic risk before transplantation, or monitored closely after transplantation. NODM is becoming a health problem also because of the impact that it may have on recovery and survival of post-transplant patients.

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Recently, nonalcoholic steatohepatitis (NASH) has been recognized as a risk factor for the development of HCC, and this likely leads to a further worsening of the underlying liver disease [2]. This implies therefore that the persistence or the recurrence of the pre-operative factors that cause NASH would lead to metabolic derangements after LT [3-5].

Metabolic disorders are common in patients after LT. In recent years, due to the greater than 90% survival at 1 year after LT, and the greater than 70% survival at 5 years, the occurrence of metabolic syndrome after LT is being recognized with increasing frequency [6]. Metabolic syndrome, which comprises obesity, hypertension, hyperglycemia, and dyslipidemia [7], predisposes to major cardiovascular diseases, liver steatosis and fibrosis, as well as reduced renal function, and these factors are responsible for low long-term survival in post-transplant patients. The incidence of post-transplant diabetes mellitus is 13% to 61% [8-10], dyslipidemia (mainly hypertriglyceridemia) is 40% to 66% [8, 10, 11] and obesity is 24% to 40% [8, 10, 12, 13] depending on the literature reviewed.

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Table 1. Predictors of NODM after Liver Transplantation ¶

Predictor	Author	*p*-value
Age	Khalili *et al.* [24]	*0.04*
	Mirabella *et al.* [31]	*0.002*
	Kuo *et al.* [32]	*<0.001*
BMI≥25kg/m2	Oufroukhi L *et al*. [29]	*0.009*
	Saliba *et al*. [33]	*<0.001*
IFG/IGT	Oufroukhi L *et al*. [29]	*0.02*
	Saliba *et al*. [33]	*0.005*
Ethnicity		
AA	Kuo *et al.* [32]	*0.06*
Indication for OLT		
HCV	Baid *et al.* [22]	*0.0001*
	Khalili *et al.* [24]	*0.02*
Alcoholic cirrhosis	Oufroukhi L *et al*. [29]	*0.01*
CNI use		
Tacrolimus	Kuo *et al*. [32]	*0.008*
Corticosteroid use	Oufroukhi *et al*. [29]	*0.05*

AA: African American race; OLT: orthotropic liver transplantation

¶= only some studies and certain risk factors with positive correlation shown in table, please read text for discussion as well as details.

Immunosuppressive medications play a significant role in the pathogenesis of NODAT. Calcineurin inhibitors (CNI), such as cyclosporine and tacrolimus, and steroids, are all associated with hypertension, hyperglycemia, and dyslipidemia [14]. Sirolimus, a non-nephrotoxic drug, can also independently contribute to dyslipidemia [15]. Other potential factors are lifestyle modifications, namely, the delay in return to normal daily life and free food intake, which contribute to weight gain and to the resultant insulin resistance [12], and in some cases the underlying liver disease itself. Hemochromatosis, alcohol abuse and autoimmune hepatitis have all been reported to be associated with diabetes [16].

This review will focus on the identification of predictive factors, in the setting of LT, that may be involved in the development of NODM which may allow a reduction in the onset of diabetes following LT. We will also discuss briefly the diagnosis of NODAT and management approaches after diagnosis of NODAT.

PATHOGENESIS OF NEW-ONSET DIABETES AFTER LIVER TRANSPLANT

Pre-existing diabetes in LT recipients is a common complication that may arise from impaired glucose metabolism or insulin resistance associated with impaired liver function, as a consequence of the underlying liver disease, or as a result of corticosteroid treatment for autoimmune chronic hepatitis.

NODAT is a growing concern because of the impact it may have on recovery and survival. In recent years the pathogenesis of NODAT has become an important matter of debate. Several factors need to be considered, when trying to clarify the pathophysiological abnormalities in this setting that ultimately result in hyperglycemia and diabetes.

