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POST-TRANSPLANT DIABETES MELLITUS (PTDM) IN PATIENTS AFTER LIVER TRANSPLANTATION – DIAGNOSIS AND TREATMENT

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ABSTRACT

Liver transplantation is an effective method for treating end-stage liver failure and certain liver cancers. Survival after this procedure is associated with the development of comorbidities, including before diagnosed diabetes mellitus and new diagnosed post-transplant diabetes mellitus (PTDM). Its pathophysiology differs from that of type 2 diabetes in the general population and reflects a complex interplay between pre-existing metabolic vulnerability (e.g. obesity, insulin resistance, impaired fasting glucose), perioperative stressors, and chronic immunosuppression. Commonly used immunosuppressive drugs, such as calcineurin inhibitors (particularly tacrolimus), mTOR inhibitors, and glucocorticosteroids, affect not only pancreatic function but also contribute to weight gain and chronic inflammation. Therapeutic goals should therefore be individualized according to time since transplantation, comorbidity burden, risk of hypoglycemia, and liver graft and renal function.

Aim of the study: The objective of this study is to summarize recent literature on the diagnosis and treatment of PTDM and type 2 diabetes mellitus after liver transplantation.

Materials and methods: In this narrative review, we searched the PubMed database to analyze the latest evidence on the treatment and diagnosis of PTDM, and type 2 diabetes mellitus diagnosed before liver transplantation.

Results: We discuss diagnostic approaches as well as pharmacological and non-pharmacological treatment strategies for these metabolic disorders in patients receiving long-term immunosuppression.

Conclusions: Interdisciplinary care and integration of lifestyle interventions are essential to optimize metabolic and cardiovascular risk management in liver transplant recipients. There remains a strong need for further clinical trials evaluating the safety and efficacy of oral antidiabetic agents in this specific patient population.

KEYWORDS

Post-Transplantation Diabetes Mellitus, PTDM, Liver Transplantation, Diabetes Mellitus Type 2, DM2

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Introduction

Liver transplantation is currently a recognized and effective method of treating end-stage liver failure and certain liver cancers, significantly prolonging life and improving quality of life in patients (Adam i in., 2012). Due to the immunosuppressive regimens used, patients are at risk of developing PTDM (post-transplant diabetes mellitus – which replaced NODAT (new onset diabetes after transplantation(Sharif i in., 2014)) or experiencing worsening of a pre-existing diabetes mellitus (Grancini i in., 2019; Peláez-Jaramillo i in., 2018).

Carbohydrate metabolism disorders after liver transplantation are associated with a higher risk of cardiovascular disease, infection, deterioration of transplanted organ function and, ultimately, reduced survival in this patient group (Peláez-Jaramillo i in., 2018; Sharif i in., 2024). Furthermore, diabetes in transplant recipients often co-occurs with other components of metabolic syndrome, such as obesity, dyslipidemia and hypertension, which further increases cardiovascular risk (Berkovic i in., 2020). It has been demonstrated that both the incidence of diabetes and its clinical course differ in patients after transplantation compared with those who have not undergone this procedure (Munoz Pena & Cusi, 2023).

Chronic immunosuppression plays a key role in the pathogenesis of type 2 diabetes after liver transplantation. Drugs such as glucocorticosteroids, calcineurin inhibitors and mTOR inhibitors have a proven effect in increasing insulin resistance and impairing insulin secretion (Grancini i in., 2019; Munoz Pena & Cusi, 2023; Sharif i in., 2014). Furthermore, liver transplant recipients constitute a highly heterogeneous group, differing in the etiology of the underlying disease leading to transplantation, the extent of damage to other organs, and time duration since transplantation, which further complicates the establishment of treatment standards (Richardson i in., 2022).

The choice of antihyperglycemic therapy must take into account not only its effectiveness in lowering blood glucose levels, but also the safety of the drugs in the context of transplanted liver function, potential interactions with immunosuppressive drugs, and the risk of adverse effects such as hepatotoxicity and nephrotoxicity (Grancini i in., 2019; Richardson i in., 2022). In recent years, new classes of antidiabetic drugs have become available, and their role in the treatment of liver transplant patients is still being researched (Munoz Pena & Cusi, 2023; Zheng i in., 2024).

The aim of this review is to analyze the most recent evidence on the pharmacotherapy of type 2 diabetes in patients after liver transplantation. We will discuss the mechanisms of action, efficacy and safety of these therapies in this specific group of patients.

Methodology

In this narrative review, we searched the PubMed database to analyze the latest evidence on the treatment and diagnosis of PTDM, and type 2 diabetes mellitus diagnosed before liver transplantation.

