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To Study the Efficacy and to Compare Conventional Insulin Versus DPP IV Inhibitor Linagliptin Versus Sulfonylurea Glimepiride in the Treatment of New Onset Diabetes After Transplant (NODAT)

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Abstract
Solid organ transplantation is currently an important option for the treatment of many types of organ failure, including kidney, liver, heart, pancreas, lung and small bowel. Out of these, kidney transplant is one of the most frequently conducted throughout the world. Renal transplantation has become a great success story overall, mainly because kidney transplant recipients (KTRs) benefit from increased survival rates and higher quality of life compared with dialysis patients. To determine the efficacy of available treatment options for New Onset Diabetes after Transplant (NODAT) by a comparative prospective study between Conventional Insulin regime versus DPP IV inhibitor Linagliptin versus Sulfonylurea Glimepiride. To compare the three study groups in terms of their role, effectiveness, side effects and treatment outcome in duration of three months after start of treatment in newly diagnosed NODAT cases. Hospital based prospective, observational study conducted in Indraprastha Apollo Hospital New Delhi for a period of 2 years between June 2017 to May 2019. Statistical analysis: The results are presented in frequencies, percentages and mean±SD. The Chi-square test was used to compare categorical variables among the groups. The one way analysis of variance (ANOVA) followed by Tukey's post hoc tests was used to compare continuous variables among the groups. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA). Three groups of 20 patients each were created and categorized as: Group A for Insulin, Group B for Glimepride and Group C for Linagliptin. Efficiency wise, Insulin brought down the sugars to the maximum extent as compared to Glimepride and Linagliptin. Glimepride and Linagliptin had comparable efficacy with Glimepride showing slightly better results in some cases. However, Glimepride also showed incidents of hypoglycemia especially in patients with deranged kidney function. Linagliptin alone was not effective in 3 of its patients so those had to be supplemented with some other oral hypoglycemia agent at the end of three months. This study concluded the potency of the three testing drugs in achieving glyceric control as follows: Insulin (Group A)>Glimepride (Group B) >Linagliptin (Group C).Insulin to be the preferred drug in uncontrolled hyperglycemia, sick complicated states, hospitalized patients and in early post-transplant period. Glimepiride to be used cautiously in patients with deranged renal parameters as it causes more incidence of hypoglycemia. Linagliptin is safe and efficacious in all cases, preferred 1st line drug in mild cases with stable sugars and as an adjunct to other hypoglycemia drugs.

INTRODUCTION

Incidence of NODAT ranges from 10-74%. This number is alarming, because NODAT is a major risk factor for cardiovascular disease and mortality[1,2] and is also associated with reduced kidney graft survival, infections and increased health care costs. Impaired glucose tolerance (IGT), which naturally precedes the onset of diabetes, has likewise been linked to mortality, indicating that an even greater number of KTRs may be at risk[3].

NODAT has commonly been viewed as resembling type 2 diabetes mellitus (T2DM)[13]. Hyperglycemia after transplantation, however, appears rapidly and the transition to full-blown diabetes is clearly much faster than in T2DM, due to a variety of transplant-specific mechanisms. Evidence suggests that beta-cell dysfunction rather than insulin resistance is the main contributing factor for NODAT development.

The risk factors of NODAT range from having preexisting ones like age more than 40, obesity to genetic predisposition to immunosuppression used with special emphasis to steroids, CNI's and motor inhibitors. Infections like hepatitis C and CMV along with inflammation from rejection and deceased donor cases are comparatively more susceptible to develop NODAT[4-6].

Treatment of NODAT has all those options available as for routine T2DM patients. Most of them are treated with conventional insulin regimen of basal bolus therapy, however use of other group drugs such as metformin, DPP IV inhibitors are also commonly used in practice. With the introduction of newer drugs in market such as GLP 1 analogues and SGLT2 inhibitors, clinicians have ample number of options to try from in the treatment of NODAT. However due to lack of sufficient available research data and paucity of randomized controlled trials comparing the efficacy of the available drug options in the treatment of NODAT, we were encouraged to research on this topic. So hereby, we aim to conduct a study to compare the efficacy of conventional insulin regimen treatment versus sulfonylurea Glimepiride versus DPP IV inhibitor Linagliptin in the treatment of NODAT along with a head on comparison of their side effects and overall potency.

Aims and Objectives:

- To determine the efficacy of available treatment options for New Onset Diabetes after Transplant (NODAT) by a comparative prospective study between Conventional Insulin regime versus DPP IV inhibitor Linagliptin versus Sulfonylurea Glimepiride.
- To compare the three study groups in terms of their role, effectiveness, side effects and treatment outcome in duration of three months after start of treatment in newly diagnosed NODAT cases[7].

