Review Article

Insulin use in transplant patients

Om J Lakhani[1], Hardik Kotecha[2]

India is the preferred destination for organ transplant in South-East Asia. Tacrolimus and Prednisolone are commonly used in the immunosuppressive regimens after transplant to prevent allograft rejection. Both of these agents potentially cause hyperglycemia leading to Post-transplantation diabetes mellitus (PTDM). Management of PTDM is a clinical challenge because it is required to achieve pristine glycemic control to avoid complications. Insulin is the preferred agent for management of PTDM both in cases of patients having pre-existing diabetes mellitus and new onset of diabetes post-transplantation (NODAT). The review focusses on use of insulin in post-transplant patient with special focus on newer 'smart' insulin protocols which can optimize glycemic management.

[*J Indian Med Assoc* 2018; **116:** 31-4 & 39]

Key words **: PTDM, NODAT.**

India is fast becoming the hub for organ transplant in Asia. India has second largest number of cases of live donor kidney transplantation in the world. There are more than 7500 cases of kidney transplant being performed in various centers across the country annually[1]. Along with this there are more than a 1000 liver transplants performed each year in India[2]. The number of cases of other organs transplants like heart transplant and combined kidney and pancreas transplant are also growing in India.

This review focusses on management of diabetes mellitus post solid organ transplant, especially with regards to use of Insulin.

Definition of Terminologies :

Patients who undergo transplant must receive immunosuppression to prevent allograft rejection. Many of the agents used in immunosuppression lead to hyperglycemia. There are two terminologies used for this- New onset of diabetes after transplantation (NODAT) and Post-transplantation diabetes mellitus (PTDM). NODAT is defined by the international consensus guidelines published in 2003 (Table 1)[3].

A decade after the first consensus meeting in 2003, a second international consensus panel met to update the criteria for NODAT. At that point of time it was decided to use the term 'Post-transplantation diabetes mellitus' (PTDM) instead of NODAT since many of the cases of diabetes diagnosed after transplant may have pre-existing diabetes mellitus and the diabetes may not be truly 'new-onset'[4]. The updated American Diabetes Association (ADA) guidelines suggest that the diagnosis of PTDM should be made after the patient is on a stable immunosuppressive regimen and is free from any acute infection[5].

Table 1 – *Definition of new-onset diabetes after transplantation: modified from the 2003 international consensus guidelines*[1]

To define Post-transplant diabetes mellitus, both the following criteria must be fulfilled

1. Raised Plasma glucose (Any one of the below)
   a. Symptoms of diabetes plus casual PG concentrations =200 mg/dL. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss OR
   b. FPG =126 mg/dL. Fasting is defined as no caloric intake for at least 8 hours or
   c. 2-hr PG =200 mg/dL during an oral glucose tolerance test. The test should be performed as described by WHO, using a glucose load containing equivalent of 75 g anhydrous glucose dissolved in water.
2. The patient has undergone solid organ transplantation, other than pancreas or islet cell transplantation

PG= Plasma glucose; FPG = Fasting plasma glucose;
WHO= World health organization

Irrespective of the name or the time-frame it is important to note that hyperglycemia after organ transplant is associated with considerable morbidity and increased risk of morality. There is also an increased risk of rejection of the transplanted organ. Hence it is imperative to achieve pristine glycemic control after transplant which is not easy to achieve.

Role of Immunosuppressents as Etiology for PTDM :

Immunosuppression after solid organ transplant is divided into two phases. The first is the initial induction regimen followed by maintenance regimen. Rabbit antithymocyte globulin along with high dose of glucorticoids are often used in the initial induction regimen to prevent acute rejection. The maintenance regimen

[1]Department of Endocrinology, Zydus Hospital, Ahmedabad 380054
[2]Department of Gastroenterology, Zydus Hospital, Ahmedabad 380054

is often composed of cyclosporine or tacrolimus combined with glucocorticoids with addition of Azathioprine or Mycophenolate mofetil. Nowadays, tacrolimus is preferred in most transplant regimens considering its improved efficacy compared to cyclosporine[6].

