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# Overview of New Onset Diabetes after Transplantation Induced by Tacrolimus

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***Author's contribution***

*The sole author designed, analysed, interpreted and prepared the manuscript.*

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## ABSTRACT

Tacrolimus is an important therapy in the post-transplant immunosuppressant regimen. However, it is responsible for the highest incidence of a specific type of diabetes called new onset diabetes after transplantation (NODAT). The dangers of NODAT are not limited to cardiovascular or nerve diseases, but also to kidney complication that may lead to loss of transplant kidney. The aim of this article is to discuss the possible theory of NODAT induces by tacrolimus and its common therapy. In addition, this research is to enhance knowledge about the pharmacokinetic and dynamic of tacrolimus. This review depends on research in reliable and popular medical databases which are PubMed, Google Scholar, Saudi Digital Library, and Web of Science (ISI). While the terms used to search the published researches are organ transplantation, immunosuppressant, tacrolimus, new-onset diabetes after transplantation, and hypoglycemic drug.

*Keywords: Tacrolimus immunosuppressant; new-onset diabetes after transplantation; hypoglycemic.*

## 1. INTRODUCTION

The most problem increase in the last 3 decade in Saudi Arabia (SA) is the end-stage renal disease (ESRD) which is a chronic disease and it leads to progressive loss of function of the kidney [1]. The treatment options are peritoneal dialysis or hemodialysis, while the best solution is a

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kidney transplant [2]. A kidney transplant is a surgical operation that placed a healthy kidney, and it needs a therapeutic regimen to protect the new organ from the immune system attack [3]. To achieve this purpose, the patient must receive immunosuppressive drugs as first-line therapy. The immunosuppressants include glucocorticoids, calcineurin inhibitors, selective interleukin-2 receptor antibodies, immunoglobulin, anti-metabolite agents or mammalian target of rapamycin inhibitors (mTORi) [4]. The protocol of treatment depends on the combination of drugs to enhance the efficacy and avoid resistance [5].

Several studies assured the direct relation between the receiving an immunosuppressive and new type of diabetes called new-onset diabetes after transplantation (NODAT) especially with calcineurin inhibitors, like tacrolimus (Tacro), and corticosteroid [6]. The pathogenesis of NODAT induced by Tacro remains not fully known. While different studies tried to explain the potential theory which suggests the direct pancreatic β-cell toxicity that leads to diminishing in both synthesis and secretion of insulin [7]. The main purpose of this review is to boost our knowledge about tacrolimus and possible theory about its role to induce NODAT.

## 2. ORGAN TRANSPLANTATION IN SAUDI ARABIA OVERVIEW

The procedure of organ transplantation was first performed by researchers in the 18th century [8,9]. Of course, they had numerous failures but the successes of organ transplant were visible in the mid-20th century [10]. Transplantation is a routine treatment option that includes transplants of livers, kidneys, pancreas, intestine, heart, and lungs [8]. Also, it includes vascularized composite allografts (VCAs), such as face and hand transplantation [3].

The first organ transplantation attempted in the Saudi Arabia (SA) was a kidney transplanted which was performed in 1979 from a live donor [11]. As a result, the Saudi Center for Organ Transplantation was established in 1985. The main goal of this center is to supervise and manage the performance of organ transplant procedures in SA [1]. It has an important role in all aspects of the transplantation process including coordination, education and procurement. In 2014, the initiative of the Saudi Center for organ transplantation promoted symmetry and notification of organ donors to achieve an average of 15 donors per million yearly [12]. The Saudi Center for organ transplantation pointed out in their last report about the prevalence of transplantation in different types of organs over 2096 cases. Kidney is the highest organ transplanted at 86.9%, then bone marrows at 5.7%, liver at 4.5%, heart at 2.5%, lungs and intestine at 0.23% and finally pancreas at 0.1% [11]. The development of the field of transplants, which includes surgical methods, tissue typing by matching donors to recipients, and the evolution of immunosuppressant drugs, is growing but a posed challenge is to enhance survival rate and reduce the risk of transplant rejection [13] (Fig. 1).