RISK FACTORS FOR NEW ONSET DIABETES MELLITUSAFTER TRANSPLANTION

There is wide variation (5-40%) in the incidence rate of NODM after liver transplantation in published studies [17-27]. In a single-center experience, the prevalence of de novo diabetes among transplanted patients was 54.1%, 53.4%, 49.2%, 41.2%, 36.2%, and 35.9%, at a distance of 15 days, 1 month, 3, 6, 9 and 12 months from transplantation [28]. Therefore hyperglycemia may occur as early as 15 days after transplantation and this is most likely related to the use of immunosuppressive therapy such as corticosteroids.

We believe that potential factors that may explain the differences in the incidence rates of NODM include: reporting bias, sample size, definition of NODM, transient nature of DM, immunosuppressive regimens, and confounding factors such as age, race, family history of DM, and body mass index. No definitive risk factors for NODM have been clearly established, yet, but characteristics such as advanced age, ethnic origin, family history, obesity, and hepatitis C virus (HCV) infection have all been implicated [23-29] (Table **1**).

RECIPIENT-RELATED FACTORS

Age: Khalili *et al.* [23] reported old age as an independent predictor for NODM in a cohort of 555 LT recipients. Mirabella *et al.* [30] also reported increased recipient age (>45 years) as a risk factor for NODM in a cohort of 899 LT

recipients, and Kuo *et al*. [31] a similar finding (age ≥50 vs <50 years, HR= 1.241). However, in some studies, age was not associated with the risk of NODM in LT recipients [32-34].

BMI and other risk factors: The other two independent pre-transplantation risk factors for NODM included impaired fasting glucose (IFG) and a maximum lifetime body-mass index (BMI) over 25 kg/m^2 [28, 32].

In a French multi-center study [32] the presence of at least 2 cardiovascular risk factors in men and, for women, a history of either having given birth to a baby weighing over 4 kg (n = 4) or developing gestational diabetes (n =1) correlated with the risk of NODM. In the same study, a significant correlation emerged with special composite cardiovascular risk factors based on the combination of at least 2 of the following items at the time of LT: male gender, BMI over 25 kg/m^2, a family history of diabetes, hypertension, dyslipidemia, age of over 50 yr, or IFG.

However discrete factors did not correlate with the development of NODM, namely: male gender, a family history of diabetes, hepatitis B status, and individually taken cardiovascular risk factors such as hypertension, dyslipidemia and smoking.

Previous studies showed a higher incidence of NODM in African American and Hispanics kidney transplant recipients , compared with white recipients [35-37]. In the Procurement and Transplant Network/United Network for Organ Sharing databases, 15,463 recipients without pretransplant diabetes were identified; the incidence of NODM was significantly higher in African American (29.3%) than in other races (26.2%) [31]. Similarly, Thuluvath et al [38] showed that HCV infected black people had a higher rate of NODM than white people. Conversely, in a cohort of 115 recipients there was no influence of recipient ethnicity on NODM [33].

Transplant-related Factors

Donor age and donor diabetes were not found to be consistently correlated with the risk of NODM [31, 39]. Living donor transplant (HR=0.628) and induction therapy (HR=0.816) were associated with a decreased risk of NODM, whereas cold ischemia time (≥6 vs.<6 hr) was associated with an increased risk for NODM [31].

Indication for transplant: Oufroukhi *et al.* [28] were among the first authors to report that alcoholic cirrhosis, as the indication for orthotopic LT, was a risk factor for NODM.

HCV and HBV infection: HCV cirrhosis, as described in the following paragraph, has been reported to cause both pretransplant diabetes and NODM. Conversely, hepatitis B status was not found to be associated with increased incidence of NODM [28].

HCV Infection

Several observational studies have shown a higher incidence of NODM in HCV infected patients [26, 29, 40, 41]. A recent metanalysis that reviewed 7 studies concluded that HCV infection increased the risk of NODM after LT [OR 2.46 (95%CI: 1.44-4.19)] and, most importantly, was also associated with increased prevalence of diabetes before LT [OR = 1.39 (95%CI: 1.06, 1.83)] [35].