Glucocorticoids enhance hepatic gluconeogenesis and increase insulin resistance both of which produces significant hyperglycemia. Tacrolimus is known to reduce insulin synthesis and secretion[4]. DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C Monitoring Versus Tacrolimus) was a randomized controlled trial that evaluated the risk of NODAT in patients who received cyclosporine based regimen versus those who received tacrolimus based regimen post-transplant. The study concluded that tacrolimus based regimen produces more NODAT compared to cyclosporine based regimen six months after transplant. This is a dose dependent effect, with higher doses of tacrolimus producing more severe hyperglycemia[7]. In our own clinical practice, we have found that hyperglycemia secondary to tacrolimus was more difficult to tackle compared to the impact of glucocorticoids which was a more predictable[8].

The Rationale for Use of Insulin In PTDM Patients :

In patients not having pre-existing diabetes mellitus, it is imperative that NODAT is diagnosed early after transplant and treated effectively. In those having pre-existing diabetes mellitus, it is important to monitor blood glucose regularly after transplant and preempt the worsening of glycemic control that we expect to occur with use of immunosuppressive agents. Needless to say, it is important to screen for diabetes mellitus in all patients before transplant. Additionally, it is also routinely recommended to perform Oral glucose tolerance test (OGTT) 5 days post-transplant amongst patients without pre-existing diabetes mellitus to diagnose NODAT. Additionally, OGTT must be repeated 12 weeks post-transplant to supplement the day 5 OGTT[4].

Many of these patients receive high dose glucorticoids immediately post-transplant to prevent acute allograft rejection. Glucocorticoids are a 'stress-test' for diagnosis of diabetes mellitus and often patients having high risk for diabetes mellitus develop hyperglycemia with high dose of glucocorticoids post-transplant. During this phase use of insulin is inevitable especially till the patient remains hospitalized and hence is vulnerable. Many of these patients need insulin-infusion to tackle the emergent hyperglycemia.

The Recent ADA guidelines suggest the following for management of patients with PTDM – a) All patients should be given Basal-bolus insulin during the hospital stay b) At the time of the discharge, if the patient had pre-existing diabetes and was well-controlled on oral medications, they may continue taking the same and c) those having persistent hyperglycemia post-transplant or poor control of diabetes mellitus before transplant, Insulin may be continued[9].

In our experience, the use of oral anti-diabetics alone in patients with PTDM is challenging. Many of the patients who come for transplant and have pre-existing diabetes, have poor baseline glycemic control. Hence, continuing the same oral anti-diabetics which the patient was taking is often not enough. Secondly, the patients who come for transplant have certain contraindications which limit the choice of oral antidiabetics. Additionally, the immunosuppressant given after transplant add fuel to fire and worsen the glycemic control post-transplant. It must also be kept in mind that we require excellent glycemic control in post-transplant patients to prevent complications. Hence most of the patients with preexisting diabetes often end up requiring insulin.

Those patients who develop diabetes mellitus de novo after transplant also benefit from Insulin use. Some of these patients require adjustment to the immunotherapy regimen which needs adjustment of the medications as well. Insulin offers the flexibility of fine tuning of the dose which is not provided by oral anti-diabetics. Oral antidiabetics are adequate for those who have mild hyperglycemia post-transplant and are adherent to the lifestyle measures prescribed for diabetes mellitus.

So in summary, insulin is probably the agent of choice for management of diabetes in most patients with PTDM irrespective of their previous glycemic status.

Insulin Protocol for PTDM :

We believe it is imperative to design 'smart' insulin regimen for patients with PTDM and not prescribe blanket basal-bolus insulin regimen or pre-mixed insulin therapy. Tarcolimus and prednisolone are often often the culprits for worsening of glycemic status post-transplant. Hence an insulin protocol needs to be designed to counteract the impact of these two agents.

(A) PTDM Patients Having Pre-existing Diabetes Mellitus :

In those patients having pre-existing diabetes mellitus, we recommend the use of basal-bolus insulin regimen with addition of insulin NPH given along with prednisolone to counteract the hyperglycemic effect of prednisolone.