Results and Discussion

1.Pathophysiology of type 2 diabetes after liver transplantation

The pathophysiology of type 2 diabetes in liver transplant recipients differs from the classic model observed in the general population, although both conditions share common features (Munoz Pena & Cusi, 2023). In this specific patient group, iatrogenic factors are of particular importance, especially the type and intensity of immunosuppression and the time elapsed since transplantation (Sharif i in., 2024). Understanding these mechanisms is essential for the effective selection of therapeutic strategies and forms the basis for the individualization of diabetes pharmacotherapy in liver transplant recipients (Richardson i in., 2022). In the pathophysiology of type 2 diabetes in transplant patients, factors present both before and after surgery play an important role: (i) insulin resistance, (ii) impaired insulin secretion by pancreatic β cells, (iii) adverse effects of immunosuppressive therapy, and (iv) inflammation.

Insulin resistance is a key factor in the development of diabetes after liver transplantation. In many patients, it is already present before the procedure, often as a result of chronic liver disease, obesity, or metabolic syndrome (Berkovic i in., 2020; Puri & Kotwal, 2022). Although liver transplantation may lead to some improvement in glucose metabolism by removing the diseased organ, this effect is often short-lived and frequently offset by factors related to immunosuppressive treatment (Grancini i in., 2019).

Another important pathophysiological mechanism is impaired insulin secretion by pancreatic β cells. Experimental and clinical studies have shown that calcineurin inhibitors can directly impair β-cell function by inhibiting nuclear factor of activated T cells (NFAT) signaling pathways, ultimately leading to reduced transcription of genes responsible for insulin secretion (Heit i in., 2006; Sharif i in., 2024; Van Hooff i in., 2005). This effect is particularly pronounced with tacrolimus and may be dose-dependent (Sharif i in., 2024;

Van Hooff i in., 2005). Furthermore, glucocorticoids may exacerbate β-cell dysfunction through chronic hyperglycemia and glucotoxicity (Weir & Bonner-Weir, 2004).

mTOR inhibitors represent another important factor in the development of diabetes after liver transplantation, as they can affect glucose metabolism by disrupting insulin signalling and negatively influencing β-cell proliferation and survival (Johnston i in., 2008; Vergès & Cariou, 2015). Although these agents are less likely to induce diabetes than calcineurin inhibitors, their use may worsen existing metabolic disturbances, particularly when combined with other immunosuppressive drugs (Sharif i in., 2024). Glucocorticoids may also increase insulin resistance by stimulating hepatic gluconeogenesis, inhibiting peripheral glucose uptake, and altering fat redistribution (van Raalte & Diamant, 2014). In addition, calcineurin inhibitors, especially tacrolimus, may further impair tissue sensitivity to insulin (Sharif i in., 2024).

Inflammatory and hormonal factors also play a significant role. In some patients after transplantation, chronic inflammation can promote insulin resistance through the action of pro-inflammatory cytokines such as TNF-α and IL-6 (Berkovic i in., 2020). Moreover, alterations in the liver–adipose tissue–skeletal muscle axis and dysregulation of adipokine secretion may impair glycemic control (Grancini i in., 2019). Liver transplant recipients also commonly experience changes in lipid metabolism and weight gain, which further adversely affect carbohydrate metabolism and contribute to hyperglycemia (Berkovic i in., 2020; Richardson i in., 2022).

2.Risk factors for developing diabetes in liver transplant recipients

The development of type 2 diabetes in patients after de novo liver transplantation results from a complex interaction of multiple factors present before transplantation, elements related to the transplantation procedure itself, and long-term immunosuppressive therapy (Table 1.) (Li, 2015; Peláez-Jaramillo i in., 2018). Due to differences between patients in the general population and those who have undergone transplantation, the term PTDM (post-transplant diabetes mellitus) has been introduced to describe patients in whom newly developed diabetes is detected after transplantation (Richardson i in., 2022). Accurate identification of these factors is crucial for risk assessment and the implementation of effective preventive and therapeutic measures (Sharif i in., 2024).

Among the non-modifiable risk factors, advanced recipient age is the most important, as ageing is associated with a natural decline in insulin sensitivity and a reduced ability of pancreatic β cells to compensate by increasing insulin secretion (Kuo i in., 2010; Peláez-Jaramillo i in., 2018). Genetic predisposition and a positive family history of type 2 diabetes may also be relevant, although available data are less conclusive (Peláez-Jaramillo i in., 2018; Sharif i in., 2024). Ethnicity and racial predisposition have also been shown to significantly increase the incidence of diabetes after organ transplantation (Kuo i in., 2010), as does the classic risk factor of male sex (Li, 2015).