Metabolic evaluation has shown that HCV-infected patients are hyperinsulinemic and have increased peripheral insulin resistance, mainly at hepatic level, in analogy to what happens in type 2 diabetes and with the characteristic insulin resistance observed in patients with cirrhosis and obesity [42-45]. Hepatic insulin resistance has been shown in liver biopsy specimens from HCV infected patients, which exhibit diminished signaling through the insulin receptor; furthermore human hepatoma cells expressing HCV core protein show suppression of insulin-induced glucose uptake [46, 47]. It has also been suggested that patients with HCV infection have an impaired β-cell responsiveness, possibly because of direct viral effects on β cell function, increasing the risk of diabetes [29]. However, the cause of β cell dysfunction in chronic HCV infection, if this really occurs, remains unclear. An autoimmune process directed against the pancreas, mediated by the virus along with an increased prevalence of other markers of autoimmunity in patients with HCV infection and diabetes, has also been proposed [40]. However, this hypothesis has not been confirmed, since anti-islet cell antibodies have rarely been detected in patients with HCV infection and diabetes [48-51]. Another possible mechanism may be represented by a direct cytopathic effect of HCV on pancreatic cells, since HCV-RNA has been identified in pancreatic cells [52].

Also in tacrolimus-treated patients, the incidence of NODM in HCV-infected patients was significantly higher than in HCV negative patients (46.7% vs. 19.3%, p = 0.0014). On cyclosporine, only 1 out of 6 (16.7%) HCV-infected patients developed NODM [32].

Another study suggests that HCV infection and high-dose steroids may act synergistically in inducing NODM after transplant [21].

Immunosuppressive Therapy

Immunosuppressive therapy is one of the major contributors to the increasing incidence of NODM; immunosuppressive drugs have been a key tool to improve the outcome in LT patients (tacrolimus, cyclosporine, steroids), and all of them may have diabetogenic effects; in the presence of HCV infection, these may simultaneously potentiate the diabetogenic effect by enhancing viral replication [53].

A meta-analysis of 16 studies which included patients receiving either tacrolimus (n = 1636) or cyclosporine (n = 1407) reported NODM in 13.4% of patients after solid organ transplantation, with a higher incidence in patients on tacrolimus compared to those on cyclosporine (16.6% vs. 9.8%). This trend was observed across renal, liver, heart and lung transplant groups. The incidence of NODM was significantly higher among tacrolimus-treated patients than in the remainder (10.4% vs. 4.5%, p < 0.00001), an effect which was observed in renal transplant (9.8% vs. 2.7%, p < 0.00001) and non-renal transplant (11.1% vs. 6.2%, p<0.003) groups [54].

Conversely a different study noted a trend for a greater incidence of hypercholesterolemia associated with cy-