We recently published a clinical trial in which we compared our novel insulin protocol for management of glucocorticoid-induced hyperglycemia amongst hospitalized patients with basal-bolus insulin which is standard of care in these patients. The essence of this protocol was that an

additional insulin was added which matches the glycemic profile of the insulin administered. For example, the hyperglycemic impact of prednisolone matches the hypoglycemic effect of insulin NPH perfectly. Hence, if Insulin NPH is given along with prednisolone it negates the effect of prednisolone. If the dose of prednisolone is changed, a corresponding change in insulin NPH can negate the impact of the change in the dose of prednisolone. The new protocol not only was more effective in achieving better glycemic control but also lead to reduced glycemic variability[10].

In our clinical experience with management of PTDM patients, we learnt that tacrolimus is a bigger challenge in our endeavor to achieve good glycemic control. Additionally, we learnt that transplant physicians and surgeons often change the doses of tacrolimus based on Serum Tacrolimus levels and clinical criteria which has significant impact on the glycemic control. Hence we designed a new protocol to negate the effect of tacrolimus along with prednisolone in patient with PTDM and also factor in the changes in doses of tacrolimus. Table 2 gives the protocol we use in PTDM patients with pre-existing diabetes. We retrospectively analyzed our protocol vis-à-vis standard basal-bolus insulin regimen and found that our protocol is as effective and safe as standard basal-bolus insulin regimen in management of PTDM in patients having pre-existing diabetes mellitus. We presented our finding in at the International Hospital Diabetes Meet in San Francisco in 2015[11]. The benefit our protocol provided was that we could safely correct the insulin regimen if the dose of the immunosuppressant was changed without risking hyperglycemia or hypoglycemia. Based on the feedback we received at the conference, we designed a new protocol exclusively for the patient who develop new onset of diabetes after transplantation (NODAT) which is discussed subsequently.

Table 2 – *Insulin protocol for patients post-transplant who have pre-existing diabetes mellitus*

1. The total dose insulin is calculated using the formula of 0.4 x body weight in kg
2. BASAL DOSE: 50% of the total dose is given as basal. The basal insulin dose is administered at bedtime. Insulin glargine is used as basal insulin.
3. BOLUS DOSE: 50% of the total dose is given as bolus, which is further divided into three equal doses and given before meals. Insulin lispro or aspart are generally used for bolus and is administered 15 min before the meal.
4. CORRECTION FOR TACROLIMUS- 10% of basal insulin dose is increased per every 1 mg/day of Tacrolimus added to the regimen (till a maximum increase of 50% basal dose)
5. CORRECTION FOR PREDNISOLONE- Insulin NPH is given in the dose of in the dose of 0.1 mg/kg for every 10 mg of prednisolone (till a maximum dose of 0.5 mg/kg) to be given along with prednisolone dose
6. Finger-stick glucose are monitored 4 times a day- three times a day before meals and at bedtime
7. The dose of Basal insulin is increased by 10% if the morning fasting blood glucose in the range of 140-199 and it is increased by 20% for if the morning fasting blood glucose is >200 mg/dl.
8. The dose of basal insulin is reduced by 10% if the morning fasting blood glucose is in the range of 70-100 mg/dl and reduced by 20% if the morning fasting blood glucose is below 70 mg/dl
9. The bolus dose of insulin is increased based on the titration regimen as described in the endocrine society guidelines.

(B) PTDM Patients Having New Onset Diabetes after Transplantation (NODAT):

As discussed above, patients not having pre-existing diabetes often develop diabetes mellitus post-transplant which is often attributed to the immunosuppressant which are used. The effect of immunosuppressant on hyperglycemia is often dose dependent with higher dose leading to more severe hyperglycemia. Though in some of these patients oral antidiabetics along with lifestyle measure suffices, a lot of these patient may end up requiring insulin. The threshold for insulin initiation in these patients should be less, as these patients need excellent glycemic control to avoid complications and transplant rejection. Additional insulin can provide an additional degree of flexibility which oral medications are unable to provide.

As discussed above, from our experience with Glucocorticoid-induced hyperglycemia and management of PTDM and based on the feedback we received from experts on Hospital hyperglycemia, we designed a new protocol for management of hyperglycemia in patients with NODAT. The protocol has two components. Insulin glargine is given to negate the effect of tacrolimus and insulin NPH is given to counter the effect of prednisolone. The dose of these insulin are adjusted based on the doses of the immunosuppressant used and patient's capillary blood glucose readings. In some cases we require additional pre-meal short acting insulin if the post meal blood glucose readings are high and patient has not achieved the target HbA1c. However, in most cases we require just two doses of insulin as described above. This protocol is described in Table 3.