Metabolic disorders present prior to transplantation, such as obesity, pre-existing insulin resistance, impaired fasting glucose, and elevated glucose levels, also play a significant role(Kuo i in., 2010; Peláez-Jaramillo i in., 2018). Patients with these risk factors have a markedly higher risk of persistence or worsening hyperglycemia after transplantation. In addition, the etiology of liver disease has prognostic significance, with particularly high rates of diabetes observed in recipients with non-alcoholic fatty liver disease and alcoholic liver disease(Burra i in., 2020).

One of the key modifiable risk factors remains the immunosuppressive regimen. Glucocorticoids have a strong diabetogenic effect, and the risk of developing diabetes depends on both dose and duration of therapy (Sharif i in., 2024). There is evidence that calcineurin inhibitors, particularly tacrolimus, are associated with a higher risk of diabetes development compared with cyclosporine (Heisel i in., 2004). mTOR inhibitors may further exacerbate metabolic disturbances, especially when used in combination therapy (Sharif i in., 2024).

Risk factors associated with the organ and donor include donor age over 60 years (Yadav i in., 2013) and donor liver damage, such as prolonged cold ischaemia time (Ling i in., 2016), organ dysfunction, and hepatic steatosis (Honda i in., 2013; Peláez-Jaramillo i in., 2018).

Post-operative factors that increase the risk of diabetes development include weight gain, limited physical activity, chronic inflammation, and viral infection (Baid i in., 2001; Ling i in., 2016; Peláez-Jaramillo i in., 2018). The early post-transplant period, characterised by metabolic stress and intensive immunosuppression, is particularly conducive to diabetes onset, especially in patients with pre-existing metabolic predisposition (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Gaglia, Hilliard, Johnson, Khunti, i in., 2024; Sharif i in., 2024). Additional contributing factors include statin therapy, which has a documented diabetogenic effect (Cho i in.,

2014), prolonged intensive care unit stay after procedure (>15 days)(Ling i in., 2016), hypomagnesaemia before surgery and one month post-transplantation (Van Laecke i in., 2010), and episodes of acute organ rejection requiring treatment with high-dose glucocorticosteroids (Yadav i in., 2013).

Table 1. Risk factors for developing diabetes in liver transplant recipients.

Category of factor	Risk factor	Mechanism/clinical observations
Non-modifiable	Advanced age of the recipient	Decreased insulin sensitivity, impaired β-cell function
	Genetic predisposition, family history	Increased susceptibility to glycaemic disorders
	Origin	Black/Hispanic race
	Gender	Male gender
Pre-transplantation	Obesity/overweight	Insulin resistance, chronic inflammation
	Insulin resistance, IFG	Risk of overt diabetes disclosure after transplantation
Factors related to the donor organ	Damage to the donor's liver	Liver dysfunction, fatty liver, cold ischaemia of the organ lasting more than 9 hours
	Donor Age	≥60 years old
Etiology of liver disease	NAFLD / NASH	Strong association with metabolic syndrome
	Alcoholic liver disease	Metabolic disorders, risk of recurrence after transplantation
Related to the procedure	on of immunosuppression	The use of drugs other than glucocorticosteroids to induce immunosuppression, e.g. basiliximab, had a protective effect against the development of PTMD
	Acute transplant rejection	Possible correlation related to high doses of glucocorticosteroids during treatment of this condition
	Stay in ICU > 15 days	marker of severe, prolonged post-operative stress and complications
Immunosuppression	Glucocorticosteroids	Intensification of gluconeogenesis, insulin resistance
	Tacrolimus	Direct damage to β cell function
	mTOR inhibitors	Insulin signalling disorders
Post-operative	Weight gain	Insulin resistance severity
	Limited physical activity	Deterioration in glycaemic control
	Hypomagnesaemia	Deterioration of insulin secretion
	Statins therapy	Statins are diabetogenic drugs.
	HCV/CMV infections	Induction of diabetogenic cytokines and damage to pancreatic beta cells

3.Diagnosis and treatment goals for type 2 diabetes after liver transplantation

The diagnosis of type 2 diabetes in liver transplant patients is based on standard diagnostic criteria, but their interpretation in this group requires special attention (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Gaglia, Hilliard, Johnson, Khunti, i in., 2024). It is crucial to distinguish between persistent hyperglycaemia and PTDM in patients in the early stages after transplantation (Munoz Pena & Cusi, 2023). The early post-transplant period is characterised by high glucose variability, which is the result of intensive immunosuppression (mainly the use of glucocorticosteroids), perioperative stress, transfusions during surgery and various other complications (Sharif i in., 2024). It is crucial to emphasise that transient hyperglycaemia post-transplantation should resolve once the patient's condition stabilises after surgery (Munoz Pena & Cusi, 2023).