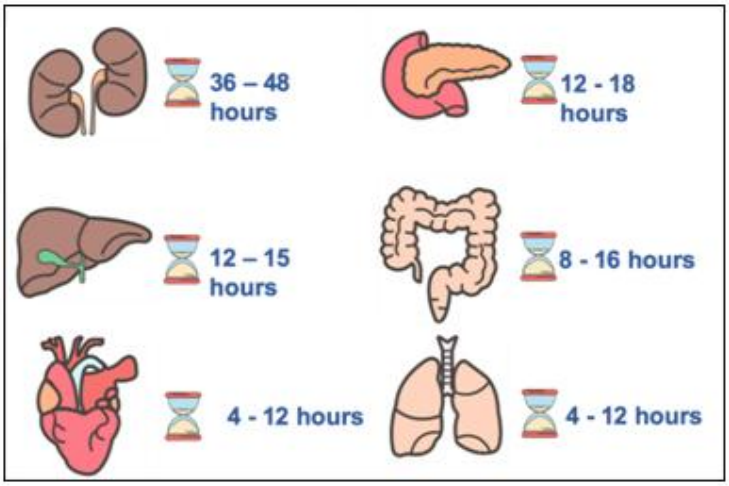


**Fig. 1. Survive duration of organs outside the body [13]**

## 3. EFFECT OF IMMUNE-SYSTEM IN TRANSPLANTED ORGAN

Normally, the immune system defends the body from foreign substances. And most importantly, is the complex of the immune reaction which is influenced by a significant mediator like T cell lymphocytes and notable cell messengers like interleukins (ILs), especially IL-1 , IL- 2 and Tumor necrosis factor-alpha factor (TNFα) [14]. Those are responsible for organ rejection that depends on the detection of molecules, which are found on cell surfaces and named as major histocompatibility complex (MHC), by lymphocyte and antigen [15]. Then, they follow up by a sequence of lymphocytes activation and immune effector mechanisms which lead to the loss of function and ultimately reject the organ [16].

The rejection can occur within minutes which is called hyper-acute rejection, when donor-specific antibodies are present during transplantation. It may occur within one week to 3 months after the transplant, which is called acute rejection [17]. But most rejection happens gradually over the first six months to years after transplant, which is called chronic rejection, even with the use of immunosuppressant. This represents 10-20% of patients [18].

But the question is whether or not there are any symptoms of rejection? Usually, there are no symptoms but it is detected by routine blood tests [19]. However, if symptoms appear, the most common signs are: fever, weight gain, decreased urine output, flu-like symptoms, swollen feet or ankles and weakness [20]. Most cases of rejection are mild and can be reversed if found early. They can be treated easily by modification of the doses of therapeutic regimen, especially immunosuppression medication [18].

## 4. PHARMACOLOGICAL BACKGROUND OF IMMUNOSUPPRESSANT DRUG

Immunosuppressive drugs form the base of the therapeutic regimen to protect the new organ together with other post-transplant medications. The history of organ transplantation therapy has gone through several stages to enhance the treatment of this critical case. It is worth mentioning that the first immunosuppressant drug used as an anti-rejection was cyclosporine, approved by the FDA in 1983. Over many years, the immunosuppressant drugs were developed for more targeting until the potent immunosuppressant drug, called tacrolimus, was approved by the FDA in 1994. Since then, tacrolimus has been adopted as the main immunosuppressant drug for organ transplantation [21]. Compared to the past, immunosuppressant drugs are powerful therapies for many diseases [22]. They are a therapeutic option in several fields:

- Organ transplantation field where it is used to avoid rejection of the new organ. They are also known as anti-rejection drugs [23]. Also, they can treat transplant-related diseases like acute kidney injury (AKI) or end-stage renal disease (ESRD) [24].
- Oncology field in which they can treat cutaneous sarcoma (Blagosklonny, 2013).
- Autoimmune diseases field where they are used to treat serious manifestations of psoriasis, lupus, rheumatoid arthritis and different conditions of allergies [25].

We must pay attention to other important post-transplant medications including antivirus (valganciclovir) and antibacterial (co-trimoxazole) medications during the first 6 months to avoid infection [3,26]. Also, antilipidemic (simvastatin) and antihypertensive drugs (amlodipine) are essential to control common problems after transplant that lead to graft loss [27].