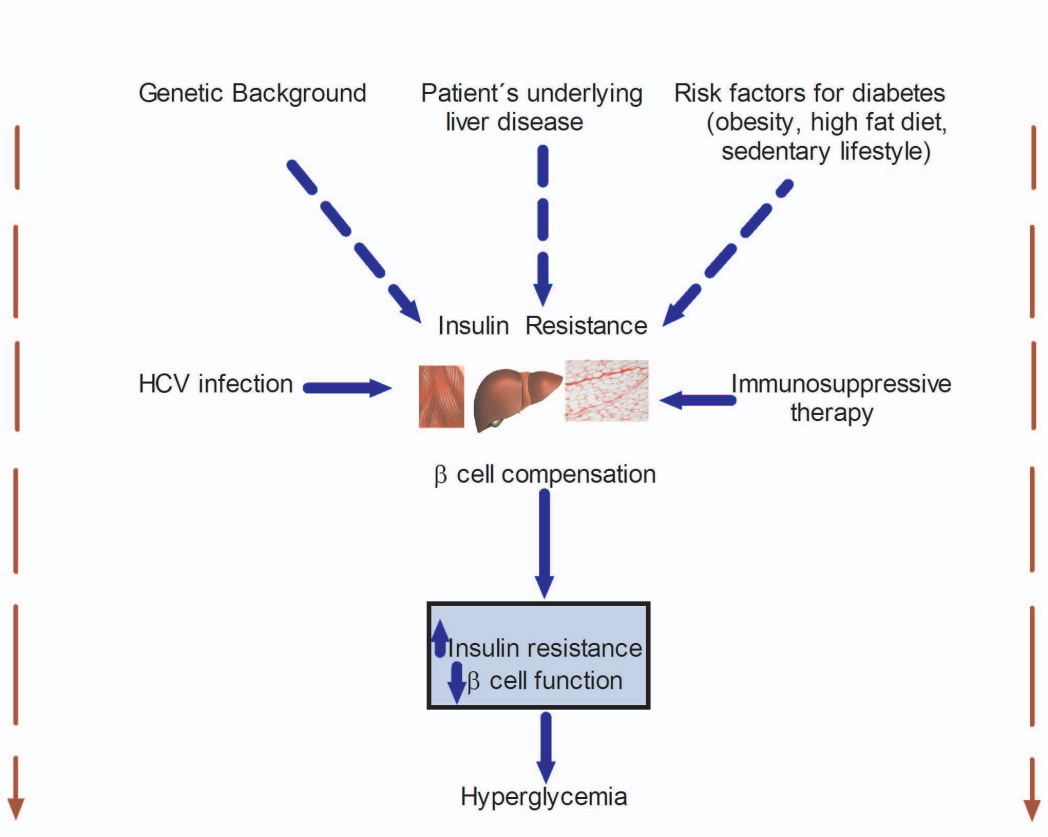

Fig. (1). Proposed mechanism for the development of hyperglycemia in post-transplanted liver patients.

closporine, and for NODM associated with tacrolimus, but the differences were not significant [55].

Calcineurin inhibitors (CNI) (tacrolimus and cyclosporine) have a potent immunosuppressive effect by inhibiting IL-2 gene transcription [56] and both of them are widely used in post-transplant patients [56]. Similar mechanisms have been proposed regarding the diabetogenic effect of these immunosuppressive medications, and include decreased insulin secretion, increased insulin resistance and inhibition of steroid metabolism. There is significant evidence linking CNI to decreased insulin secretion. A dose-dependent cyclosporine-induced decrease in insulin secretion has been observed in rat, human islet cells and in dogs treated with cyclosporine [57-60]. Decreased insulin secretion may result from compromised insulin production either via direct β cell toxicity or via inhibition of DNA synthesis. Morphological changes indicating β cell toxicity after exposure to cyclosporine or tacrolimus include vacuolization and degranulation [58, 61]. Also insulin resistance has been shown in patients receiving CNI [62, 63].

This diabetogenic effect has not been clearly showed for sirolimus (SRL) when used as monotherapy, while for mycophenolate mofetil and azathioprine a diabetogenic effect has been excluded.

In a large single-center experience using SRL as a CNI-sparing regimen to reduce nephrotoxicity and other adverse effects, it was noted that SRL reduced the incidence of hypertension and new-onset diabetes mellitus after ortothopic LT [64]. In a recent cross-sectional study at the same center on a large number of orthotopic LT patients on CNI treatment, the prevalence of hypertension and NODM was 53.7% and 29.4%, respectively [65]; while in the SRL study, hypertension and NODM were observed in 43.5% and 16.6% of all patients on SRL. When only the patients who received SRL as the main immunosuppressant in a CNI-sparing regimen were considered, the prevalence of hypertension and new-onset diabetes dropped to 34.1% and 10.5%, respectively.