Fasting blood glucose measurement and oral glucose tolerance test are still the basic diagnostic methods, but their predictive value may be limited in the first weeks after transplantation (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Gaglia, Hilliard, Johnson, Khunti, i in., 2024; Sharif i in., 2024). Glycated haemoglobin (HbA1c) testing is commonly used to monitor glycaemic control, but in liver transplant recipients its interpretation may be distorted by anaemia, blood transfusions and shorter red blood cell survival, especially in the early postoperative period (Sharif i in., 2024). Therefore, some authors suggest relying on serial blood glucose measurements or continuous glucose monitoring to more accurately assess carbohydrate metabolism disorders (Sharif i in., 2014).

The diagnosis of PTDM is similar to the diagnosis of type 2 diabetes for the general population, i.e. one of two criteria: double measurement of elevated glucose concentration ≥126 mg/dL; in an oral glucose tolerance test (OGTT) after consuming 75 mg of glucose, ≥200 mg/dL of glucose in plasma after 2 hours; glycated haemoglobin A1c (A1c) concentration ≥ 6.5% or a patient with classic symptoms of hyperglycaemia (including polyuria, polydipsia) and glucose concentration ≥200 mg/dL. (ElSayed i in., 2023).

Treatment of type 2 diabetes after liver transplantation should be tailored to the individual needs of the patient, considering their age, the time elapsed since transplantation, the risk of hypoglycaemia, comorbidities and the function of the transplanted organ (Munoz Pena & Cusi, 2023; Sharif i in., 2024). Unlike the general population, in the case of liver transplant recipients, particular attention is paid to the safety of therapy and minimising interactions with drugs, especially immunosuppressants (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Gaglia, Hilliard, Johnson, Khunti, i in., 2024; Sharif i in., 2024).

For most stable patients in the late post-transplant period, the goal is to achieve HbA1c values similar to those recommended for the general population, while avoiding hypoglycaemia (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Gaglia, Hilliard, Johnson, Khunti, i in., 2024; Sharif i in., 2024). The early post-transplant period and the presence of multiple comorbidities may require less restrictive glycaemic targets (Munoz Pena & Cusi, 2023). An important element of the therapeutic strategy is also the control of other aspects of metabolic syndrome, such as body weight, lipid profile and blood pressure (Sharif i in., 2024).

The importance of interdisciplinary cooperation in the treatment of diabetes after liver transplantation is emphasised, including the transplant surgeon, endocrinologist, dietitian and nursing team (Sharif i in., 2024). Early diagnosis of carbohydrate metabolism disorders and appropriate treatment goals are crucial for effective and safe pharmacotherapy in this specific group of patients (Munoz Pena & Cusi, 2023; Sharif i in., 2024).

4.General principles of pharmacotherapy for type 2 diabetes after liver transplantation

Pharmacotherapy of type 2 diabetes in patients after liver transplantation requires a tailored approach that considers the unique pathophysiology of the disease, the specific characteristics of the post-transplant period, and the need for long-term immunosuppressive therapy (Grancini i in., 2019; Munoz Pena & Cusi, 2023; Richardson i in., 2022). Unlike in the general population, therapeutic decisions in this group must prioritize treatment safety and consider the potential effects of antidiabetic agents on the function of the transplanted organ (Grancini i in., 2019; Zheng i in., 2024).

The fundamental principle of treatment is the selection of individualized therapy based on the degree of hyperglycemia, time elapsed since transplantation, liver and kidney function, and the risk of hypoglycemia. In the early post-transplant period, insulin therapy is preferred because of its predictable efficacy and the ability to flexibly adjust doses in response to rapidly changing clinical conditions (Sharif i in., 2024). In later stages,

in patients with stable metabolic control, non-insulin therapies may be gradually introduced (Munoz Pena & Cusi, 2023).

An important aspect of pharmacotherapy is the evaluation of potential drug–drug interactions. Many oral antidiabetic agents are metabolized by cytochrome P450 enzymes; a well-documented example is the interaction between cyclosporine and repaglinide (Kajosaari i in., 2005), which may also extend to interactions with calcineurin inhibitors and mTOR inhibitors (Scheen, 2005). Alterations in immunosuppressant drug concentrations may increase the risk of graft rejection or organ toxicity; therefore, the selection of antidiabetic therapy should carefully consider the pharmacokinetic profiles of individual agents (Scheen, 2005).