### 4.1 Classification of Immunosuppressive Drugs

It could be argued that the immunosuppressive drugs can be classified into six different types listed in the Table (1), comprising of glucocorticoids like prednisolone, calcineurin inhibitors like tacrolimus and cyclosporine, antiproliferative agents like azathioprine and mycophenolic acid, selective interleukin-2 receptor antibodies like basiliximab and daclizumab, immunoglobulin-like polyclonal anti-thymocyte globulin (ATG) [25] or mTOR-inhibitors like sirolimus and everolimus [28].

For further focus, they categorized the drugs into two types according to the duration of use in the organ transplantation field:

1- Induction drugs: potent anti-rejection drugs used during transplant, to decrease acute rejection. They include daclizumab, basiliximab as selective IL-2 receptor antibodies and polyclonal anti-thymocyte globulin as immunoglobulin-like "rabbit anti-thymocyte globulin" (ATG) (Table 2) [29].

**Table 1. Sites of action of immunosuppressive agents on T-cell activation [28]**

| Immunosuppressive Agent | Site of Action |
|---|---|
| Cyclosporine and tacrolimus | Calcineurin (inhibits phosphatase activity) |
| Mycophenolic acid | Inosine monophosphate dehydrogenase (inhibits activity) |
| Sirolimus and everolimus | Protein kinase involved in cell cycle progression (mTOR)(inhibit activity) |
| Azathioprine | Deoxyribonucleic acid (false nucleotide incorporation) |
| Daclizumab and basiliximab | IL-2 receptor (block IL-2–mediated T-cell activation) |
| Alemtuzumab | Cell surface glycoprotein CD52 |
| Glucocorticoids | Glucocorticoid response elements in DNA (regulate gene transcription) |

**Table 2. Induction immunosuppressant therapy [29]**

| Drugs | Type of transplant |
|---|---|
| Daclizumab | Kidney |
| Basiliximab | Kidney |
| Anti-thymocyte globulin (ATG) | Kidney |
| Thymoglobulin | Kidney |
| Muromonab C3 | Liver, Pancreas |

2- Maintenance drugs: they are anti-rejection drugs used for a long time, to decrease chronic rejection. They include tacrolimus or cyclosporine as calcineurin inhibitors, prednisolone as glucocorticoids, mycophenolate mofetil, or azathioprine as antiproliferative, and sirolimus as mTOR inhibitor (Table 3) [23].

**Table 3. Maintenance immunosuppressant therapy [23]**

| Drugs | Type of transplant |
|---|---|
| Cycluosporine | Kidney, Liver, Heart |
| Tacrolimus | Kidney Liver, Heart, Bone marrow |
| Prednisolone | Kidney |
| Sirolimus | Kidney |
| Azathioprine | Kidney |
| Mycophenolate mofetil | Kidney, Liver, Heart |

## 5. TREATMENT REGIMENS

The transplant medical team commonly starts with induction immunosuppressant therapy, in parenteral dosage form, which is used during a transplant operation. They then complete the therapeutic regimen by oral maintenance anti-rejection drugs that are used for a long period [30].

The aim of the therapeutic regimen is to control the suppressing of the immune system with the least harmful side effects. So, the best method is to use a combination of drugs to reduce toxicities such as severe nephrotoxicity and withdrawal effects that have a high risk of rejection [31].

In principle, the maintenance immunosuppressive regimen must contain three types of drugs from the main categories. These categories are: 1- Purine antagonists like methotrexate or mycophenolate mofetil or azathioprine. 2- Glucocorticosteroids like prednisone or prednisolone. 3- mTOR- inhibitors like sirolimus or everolimus. 4- Calcineurin inhibitors like cyclosporine or tacrolimus.

So, the therapeutic regimen is one of these options: 1- tacrolimus + methotrexate + mycophenolate mofetil. 2- sirolimus +prednisone + tacrolimus or cyclosporine or mycophenolate mofetil. 3- mycophenolate mofetil +prednisone +tacrolimus or cyclosporine, and this regimen is most commonly used [28].

The regimen drugs must be taken in an accurate dose and time because the effectiveness may change when taken at an irregular time or when taken with other drugs or food [5].

Also, blood tests must be done regularly during the use of an immunosuppressant regimen because these tests help the physician monitor the efficacy of the drug, or if the dosage requires changes and estimate the sign of rejection [23]. Also, the tests can detect potential complications and their intensity. These complications can begin with cardiovascular disease and end with the rejection of the graft [6]. Unfortunately, most complications happen in the first months after the transplant. However, they can also develop after several years [32].