MATERIALS AND METHODS

This study is hospital based, single center, prospective, observational study conducted in the department of Nephrology of Indraprastha Apollo Hospital New Delhi for a period of 2 years between June 2017 to May 2019. On the basis of previous study, prevalence of NODAT was 10-74%[12]. Taking this value as reference, the minimum required sample size with 2.5% margin of error and 2.5% level of significance is 20 patients. So total sample size taken is 60 patients with 20 patients in each of the 3 treatment groups.

Inclusion Criteria:

- Post-transplant patients newly diagnosed to be NODAT as per the recent guidelines of diagnostic criteria (Fasting glucose >126 mg/dL (7 mmol/L) on more than one occasion., Random glucose >200 mg/dL (11.1 mmol/L) with symptoms., Two-hour glucose after a 75-g OGTT of >200 mg/dL (11.1 mmol/L) and HbA1c >6.5%[8,9].
- Patients with stable graft function in the last 3 months with no significant change of KFT's over this time.

Exclusion Criteria:

- No past history of T2DM.
- Patient on maintenance immunosuppression with no history of being administered pulse steroids in the past three months excluding any rejection.
- No history of any active infection be it viral, fungal or bacterial at the time of enrolment in the study.
- Positive status of CMV DNA PCR or of BK Virus DNA PCR.
- Positive status of Hepatitis C.
- Tobacco chewers or Alcohol consumers. After fulfilling this inclusion and exclusion criteria, selected patients were enrolled for the study.

Three groups of 20 patients each were made and treatment regimens were created. First group was given conventional INSULIN basal bolus regimen, second group was given Sulfonylurea GLIMEPRIDE and the third group was given DPP IV inhibitor LINAGLIPTIN. All drugs were given in their appropriate dosing in each group and according to the requirement of each patient. Free, Full and informed consent of the

patients was taken. All investigations and work up were done for them as per the pre-structured preform. Detailed history was extracted from the patients which included their basic disease, donor details, transplant details in terms of ABO compatibility and use of induction agent. Time since transplant for diagnosis of NODAT was also recorded in data along with current immunosuppression which the patient is taking. Baseline renal functions at start of study were also recorded. Infection was ruled by exhaustive clinical examination along with labs of blood cultures and urine cultures. Transplant related viral infections like CMV and BK virus were also ruled out by their DNA PCR testing[10,11].

Hepatitis C virus status was estimated by anti HCV antibody positivity and those coming positive were excluded from the study. Glycaemic status of the patient was analysed using investigations of FBS, PPBS and HbA1c done both at the start of the study and at the end of three months. Side effects such as hypoglycemia with the use of any of the particular drug were also recorded in our investigating data. Drug efficacy was also judged by need of any second ant hypoglycemia agent in these three months in any of the testing groups and this was also recorded[12,13].

Statistical Analysis: The results were expressed in frequencies, percentages and mean±SD. The Chi-square test was used to compare categorical variables among the groups. The one way analysis of variance (ANOVA) followed by Tukey's post hoc tests was used to compare continuous variables among the groups. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS AND DISCUSSIONS

20 patients each were enrolled into three different treatment groups each of Insulin, Glimepiride and Linagliptin. They were followed up for next three months and head on comparison done. Group A: Insulin, Group B: Glimepride, Group C: Linagliptin.

None of the patients enrolled in the study were tobacco chewers or alcohol consumers. Active infection was ruled out by blood cultures and urine cultures and none of the patients were positive for them. Any patients having Hepatitis C positive status, CMV PCR or BK virus DNA PCR positive status were excluded from the study as per exclusion criteria. Only 2 patients in each group were on mTOR inhibitors and this difference was not statistically significant (p value>0.05).Patients were on same dose of immunosuppression during the course of the study period of three months and any of those patients requiring dose modification in the same were excluded from the study as per the exclusion criteria[14].

The mean age of patients of Group A, Group B and Group C was 47.25±12.28, 43.65±12.88 and 45.05±11.25 years respectively. There was no significant (p>0.05) difference in age among the groups showing comparability of the groups in terms of age. More than half of patients of Group A (60%), Group B (65%) and Group C (60) were males. There was no significant (p>0.05) difference in gender among the groups showing comparability of the groups in terms of gender. The mean BMI of patients of Group A, Group B and Group C was 23.45±2.49, 22.42±2.01 and 22.86±2.13 years respectively. There was no significant (p>0.05) difference in BMI among the groups showing comparability of the groups in terms of BMI.