In a multi-center experience tacrolimus use after discharge and steroid use after discharge were associated with an increased risk of NODM in LT recipients, at univariate and multivariate analyses, whereas induction therapy was associated with a decreased risk [31]. The use of mycophenolate mofetil /mycophenolic acid or mammalian target of rapamycin inhibitors after discharge was not associated with the risk of NODM [31].

On the other hand, corticosteroids have a well-recognized diabetogenic effect; the main mechanism underlying this effect is insulin resistance, which at hepatic level causes increased gluconeogenesis [66]. In adipose tissue and muscle, the main effect of corticosteroids involves antagonism of insulin-induced glucose utilization by multiple mechanisms, including decreased insulin receptor affinity and defects at the post receptor level; these drugs may also inhibit insulin secretion and stimulate glucagon release [66-68]. Oufroukhi *et al.* [28] studied 141 non-diabetic patients who underwent ortothopic LT for NODM within 1-year post transplant. Amongst other factors, they found that the cumulative dose of steroids at 1 year had a significant impact on the development of NODM, that is, for each 100 mg of prednisone

taken by the patient, the risk of NODM increased by 1.2%. In the past, some researchers found that the use of oral steroid therapy had no effect on the development of NODM [22], whereas, in a multivariate analysis of 176 OLT patients, it was reported that the use of methylprednisolone pulses was an independent risk factor for development of NODM: that is, each administered bolus increased the risk of NODM by 9% [21].

Thus NODM occurs as a consequence of the combination of different factors (Fig. **1**): the patient underlying liver disease and the coexistence of traditional risk factors may causes insulin resistance (mainly at hepatic level) generating a suitable environment for the development of hyperglycemia, and when HCV infection and the use of immunosuppressive therapy act on this environment, the patient is at an even greater risk of worsening of hyperglycemia and development of diabetes; the genetic background of the patient will have an unknown impact for NODM, as it occurs for type 2 diabetes.

SCREENING OF SUBJECTS AT RISK FOR DIABETES BEFORE AND AFTER TRANSPLANT

The natural history of NODM appears to be similar to that of type 2 diabetes, even though the etiology of the pathophysiological abnormalities may differ in several subjects. The similarities between type 2 diabetes and NODM have led to the development of a consensus recommending that the diagnosis of NODM be based on the American Diabetes Association criteria for the diagnosis of diabetes [69]. According to this, NODM is diagnosed by finding two fasting plasma glucose (FPG) values >125mg/dl or a plasma glucose level >199mg/dl at 2 h during a 75g oral glucose tolerance test (OGTT), or a random plasma glucose of at least 200mg/dl in a patient with typical symptoms of diabetes [69]. The use of glycosylated hemoglobin (HbA1c) for diagnosis of diabetes or prediabetes during the peritransplant period is not recommended [70-72].

Pretransplant Screening

The presence of the classical risk factors for diabetes should be investigated once individuals are placed on the transplant registry and a FPG test should be recorded. In patients with normal FPG levels, the updated International Consensus Guidelines recommends performing a 75g OGTT to detect the presence of impaired glucose tolerance (IGT) [72]. A pretransplant finding of IGT or impaired fasting glucose (IFG) is associated with more than 2.5-fold increase in the incidence of NODM, compared to normoglycemic patients. Within the indeterminate period of time that patients spend on transplant waiting lists, the optimal timing of pretransplant screening has not been established, but it should be as close as possible to LT. Patients with risk factors for diabetes should receive counseling on weight control, diet and exercise during the pretransplant period, and other cardiometabolic risk factors (hypertension, dyslipidemia and smoking) should be taken care of.

Post-transplant Screening

Patients who develop hyperglycemia immediately after LT need to receive treatment accordingly; patients without hyperglycemia should have FPG measurements every day during the first week, then at least weekly during the first month, every 3 months in the first year, and annually thereafter. If IFG is detected at any time, an OGTT should be performed to increase diagnostic yield; persons identified as having abnormal IFG or IGT should receive lifestyle counseling [70, 72]. OGTT should also be performed annually in case of normal FPG, and every 6 months in case of IGT [73].