We conducted a small prospective pilot trial to compare our protocol with standard basal-bolus insulin regimen. The results of our study were presented at the Endocrine society conference in Boston in 2016. We found that our new protocol performed as well as standard basal-bolus insulin protocol to achieve good glycemic control. However, our new protocol had significantly less glycemic variability compared to standard basal-bolus insulin regimen. Additionally, we were able to able achieve an acceptable glycemic control with use of just two insulin doses in a day. Finally, the protocol provided a reasonable degree of safety if the doses of the immunosuppressant were changed[12]. The limitation of our study was that it was based on a small number of patients and conduct of a

larger prospective trial based on the above principle can help bring out more clarity to the management of hyperglycemia in NODAT patients.

Future Prospects :

With the increasing number of organ transplant being conducted across the country, management of PTDM is going to a major challenged faced by Endocrinologists and physicians who work in transplant centers. Development of immunosuppressant which donot cause hyperglycemia may be a potential solution, however the quality of immunosuppression also cannot be compromised to prevent rejection of allograft. Hence, it is important for physicians to understand the pathophysiology of how these agents can cause hyperglycemia and design a protocol which can negate the effect of the same. Continuous glucose monitoring (CGMS) is an effective tool for not only understanding the hyperglycemic effect of these immunosuppressive agents but also in effectively tackling hyperglycemia by using the CGMS to guide deployment of insulin regimen. Fig 1 shows the CGMS findings of a patient post liver transplant who developed NODAT secondary to use of tacrolimus and prednisolone. The hyperglycemia was effectively managed using insulin regimen leading a good glycemic control (Fig 1).

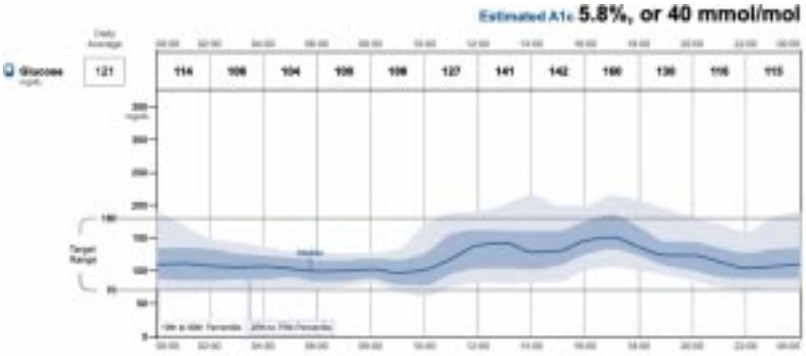

Fig 1 — CGMS report of a patient having NODAT post-transplant managed effectively using insulin regimen

Table 3 — *Insulin Protocol for management of NODAT patients*

STEP 1 : NEGATE THE EFFECT OF PREDNISOLONE

- A patient receiving Prednisolone would be given 0.1 units/kg of Insulin NPH (along with the Prednisolone) for every 10 mg of Prednisolone to a maximum of 0.4 units/kg of Insulin NPH.
- The dose can be subsequently titrated depending on the dose of prednisolone.

STEP 2: NEGATE THE EFFECT OF TACROLIMUS

Patients on tacrolimus would receive Insulin Glargine in a dose of 0.15 units/kg plus 10% additional dose for every 1 mg of Tacrolimus (rounded to the nearest whole number) at bedtime. If no tacrolimus is given then, no glargine is added.

STEP 3: FIX THE FASTING (if pre-breakfast blood glucose in not in target range)

- Once the dose of tacrolimus and prednisolone are fixed, the dose of Insulin glargine is titrated based on the pre-breakfast blood glucose with a target range of 100-140 mg/dl. If pre-breakfast blood glucose is >140 mg/dl, the dose of glargine is increased by 20% the next day and if the pre-breakfast blood glucose is <100 mg/dl, the dose of insulin glargine is reduced by 20% the next day. If the pre-breakfast blood glucose is already in the target range, then no adjustment of glargine dose is required.
- If the patient was not on tacrolimus and was not given any glargine as per step 3 and if the pre-breakfast blood glucose is above 140mg/dl, then 0.2 units/kg of glargine is added at bedtime and subsequently titrated.
- All this is based on the assumption that prednisolone is given in the morning time with breakfast. If prednisolone is given at any other time, then the titration of the insulin dose is done based on the blood glucose reading taken before the prednisolone is given.