## 6. PHARMACOLOGICAL BACKGROUND OF TACROLIMUS (TACRO)

Tacrolimus (Known as FK-506) is an immunosuppressive drug, which is used in organ transplant as the main drug, especially in kidney, liver, heart, and bone marrow transplants [33]. It reduces the immune system activity and decreases the chance of organ rejection. In 1984, it was discovered by fermentation of a sample of Japanese soil that contains the Streptomyces tsukubaensis bacteria [34]. It was approved in 1994 with the brand name as prograf and it is available in the oral and intravenous dosage form [35]. The common dosage form is a regular or extended-release capsule, which has different strengths including 0.5, 1, 3 and 5 mg (Fig. 2). Also, another oral form is granules for suspension with a strength of 0.2 mg or 1 mg. The other dosage form is a sterile solution for intravenous infusion whose strength is 5 mg. However, therapeutic drug monitoring (TDM) is recommended routinely when receiving Tacro [36].

### 6.1 Pharmacokinetics Properties

- Absorption of Tacro is variable where bioavailability in kidney transplantation is 17±10%, while in liver transplantation it is 22±6%. Also, the maximum blood concentrations and area under the curve are greatest when received without food, Cmax is reduced by 71% and AUC is reduced by 39% when taken immediately after a meal [9].
- Volume distribution (VD) of Tacro is variable according to the status of renal and hepatic impairment. VD in renal impairment is 1.07 ± 0.20 L/kg while VD in hepatic impairment is 3.7 ± 4.7 L/kg [9].
- Tacro is highly protein binding which binds in 99% to plasma proteins especially albumin and alpha-1-acid glycoprotein [36].
- Tacro is extensively metabolized in the liver by CYP3A4 and produces an active metabolite called 13-demethyl tacrolimus [36].
- The half-life of Tacro is variable according to the type of transplantation. It lasts for 12 hours in liver transplantation, 19 hours in kidney transplantation, and 24 hours in heart transplantation [33].
- The primary route of Tacro excretion is via urine. And the clearance is variable according to the type of transplantation. It is 0.051 L/hr/kg in heart transplantation, 0.053 L/hr/kg in liver transplantation, and 0.083 L/hr/kg in kidney transplantation [33].

### 6.2 Pharmacodynamic Properties

The mechanism of action begins by inhibiting T-lymphocyte activation through binding to an intracellular protein called immunophilin FKBP-12 or FK506 binding protein [28]. Then, the new complex is formed that consists of tacrolimus-FKBP-12, calmodulin, calcium, and calcineurin. This complex inhibits the phosphatase activity of calcineurin. This action prevents dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT) (Fig. 3). Also, the Tacro inhibits the transcription of genes that encode the following cytokines: IL-3, IL-4, IL-5, and TNF-a.

In addition, Tacro inhibits nitric oxide release and IL-2 receptor expression, so it induces apoptosis and promotes the production of transforming growth factor-beta that leads to immunosuppressive activity [36].

On the other hand, Tacro inhibits mediators from basophils and skin mast cells, so it is effective in the topical treatment of eczema [33].

### 6.3 Most Common Adverse Effects

#### 6.3.1 Gastrointestinal

The following side effects were reported after marketing:

Colitis, gastroesophageal reflux disease, hepatic necrosis, fatty liver, bile duct stenosis, impaired gastric emptying, mouth ulceration, pancreatitis necrotizing, pancreatitis hemorrhagic, stomach ulcer [38].

#### 6.3.2 Weight gain

Obesity resulting from the use of Tacro, after kidney transplantation is quite a common clinical condition. However, a number of studies showed that the weight gain average, by Tacro, in the first year of transplant is between 8-14 kg. Another study mentioned the percent of overweight which increased from 42% in pre-transplant to 72% in post-transplant, while the percent of obesity increased from 10.3% in pre-transplant to 32% in post-transplant [39]. Another cofactor that increases the incidence of obesity is receiving a regimen containing corticosteroid with Tacro. The

patients who use this regimen have a chance of weight gain of more than 30% [40]. Because the weight gain after transplantation has multiple different factors, the main option is lifestyle modification which includes intensive nutrition intervention [41] and physical activity [42]. Another option is taking drugs for other conditions like diabetes or depression, to minimize weight gain [39].