TREATMENT

Physical activity along with healthy nutrition plays an important role in ameliorating glucose metabolism in type 2 diabetes; therefore for NODM the best initial therapeutic approach should similarly consist of prevention, trying to optimize modifiable risk factors such as obesity and immunosuppressive therapy, and encouraging a healthy life-style [70] (Table **1**).

When lifestyle modifications fail to reach adequate glycemic control, medical intervention is necessary. Given the lack of data regarding to the use of antidiabetic compounds in patients with NODM, it is important to use clinical judgment and to tailor the antidiabetic therapy based on the patient's underlying conditions. When NODM resembles type 2 diabetes, it is therefore appropriate to start therapy with oral antidiabetic compounds. The mechanism of action of oral antidiabetic compounds target insulin sensitivity (metformin, pioglitazone and rosiglitazone), insulin secretion (sulfonylureas and meglitinides) or reduce glucose absorption (acarbose). The real constraint of most antidiabetic compounds such as pioglitazone or sulphonylureas, is that these are metabolized by the liver, hence their use should be limited to patients with stable and normal graft function. Alternatively, metformin and acarbose could represent safe drugs in liver recipients, as these are excreted by the kidney [73]. A new promising approach may be represented by GLP 1 agonist receptors that induce a glucose-dependent insulin secretion and are eliminated by the kidney [74]. The side effects of GLP 1 agonist receptors are represented by decreased gut motility, nausea, occasional emesis that may interfere with the absorption of the post-transplant immunosuppressive agents [71]. Although dipeptidyl peptidase 4 inhibitors have a safe pharmaceutical profile; they are less likely to induce hypoglycemia, compared with sulphonylureas, careful attention must be paid to their administration to liver recipients, because these medications partly undergo hepatic metabolism [75].

Insulin therapy should be used to control severe hyperglycemia which could be associated with an acute rejection episode that is being treated with high dose glucocorticoids, or that could occur in the early post-transplantation period, resembling type 1 diabetes [73]. In these situations insulin therapy may be interrupted once the acute event has resolved, and the patient has achieved a satisfactory metabolic control suitable for treatment by oral antidiabetic agents. However, if therapeutic goals are not reached, insulin monotherapy should be taken into consideration; since the concomitant use of oral agents and insulin therapy has not been evaluated in transplant recipients [76]. There is however anon going randomized controlled trial that is evaluating whether improved glycemic control using intensive insulin

treatment immediately postoperatively will improve outcomes in patients undergoing LT (www.clinicaltrials.gov NCT01211730).

To optimize glucose control, it seems of paramount importance to use the immunosuppressant having the least diabetogenic effect. Decreased risk of NODAT was associated with the use of steroid free or sparing regimens [77, 78], although any reduction in corticosteroid dose should be balanced against the risk of graft rejection. Given the deleterious effect of tacrolimus on insulin secretion [79], patients receiving this medication may benefit from a switch to the less diabetogenic cyclosporine [80].

CONCLUSIONS

NODM represents a major metabolic complication of transplantation. Based on this statement, all prospective transplant patients should be alerted of the potential risk of developing diabetes after transplant and they should be encouraged to adopt appropriate lifestyle measures before LT, in order to decrease the risk of developing diabetes. In addition, screening for glucose dysregulation should be systematic and should be performed in all phases of the transplant process. Since the extent of hyperglycemia could vary among subjects with NODM, it is important to choose the most appropriate pharmacotherapy in order to achieve an acceptable glucose control. The antidiabetic therapy should be tailored on each patient, based on the restored function of the transplanted organ and the toxicity profiles of antidiabetic agents. Therefore, optimizing the prevention and the management of NODM may minimize the acute and long-term risks associated with this condition.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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