Treatment safety also involves assessment of hepatotoxicity and nephrotoxicity risks. Although liver transplantation generally restores normal hepatic metabolic function, some patients may experience episodic graft dysfunction, which can influence drug metabolism (Grancini i in., 2019; Scheen, 2014). Furthermore, chronic kidney disease, which frequently occurs in liver transplant recipients, represents a significant limitation for the use of certain antidiabetic medications (Alicic i in., 2017).

When selecting pharmacotherapy, increasing attention is being paid to the effects of antidiabetic drugs on body weight, cardiovascular risk, and other components of metabolic syndrome. Agents associated with weight gain or an increased risk of hypoglycaemia may be less suitable for transplant recipients, who often present with obesity and cardiovascular comorbidities (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Das, Ekhlaspour, Hilliard, Johnson, Khunti, i in., 2024; American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Kushner, i in., 2024; Zheng i in., 2024).

In summary, the general principles of pharmacotherapy for type 2 diabetes after liver transplantation include individualised treatment, preference for agents with a favourable safety profile, and close monitoring of therapeutic efficacy and adverse effects (Grancini i in., 2019; Munoz Pena & Cusi, 2023). This framework provides a foundation for the subsequent discussion of individual classes of antidiabetic drugs in the following chapters of this work (Zheng i in., 2024).

5. Insulin therapy

Insulin therapy plays a key role in treating carbohydrate metabolism disorders in patients after liver transplantation, especially in the first 7 days after surgery (Hecking i in., 2013; Sharif i in., 2024). This is primarily due to its high efficacy, predictable action and the possibility of flexible dose adjustment to the rapidly changing clinical condition of the patient (Hecking i in., 2013; Munoz Pena & Cusi, 2023). Insulin is also the preferred treatment for individuals with severe hyperglycaemia, unstable graft function, or contraindications to non-insulin medications (Munoz Pena & Cusi, 2023; Sharif i in., 2024).

Hyperglycaemia often occurs in the first few weeks after transplantation (the first 45 days after surgery) (Sharif i in., 2014), which is closely associated with intensive immunosuppression, particularly with high doses of glucocorticosteroids (Sharif i in., 2024). During this time, insulin therapy allows for effective control of blood sugar levels, regardless of liver and kidney function, while minimising the risk of significant drug interactions(Hecking i in., 2012; Sharif i in., 2024). Research suggests that early initiation of insulin therapy may help reduce glucotoxicity and promote partial preservation of pancreatic β-cell function (Hecking i in., 2012; Poitout & Robertson, 2008).

The insulin therapy regimens used may include both basal-bolus therapy and simplified regimens using basal insulin, depending on the severity of hyperglycaemia and the patient's general condition. In hospital settings, intensive insulin therapy regimens administered via continuous infusion are often preferred, but once the patient's clinical condition has stabilised, treatment can be gradually simplified (Mukuba i in., 2026; Sharif i in., 2024). As glucocorticoid doses are reduced, insulin requirements usually decrease, necessitating regular dosage adjustments (Sharif i in., 2024).

In the late stage after transplantation, insulin therapy may be continued in patients with established diabetes, especially when treatment with oral antidiabetic drugs is ineffective or contraindicated (Munoz Pena & Cusi, 2023; Sharif i in., 2024). In some cases, it is possible to gradually reduce or completely discontinue insulin, and patients can switch to oral therapy, especially when metabolic control improves and graft function is stable (Mukuba i in., 2026; Munoz Pena & Cusi, 2023).

If a decision is made to continue insulin therapy after a patient with PTDM leaves hospital, a safe regimen confirmed in numerous studies is to include basal insulin in a 3-0-3 regimen. Then, if glucose measurements are in the range of 80-110 mg/dl, the insulin dose is increased by 3 units; if lower than 80 mg/dl, it is reduced by 3 units. For measurements 2 hours after a meal, if the results are above 140 mg/dl, increase by 1-2 units; if the results are below 70 mg/dl, decrease by 1-2 units (Meneghini, 2013; Peláez-Jaramillo i in., 2018).

The main limitations of insulin therapy are the risk of hypoglycaemia and weight gain, which may be clinically significant for liver transplant patients (Munoz Pena & Cusi, 2023; Sharif i in., 2024). The risk of hypoglycaemia is particularly important in people with impaired kidney function and in the elderly, which highlights the need for individualised treatment selection and careful monitoring of glucose levels (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Lingvay, i in., 2024; Sharif i in., 2024). Despite these limitations, insulin remains the key and safest antidiabetic drug in specific clinical situations in liver transplant recipients (Mukuba i in., 2026; Munoz Pena & Cusi, 2023).