| Patient Population | PROGRAF Capsules* Initial Oral Dosing | Whole Blood Trough Concentration Range |
|---|---|---|
| Kidney Transplant | | |
| With Azathioprine | 0.2 mg/kg/day, divided in two doses, administered every 12 hours | Month 1-3: 7-20 ng/mL<br>Month 4-12: 5-15 ng/mL |
| With MMF/IL-2 receptor antagonist† | 0.1 mg/kg/day, divided in two doses, administered every 12 hours | Month 1-12: 4-11 ng/mL |
| Liver Transplant | | |
| With corticosteroids only | 0.10-0.15 mg/kg/day, divided in two doses, administered every 12 hours | Month 1-12: 5-20 ng/mL |
| Heart Transplant | | |
| With azathioprine or MMF | 0.075 mg/kg/day, divided in two doses, administered every 12 hours | Month 1-3: 10-20 ng/mL<br>Month ≥ 4: 5-15 ng/mL |

**Fig. 2. Initial oral dose of tacrolimus (with azathioprine or mycophenolate mofetil) and its whole blood trough concentration [36]**

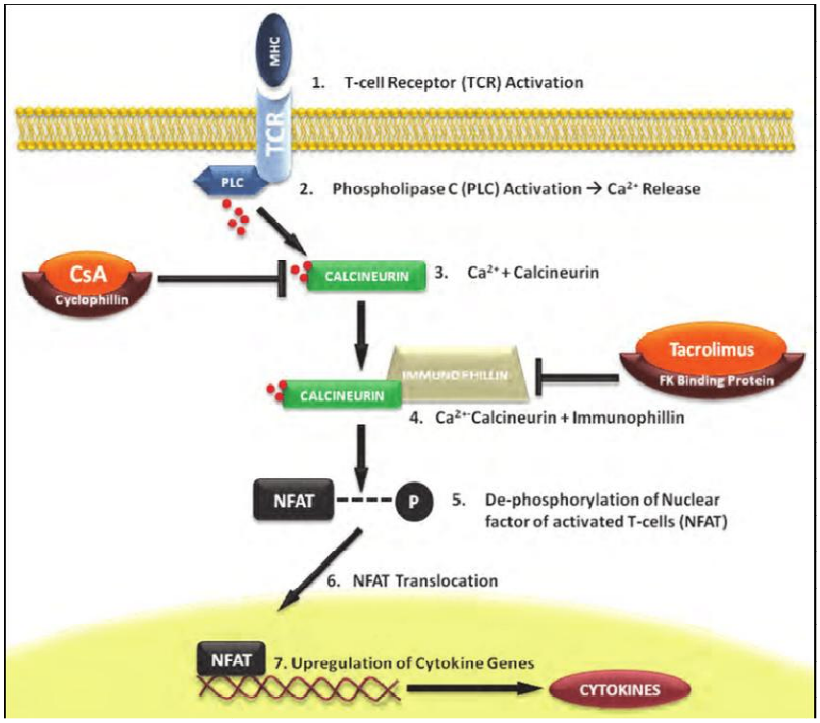


**Fig. 3. Mechanism of action of tacrolimus [37]**

*MHC= Major histocompatibility complex, TCR= T-cell Receptor, PLC= Phospholipase C,NFAT= Nuclear factor of activated T-cells*

**Table 4. Common side effects of Tacrolimus [36]**

| Body system | Adverse reactions | Percentage |
|---|---|---|
| Metabolic | Hypophosphatemia | 49% |
| | Hypomagnesemia | 34% |
| | Hyperlipidemia | 31% |
| | Hyperkalemia | 31% |
| | Diabetes Mellitus | 24% |
| | Hyperglycemia | 22% |
| Gastrointestinal | Diarrhea | 44% |
| | Nausea | 38% |
| | Constipation | 35% |
| Cardiovascular | Hypertension | 50% |
| Hemic and Lymphatic | Anemia | 30% |
| | Leukopenia | 15% |
| Nervous System | Headache | 44% |
| | Insomnia | 32% |
| | Dizziness | 19% |
| Skin | Rash | 17% |
| | Pruritus | 15% |
| Urogenital | Creatinine Increased | 45% |
| | Urinary Tract Infection | 34% |
| Respiratory System | Cough Increased | 18% |
| Miscellaneous | Infection | 45% |
| | Peripheral Edema | 36% |
| | Abdominal Pain | 33% |
| | Optic Neuropathy | 30% |

#### 6.3.3 Infection

Receiving Tacro increases the risk of developing viral, bacterial, fungal, and protozoal infections [33].