More than one third of patients of Group A (35%), 40% of Group B and 20% of Group C had HTN. However, 30% of Group A, 35% of Group B and 45% of Group C had CGN. There was no significant (p>0.05) difference in basic renal disease among the groups. Majority of patients of Group A (90%), Group B (90%) and Group C (90%) had compatibility. However, 10% in each group A, B and C were transplants having ABO incompatible donors. There was no significant (p>0.05) difference in compatibility among the groups.

More than half of patients of Group A and Group B (55%) and 40% of Group C had ATG as induction agent. However, 15% of Group A and Group B and 25% of Group C had BASILIXIMAB as induction agent. There was no significant (p>0.05) difference in induction agent among the groups.

The baseline serum creatinine was 1.01±0.22, 1.16±0.29 and 1.14±0.26 in patients Group A, Group B and Group C respectively. There was no significant (p>0.05) difference in baseline serum creatinine among the groups.

The baseline steroid dose was 7.00±4.10, 5.00±0.00 and 5.375±1.22 in patients Group A, Group B and Group C respectively. There was significant (p<0.05) difference in baseline steroid dose among the groups[16,17].

The time of NODAT was <6 months among 80% patients of Group A, 35% of Group B and 30% in Group C. However, the time of NODAT was >12 months in 15% patients of Group A and Group B and in 25% of Group C. There was significant (p = 0.006) difference in the time of NODAT among the groups. The time of NODAT was also significantly different between Group A and Group B (p = 0.004) and Group B and Group C (p = 0.003).

The analysis of variance showed that there was significant (p = 0.0001) difference in baseline FBS and PP among the groups. The post-hoc tests showed that FBS and PP were significantly (p = 0.0001) higher in Group A than Group B and Group C at baseline[18,19].

The analysis of variance showed that there was significant (p = 0.0001) difference in baseline HbA1C

among the groups. The post-hoc tests showed that HbA1C was significantly (p = 0.0001) higher in Group A than Group B and Group C at baseline.

The incidence of hypoglycemia was in 25% patients of Group B (5 patients) and in 5% patients of Group C (1 patient). There was no significant (p>0.05) difference in the incidence of hypoglycemia among the groups.

The analysis of variance showed that there was significant difference in baseline FBS (p = 0.002) and PP (p = 0.0001) among the groups after 3 months. The post-hoc tests showed that FBS and PP were significantly (p<0.05) higher in Group A than Group B and Group C after 3 months.

The analysis of variance showed that there was significant (p = 0.0001) difference in HbA1C among the groups after 3 months. The post-hoc tests showed that HbA1C was significantly (p = 0.0001) higher in Group A than Group B and Group C after 3 months.

HbA1C was decreased from baseline to after 3 months in all the groups. However, the mean change in HbA1C was higher in Group A than Group B and Group Which is statistically significant.

Solid organ transplants are the need of the hour and kidney transplant among all holds a special place. Kidney transplant offers freedom from dialysis and improves a patient's quality of life by leaps and bounds. It is associated with excellent survival benefit with minimum associated morbidity and mortality. NODAT or New Onset Diabetes after Transplant is a frequent associated entity with all kinds of solid organ transplants especially Renal transplant. Its incidence ranges from 10-74%. Risk factors responsible for NODAT range from pre-existing ones like increasing age and obesity to immunosuppression being used with special emphasis to steroids, CNI's and mTor inhibitors. Genetic predisposition along with inflammation due to multiple factors including rejection and infections such as hepatitis C and CMV also play a vital role in causing NODAT. Treatment options for NODAT include all those which are available for Type II DM. Starting from conventional Insulin in hospitalized, sick and uncontrolled Glycaemic status patients to oral hypoglycemia agents in stable outpatient ones with apparently controlled Glycaemic status. The commonly used OHA's include sulfonylurea like Glimepiride and Repaglinide, Biguanides like Metformin, DPP IV inhibitors like Sitagliptin and Linagliptin, GLP 1 analogues and SGLT2 inhibitors like Empagliflozin and Canagliflozin. There is paucity of data comparing all these available options to treat NODAT. So a need to streamline the management of NODAT, multiple large center studies is required. We aimed to do the same in this study. As per study by Mathew JT, Rao M, Job V *et al.* (14/31) and a study by Joss N, Staatz CE, Thomson AH, Jardine AG[15],