6. Oral antidiabetic medications

In the later stages after liver transplantation, in patients with stable graft function and moderate disturbances of carbohydrate metabolism, the use of non-insulin antidiabetic agents may be considered (Grancini i in., 2019; Munoz Pena & Cusi, 2023). The choice of appropriate therapy should consider its effectiveness in lowering blood glucose levels, safety profile, potential interactions with immunosuppressive drugs, as well as its effects on body weight and cardiovascular risk (Grancini i in., 2019; Hu & Lan, 2025; Zheng i in., 2024). These medications include the following classes: (i) biguanides, (ii) sulfonylureas, (iii) dipeptidyl peptidase-4 inhibitors, (iv) glucagon-like peptide-1 (GLP-1) receptor agonists, (v) sodium–glucose cotransporter 2 inhibitors, and (vi) thiazolidinediones.

6.1 Metformin

In most cases, metformin is the first-line agent for the treatment of type 2 diabetes. It primarily acts by reducing hepatic gluconeogenesis, increasing insulin sensitivity in peripheral tissues, and decreasing intestinal glucose absorption (National Institute of Diabetes and Digestive and Kidney Diseases; 2012-., b.d.). For many years, its use in liver transplant recipients was limited because of concerns regarding safety, particularly the risk of lactic acidosis in patients with impaired renal function (Grancini i in., 2019). These concerns were heightened because in early stages after transplantation can have acute kidney injury connected with hemodynamic instability which may increase the risk of drug accumulation. (Munoz Pena i Cusi, 2023; Hecking i in., 2013). However, current observational data suggest that metformin can be used safely in patients with stable graft function and without severe renal impairment (Kurian i in., 2008; Munoz Pena & Cusi, 2023).

Metformin's favourable effects on insulin resistance and body weight make it an attractive therapeutic option in this patient population (Yale i in., 2020). This is particularly important in patients who have undergone transplantation due to non-alcoholic fatty liver disease, in whom insulin resistance is the main mechanism underlying both post-transplant diabetes and disease recurrence in the transplant. (Burra i in., 2020; Cigrovski Berkovic i in., 2020). Nevertheless, its use requires regular monitoring of renal function, particularly serum creatinine levels, as well as ongoing assessment of the patient's overall metabolic status (Munoz Pena & Cusi, 2023). It is also recommended that metformin be temporarily discontinued in situations of increased risk of hypoxia, dehydration, systemic infections or sudden deterioration of renal function. This approach is consistent with the general principles of treatment safety for patients with liver disease and post-transplant patients (Scheen, 2014; Munoz Pena i Cusi, 2023).

6.2 Sulphonylureas and glinides

Sulphonylureas and glinides are effective in lowering blood glucose levels by stimulating insulin secretion from pancreatic β cells. This mechanism involves closing ATP-dependent potassium channels in the cell membrane of β cells. This leads to depolarisation, calcium influx and increased insulin secretion, regardless of the current glucose level (Weir & Bonner-Weir, 2004). However, their use in liver transplant recipients is limited by several factors, including an increased risk of hypoglycaemia and weight gain (Dimakos i in., 2023; Grancini i in., 2019). In addition, these agents may interact with immunosuppressive drugs because they share common metabolic pathways; for example, glibenclamide may enhance the effects of cyclosporine (Richardson i in., 2022). These interactions are mainly related to liver metabolism involving cytochrome P450 isoenzymes. This may lead to higher concentrations of immunosuppressive drugs and increase the risk of their toxicity(Scheen, 2005, 2014). Such drug–drug interactions further restrict their use in transplant patients (Scheen, 2014). As a result, these drugs are now mainly considered as second- or third-line options, but only in carefully selected patients who have stable graft function, a low risk of hypoglycemia and are under close clinical supervision (Grancini et al., 2019; Richardson et al., 2022).

6.3 Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)

Dipeptidyl peptidase-4 (DPP-4) inhibitors exert their glucose-lowering effects by inhibiting the degradation of glucagon-like peptide-1 (GLP-1), thereby enhancing glucose-dependent insulin secretion and suppressing glucagon release(National Institute of Diabetes and Digestive and Kidney Diseases; 2012-., b.d.). This mechanism enables better glycemic control while maintaining the body's natural response to glucose levels, which significantly reduces the risk of hypoglycemic episodes. (Scheen, 2012). These agents are characterised by a favourable safety profile and a low risk of hypoglycaemia. Available evidence suggests that DPP-4 inhibitors can be used in liver transplant recipients without clinically significant interactions with immunosuppressive therapy (Munoz Pena & Cusi, 2023) Unlike sulphonylureas, DPP-4 inhibitors do not significantly affect the levels of calcineurin inhibitors or mTOR drugs, making them a safe option for long-term treatment of diabetes after transplantation. (Grancini et al., 2019; Richardson et al., 2022). They represent a particularly suitable therapeutic option for older patients, as they are generally well tolerated and have a neutral effect on body weight(Scheen, 2012; Zheng i in., 2024).