Some studies reported an increased risk of cytomegalovirus associated with Tacro use. Furthermore, it caused a significant incidence of BKV nephropathy that leads to polyoma virus-associated nephropathy (PVAN). Also, it increased the incidence of the JC virus that leads to progressive multifocal leukoencephalopathy (PML), which is sometimes fatal [43]. Therefore, the therapeutic level of Tacro should be monitored to maintain the effective dose and avoid this side effect.

#### 6.3.4 Diabetes mellitus

Tacro caused a specific type of diabetes called new-onset diabetes after transplantation (NODAT) which puts kidney transplant patients are at high risk. In some patients, this type of diabetes may be reversible. The blood glucose level and HbA1c percentage should be monitored [7].

### 6.4 Drug-Drug interaction

- Warfarin: There is no interaction found.
- Azathioprine: It must be avoided because both increase immunosuppressive effects and increase the risk of infection.
- Metformin: It decreases the effect of metformin due to pharmacodynamic antagonism.
- Vorinostat: There is no interaction found [9].

### 6.5 Role of Tacrolimus to Induce Diabetes

The main side effect associated with Tacro is hyperglycemia along with other problems like neurotoxicity, hypertension and hyperkalemia. Regrettably, the pathogenesis theory of diabetes generated by Tacro remains unclear, but the researchers mentioned relative opinions about it. Perhaps the answer is that Tacro raises disturbance in the metabolic pathway especially in glucose metabolism through increased oxidative stress. Also, it enhances the autophagy process that works as the adaptive mechanism to maintain the survival of cells during the oxidative stress status.

But the extensive or inadequate clearance of autophagy results in destroying pancreatic islets that leads to reducing the mass of the cell or enhancing apoptosis of β-cell [7]. This result can, therefore, be considered as type 1 diabetes in which β cells are damaged [44]. Alternatively, it may be considered as type 2 diabetes that relates to insulin secretion deficiency and increased insulin resistance [45]. The final stage of this cycle leads to hyperglycemia and results in an unusual type of diabetes called NODAT, which is the famous name [46]. It is also called Post-transplant diabetes mellitus (PTDM) [45].

## 7. NEW-ONSET DIABETES AFTER TRANSPLANT OVERVIEW

### 7.1 Incidence of NODAT

According to several researchers' studies, a strong link was found between the use of immunosuppressive drugs, especially Tacro, and the development of diabetes.

A study that depends on retrospective records, described the NODAT and proved that approximately 30% of kidney transplant recipients who receive immunosuppressant drugs suffer from this complication which leads to an increased risk of cardiovascular disease two to three times [47].

NODAT was hard to define due to the insufficiency of a standard definition for the situation. But we can define it as post-transplant diabetes which is the level of random glucose above 200 mg/dL or by the level of fasting glucose above 140 mg/dl [46].

Generally, NODAT occurs in 10%-25% of the patients receiving Tacro [48]. The rates of NODAT incidence differ according to the type of transplanted organ and post-transplant period. In a previous report based on the follow-up of 388 patients over a period of 52 months, the incidence of NODAT in various durations after post-transplantation was as follows: 15.8% after 1 year, 22.8% after 3 years and 24.5% after 5 years [49]. Also, in a study conducted for 12 months, the rate of NODAT occurrence after the transplant was evaluated for different organs. While the kidney transplant had a high percent of 20–50%, the liver transplant was about 9–21% and finally lung transplant was about 20% [50].

The percentage of the incidence of NODAT is different between combination therapies. The patients treated with Tacro and mycophenolate mofetil or azathioprine have (19%) of the incidence of NODAT. Patients who are treated with sirolimus and mycophenolate mofetil or azathioprine have (17.8%) of the incidence of NODAT. Finally, patients treated with cyclosporine in combination with mycophenolate mofetil or azathioprine will have the lowest incidence of NODAT (15.6%) [49,51].

### 7.2 Risk Factors of NODAT

In another study, the researcher Adnan Sharif (2010) discussed the main risk factors for hyperglycemia in transplant patients which can be divided into non-modifiable and modifiable risk factors.