Conclusion :

Post-transplantation diabetes mellitus (PTDM) is an important clinical problem for Endocrinologists and physicians who work in transplant centers across the country. Immunosuppressant like tacrolimus and prednisolone which are used in transplant patients often lead to significant hyperglycemia which is often challenging to tackle. Use of insulin protocols which take into account the effect of these immunosuppressive agents can help manage diabetes mellitus more effectively in transplant patients.

References

1 Shroff S — Current trends in kidney transplantation in India. Indian J Urol [Internet]. 2016 [cited 2018 Jan 5];32(3):173-4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27555672

2 Soin A, Thiagarajan S — Liver transplant scene in india. MAMC J Med Sci [Internet]. 2016 [cited 2018 Jan 5];2(1):6. Available from: http://www.mamcjms.in/text.asp?2016/2/1/6/174841

3 Davidson JA, Wilkinson A — International Expert Panel on New-Onset Diabetes after Transplantation. New-Onset Diabetes After Transplantation 2003 International Consensus Guidelines: an endocrinologist's view. Diabetes Care [Internet]. 2004 Mar 1 [cited 2018 Jan 2];27(3):805–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14988309

4 Shivaswamy V, Boerner B, Larsen J — Post-Transplant Diabetes Mellitus: Causes, Treatment, and Impact on Outcomes. Endocr Rev [Internet]. 2016 Feb [cited 2018 Jan 5];37(1):37–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26650437

5 Introduction: Standards of Medical Care in Diabetes—2018. Diabetes Care [Internet]. 2018;41(Supplement 1):S1–2. Available from: http://care.diabetesjournals.org/lookup/doi/10.2337/dc18-Sint01

6 Sharma R, Rajasekar MR, Raghuvanshi A — Immunosuppression strategies after liver transplantation: a single centre experience in 57 liver transplant recipients. Indian J Surg [Internet]. 2007 Oct 30 [cited 2018 Jan 5];69(5):187–90. Available from: http://link.springer.com/10.1007/s12262-007-0018-0

(Continued on page 39)

(Continued from page 34)

7 Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, *et al* — Results of an International, Randomized Trial Comparing Glucose Metabolism Disorders and Outcome with Cyclosporine Versus Tacrolimus. Am J Transplant [Internet]. 2007 Jun [cited 2018 Jan 5];7(6):1506–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17359512

8 Lakhani OJ, Kumar S, Tripathi S, Desai M, Seth C — Comparison of Two Protocols in the Management of Glucocorticoid - induced Hyperglycemia among Hospitalized Patients. 2017;

9 American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care [Internet]. 2018 Jan 8 [cited 2018 Jan 5];41(Supplement 1):S13–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29222373

10 Lakhani OJ, Kumar S, Tripathi S, Desai MA, Seth C — Correlation between Basal Insulin Glargine Dose Required in Achieving Target Fasting Blood Glucose and Various Clinical and Laboratory Parameters in Hospitalized Noncritical Patients. 2017;1-4.

11 Lakhani O, Kumar S, Desai M, Goyal A— Analysis of Protocol-Based Post-Transplant Diabetes Mellitus... In: International Hospital Diabetes Meeting [Internet]. San Francisco; 2015 [cited 2018 Jan 5]. Available from: https://www.diabetestechnology.org/ihdm/submitted-abstracts.pdf

12 Lakhani O, Kumar S — Novel Insulin Algorithm for Management of Hyperglycemia in Hospitalized Patients with New Onset of Diabetes after Transplant (NODAT): A Pilot Study?: Novel Treatment for Diabetes (posters). In: Endocrine Society's 98th Annual Meeting and Expo [Internet]. Boston; 2016 [cited 2018 Jan 5]. Available from: http://press.endocrine.org/doi/abs/10.1210/endo-meetings.2016.DGM.22.FRI-692.