6.3 Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)

DPP-4 inhibitors affect the degradation of the satiety hormone GLP-1, thereby increasing insulin secretion and reducing glucagon secretion(National Institute of Diabetes and Digestive and Kidney Diseases; 2012-., b.d.). They have a favourable safety profile and a low risk of hypoglycaemia. Available studies suggest that they can be used in liver transplant patients without significant interactions with immunosuppressive drugs(Munoz Pena & Cusi, 2023). They are a good therapeutic option, especially for older people, as they have a neutral effect on body weight and are well tolerated(Scheen, 2012; Zheng i in., 2024).

6.4 GLP-1 receptor agonists

GLP-1 receptor agonists appear to be a promising group of drugs for liver transplant patients, as they may have beneficial effects on body weight, glycaemic control, and cardiovascular risk factors(Munoz Pena & Cusi, 2023). Their mechanism of action promotes the release of endogenous insulin by activating the GLP-1 receptor on pancreatic beta cells (Ninčević i in., 2019). Although the available clinical data are limited, they suggest that use of these agents may be safe in stable transplant recipients (Zheng i in., 2024). However, caution should be exercised given the possible adverse effects on the gastrointestinal system and their potential impact on the absorption of immunosuppressive drugs(Calvarysky i in., 2024). Due to their effect on gastric emptying, they may delay the absorption of calcineurin inhibitors and MMF. There is no evidence in the literature of liver damage associated with their use(Sharif i in., 2024).

6.5 Sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors)

SGLT2 inhibitors reduce renal glucose reabsorption, leading to glucosuria. They have proven metabolic benefits and cardioprotective properties; however, their use in liver transplant patients remains understudied (Munoz Pena & Cusi, 2023; Zheng i in., 2024). The potential benefits must be balanced against the risks of urinary tract infections (most commonly fungal, but also bacterial), dehydration, and euglycaemic ketoacidosis(Hu & Lan, 2025; Zheng i in., 2024). They are not recommended for use in patients with advanced renal impairment (G4)(Grancini i in., 2019). This group is significant recommended for patients with heart failure and chronic kidney disease (Metra i in., 2025). Among known drug interactions, the effect of cyclosporine on increased accumulation of canagliflozin should be highlighted(Richardson i in., 2022).

6.6 Thiazolidinediones

Thiazolidinediones improve tissue sensitivity to insulin through activation of PPAR-γ receptors; however, their use in liver transplant recipients is limited due to the risk of fluid retention, weight gain, and potential cardiovascular side effects(Grancini i in., 2019). No dose modification is required based on renal function. There are reports of interactions between rosiglitazone and MMF resulting in toxicity(Sharif i in., 2024). Due to their adverse effect profile, thiazolidinediones currently have marginal clinical significance in this patient population(Munoz Pena & Cusi, 2023).

7. Non-pharmacological treatment support

Non-pharmacological interventions constitute a fundamental component of comprehensive care for patients with type 2 diabetes after liver transplantation and should be implemented alongside pharmacotherapy (Peláez-Jaramillo i in., 2018; Richardson i in., 2022). These measures are particularly important given the high prevalence of weight gain, obesity, and metabolic syndrome observed in transplant recipients (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Kushner, i in., 2024; Peláez-Jaramillo i in., 2018).

Dietary modification forms the cornerstone of non-pharmacological management and aims to improve glycaemic control, promote weight reduction, and reduce cardiovascular risk (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Kushner, i in., 2024; Peláez-Jaramillo i in., 2018). Nutritional recommendations for liver transplant recipients are generally consistent with those for the general population with type 2 diabetes; however, they require an individualised approach that accounts for graft function, immunosuppressive therapy, and potential post-transplant complications(Peláez-Jaramillo i in., 2018; Richardson i in., 2022). Emphasis is placed on limiting the intake of simple sugars and saturated fats, as well as on controlling overall caloric intake (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Kushner, i in., 2024).

Regular physical activity is essential for improving insulin sensitivity and maintaining healthy body weight(American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Kushner, i in., 2024; Richardson i in., 2022). Liver transplant recipients are encouraged to gradually increase their level of physical activity, tailored to their overall clinical condition, time elapsed since transplantation, and cardiovascular status(American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Lingvay, i in., 2024; Richardson i in., 2022). Evidence suggests that even moderate exercise can lead to significant improvements in metabolic parameters in this patient group (American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Hilliard, Johnson, Khunti, Kushner, i in., 2024). Physical activity also supports post-transplant rehabilitation and facilitates a return to normal daily functioning.