Non-modifiable risk factors include age, gender, ethnicity, family history of diabetes, causes of end-stage renal failure, genetic susceptibility, innate immunity, donor characteristics, and education.

On the other hand, modifiable risk factors, involve previous stress diabetes, obesity (BMI), metabolic syndrome, high level of pre-transplantation triglyceride, cytomegalovirus infection, hepatitis C virus infection, immunosuppressive drugs (Tacro, sirolimus, ciclosporin, corticosteroids), rejection episodes, antihypertensive agents (thiazide diuretics, β-blockers), impaired glomerular filtration rate and biochemical abnormalities (low magnesium, high uric acid).

Understanding these factors is critical to guide the therapeutic regimen and help physicians carry out protective strategies [52].

### 7.3 Severity of NODAT Overview

Gradually within a long term, the seriousness of NODAT can cause complications for many parts of the body like the nerve, heart, eye and kidneys. It shows by increasing risks of organ rejection, cardiovascular disease, infection, or death [53].

The common problem is cardiovascular disease that includes cardiovascular troubles and may be fatal such as heart attack, coronary artery disease like angina, stroke and atherosclerosis [54]. The chances of stroke in diabetic patients are 1.5 times higher than in normal people [55].

On the other hand, diabetic patients suffer from poor circulation due to narrow and hardened blood vessels, especially in their feet and legs.

This leads to attacks by infection, delays in healing, and the development of gangrene that needs amputation, which is present 25 times more than in normal people [54].

Kidney disease or diabetic nephropathy results from damage in small blood vessels and filtering units in the kidneys. Early damage may be unnoticed but the first sign is an elevated microalbumin level in the urine. If diabetic nephropathy is untreated, it raises blood pressure and increases protein release into the urine. Advanced stages are characterized by impaired kidney function and rises of serum creatinine. Finally, the case may suffer the kidney failure stage and may require dialysis or further new transplantation [56].

## 8. TRADITIONAL TREATMENT OF NODAT

### 8.1 Classical Therapy for NODAT

In 2003, the international Expert Panel which consists of specialists from both diabetes and transplant fields, formed the International Consensus Guidelines for the diagnosis and management of NODAT [46].

In the same way, another study discusses the strategies and drugs that can be used for NODAT (Fig. 4) [57].

First, glucose, blood pressure, and lipid levels must be monitored routinely as a suggestion of American diabetes association guidelines. Second, Hemoglobin A1c levels must be monitored every 3 months while the target level is <7.0%. Third, lifestyle modification is an important strategy where patients must adhere to a diet with regular exercise leading to weight loss and reducing insulin resistance [6].

On the other side, the pharmacologic therapy for NODAT is based on a modification of immunosuppressive dose with oral hypoglycemic agents and insulin which is selected according to the severity of the case (Fig. 5). Oral hypoglycemic agents, which can be used as monotherapy or in combination with other oral agents and/ or insulin, include the oldest classes. They cover sulfonylureas, biguanides, thiazolidinediones as well as alpha-glucosidase inhibitors and well the familiar one is metformin. Insulin therapy is started when glycemic control fails to achieve fasting plasma glucose <120 mg/ dl (6.7 mmol/l) or HbA1C <7% [57].