Patient education represents another key element of non-pharmacological management. It should encompass instruction on self-monitoring of blood glucose, recognition of hypoglycaemia symptoms, and adherence to therapeutic recommendations(American Diabetes Association Professional Practice Committee, ElSayed, Aleppo, Bannuru, Bruemmer, Collins, Ekhlaspour, Gaglia, Hilliard, Johnson, Khunti, i in., 2024; Sharif i in., 2024). This is particularly important in liver transplant recipients, who often require complex medication regimens and long-term outpatient follow-up(Richardson i in., 2022). Emphasising regular self-monitoring of blood glucose actively engages patients in the treatment process and supports optimal long-term outcomes.

8. Future research directions

Although the number of studies addressing disorders of carbohydrate metabolism in liver transplant recipients is increasing, many aspects of type 2 diabetes pharmacotherapy in this population remain insufficiently understood(Munoz Pena & Cusi, 2023; Sharif i in., 2024). One of the key priorities for future research should be the evaluation of the efficacy and safety of newer antidiabetic agents in transplant recipients(Munoz Pena & Cusi, 2023; Zheng i in., 2024). Current evidence regarding glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors is derived primarily from small observational studies, and their long-term effects on graft function, rejection risk, and patient survival remain unclear(Hu & Lan, 2025; Zheng i in., 2024). Well-designed prospective studies involving larger patient cohorts are needed to assess not only glycemic control but also hard clinical endpoints, such as cardiovascular events and transplanted organ function(Hu & Lan, 2025; Sharif i in., 2024).

Another important area for future investigation is the optimization of immunosuppressive regimens, particularly in relation to diabetes risk(Sharif i in., 2014, 2024). Evaluation of strategies aimed at reducing glucocorticoid exposure, implementing calcineurin inhibitor–sparing protocols, and individualizing immunosuppressive therapy may help to decrease the incidence of metabolic complications without increasing the risk of graft rejection (Berkovic i in., 2020; Hecking i in., 2012).

Growing emphasis is also being placed on personalised approaches that incorporate genetic, metabolic, and clinical factors predisposing patients to the development of diabetes after transplantation(Berkovic i in., 2020; Sharif i in., 2024). The identification of predictive biomarkers could enable early risk stratification and facilitate the selection of the most appropriate preventive and therapeutic strategies (Sharif i in., 2014, 2024).

Conclusions

Type 2 diabetes represents a serious clinical challenge in patients after liver transplantation. It results from a complex interaction of multiple factors, including metabolic abnormalities, iatrogenic influences, and conditions related to the underlying liver disease(Berkovic i in., 2020; Peláez-Jaramillo i in., 2018). Both pre-existing diabetes and diabetes that develops de novo after transplantation are associated with poorer prognosis, increased risk of cardiovascular complications and infections, damage to other organs (particularly the kidneys), and deterioration of graft function(Peláez-Jaramillo i in., 2018; Sharif i in., 2024).

Pharmacological management of type 2 diabetes in liver transplant recipients requires particular caution and individualisation of therapy(Grancini i in., 2019; Sharif i in., 2024). Insulin treatment plays a central role in the early post-transplant period and in patients with severe hyperglycaemia. In later stages, selected non-insulin antidiabetic agents may be considered in patients with stable graft function(Munoz Pena & Cusi, 2023; Sharif i in., 2024). The choice of therapy should account for the safety profile of the drug, potential interactions with immunosuppressive agents, and its effects on body weight and hypoglycaemia risk(Grancini i in., 2019; Munoz Pena & Cusi, 2023).

Modern antidiabetic therapies, including glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors, offer promising therapeutic potential(Munoz Pena & Cusi, 2023; Zheng i in., 2024). However, their role in the management of liver transplant recipients has not yet been fully defined(Sharif i in., 2024; Zheng i in., 2024). The limited availability of high-quality clinical trials and the absence of dedicated treatment guidelines underscore the need for continued research in this field (Hu & Lan, 2025; Sharif i in., 2024).

Effective management of type 2 diabetes in liver transplant recipients should be grounded in interdisciplinary collaboration and a holistic approach that integrates both pharmacological and non-pharmacological interventions(Peláez-Jaramillo i in., 2018; Richardson i in., 2022). Ongoing advances in research and the development of consistent, evidence-based clinical recommendations may substantially improve long-term outcomes and quality of life for this unique patient population(Sharif i in., 2024).

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