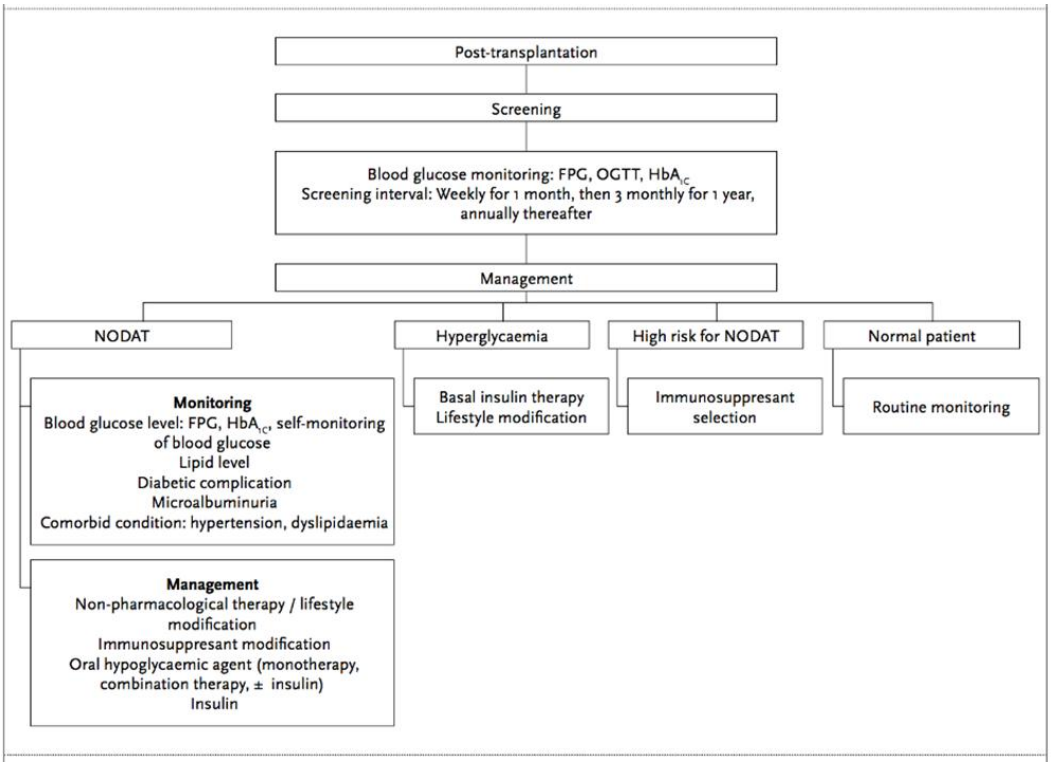


**Fig. 4. Post-transplantation screening and management [57]**

*FPG= Fasting plasma glucose, OGTT= Oral glucose tolerance test, Hb A 1c= Hemoglobin A1c*

| | Metformin | Sulfonylureas & Glitinides | Thiazolidinediones | α-glycosidase Inhibitors |
|---|---|---|---|---|
| **Main Mechanism** | Decrease production of hepatic glucose. | Increase secretion of insulin. | Increase sensitivity to insulin. | Delay carbohydrate gastrointestinal absorption. |
| **Range of dose** | 500 – 2550 mg/day. | Glipizide: 2.5- 40 mg/ day.<br>Glyburide: 1.25-20 mg/day.<br>Repaglinide: 0.5- 4 mg/ day.<br>Nateglinide: 60-120 mg /day. | Rosiglitazone: 4-8 mg/day.<br>Pioglitazone: 7.5-45 mg/day. | Acarbose: 25 -100 mg/day.<br>Miglitol: 50 -100 mg/ day. |
| **Reduction in HbA1c (%)** | 1 - 2 | 1 - 2 | 0.5 - 1 | 0.5 - 1 |

**Fig. 5. Oral hypoglycemic drugs for new onset diabetes after transplant [57]**
*Hb A 1c= Hemoglobin A1c*

## 8.2 Complication of Classical Therapy

It is well known that classical hypoglycemic drugs have several side effects that may be dangerous for transplantation. The significant effects are lactic acidosis, hypoglycemia, anemia, weight gain, congestive heart failure, cancer, fractures, peripheral and pulmonary edema [46].

Lactic acidosis may have a severe and potentially fatal effect. Usually, the lactic acid is associated with hypoglycemic drugs and its levels become excessive during treatment. The kidney excreted both of them, but the effectiveness of elimination is lower than normal in the transplantation state.

So, the drugs with lactic acid become accumulated in the body and cause many complications such as kidney failure that damage the graft [58].

## 9. CONCLUSION

In conclusion, the requirement for organ transplants remains ongoing. Moreover, this field has the challenge to protect organs from rejection.

We note that the immunosuppressive drug is very important in organ transplantation to suppress the immune system with the least harmful side effects.

However, the immunosuppressant has long-term risks like the development of infections, diabetes, osteoporosis and cancer.

Tacro is a potent immunosuppressive drug but it causes a specific type of diabetes called NODAT. It consists of oxidative stress, autophagy and apoptosis process of β-cell. In fact, NODAT causes severe complications while patients may need further new transplantation.

Therefore, it should promote cooperation between organ transplantation teams and immunologist and endocrinologist researchers to improve the transplantation status and suggest new methods of therapy for NODAT to avoid rejection of organs.

## DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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