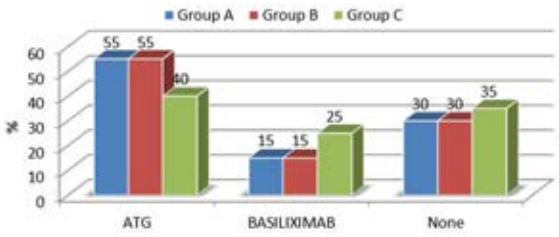

Fig 1: Shows the comparison of induction agent among the study participants groups

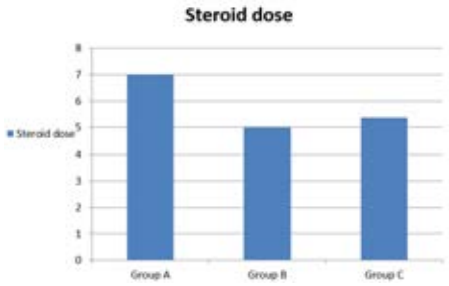

Fig 2: Shows the comparison of baseline steroid dose among the groups

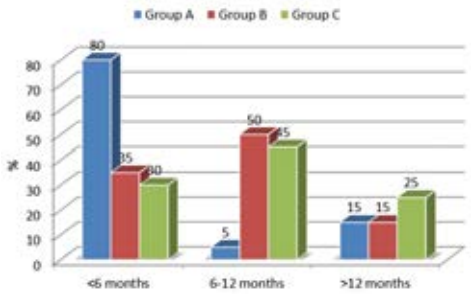

Fig 3: Shows the comparison of time of NODAT among the groups

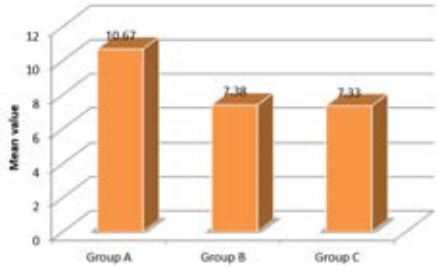

Fig 4: Shows the comparison of baseline HbA1C level among the groups

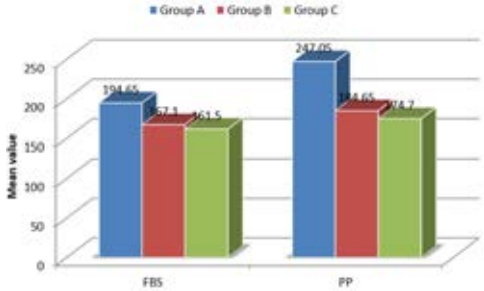

Fig 5: Shows the comparison of sugar level after 3 months among the groups

Table 1: Showing the baseline characteristics of the study participants

	Baseline characteristics comparison of the three groups			
Variables	**Insulin**	**Glimepride**	**Linagliptin**	**p-value**
Age	47.25±12.28	43.65±12.88	45.05±11.25	0.64a
Male gender	12 (60.0)	13 (65.0)	12 (60.0)	0.93b
MI	23.45±2.49	22.44±2.01	22.86±2.13	0.35 a
Basic renal disease				
ADPKD	3 (15.0)	1 (5.0)	2 (10.0)	0.78 b
CGN	6 (30.0)	7 (35.0)	9 (45.0)	
CIN	4 (20.0)	4 (20.0)	5 (25.0)	
HTN	7 (35.0)	8 (40.0)	4 (20.0)	
ABO compatibility	18 (90.0)	18 (90.0)	18 (90.0)	1.00 b
Induction agent	14 (70.0)	14 (70.0)	13 (65.0)	0.92 b
Baseline creatinine	1.01±0.22	1.16±0.29	1.14±0.26	0.16a
Tobacco chewing	0 (0.0)	0 (0.0)	0 (0.0)	- b
Alcohol consumers	0 (0.0)	0 (0.0)	0 (0.0)	- b
Hemoglobin	12.07±1.12	12.04±1.12	12.31±1.35	0.74 a
Hepatitis C status	0 (0.0)	0 (0.0)	0 (0.0)	- b
CMV PCR status	0 (0.0)	0 (0.0)	0 (0.0)	- b
BKV DNA PCR status	0 (0.0)	0 (0.0)	0 (0.0)	- b
Cultures blood and urine	0 (0.0)	0 (0.0)	0 (0.0)	-
Steroid dose	7.00±4.10	5.00±0.00	5.375±1.22	0.03a
CNI dose (TAC levels)	7.10±1.10	6.73±1.15	6.48±1.07	0.28 a
mTOR use	2 (10.0)	2 (10.0)	2 (10.0)	1.00 b

Table 2: Shows the comparison of baseline sugar level among the groups

Groups	**FBS (Mean±SD)**	**PP (Mean±SD)**
Group A	402.95±109.46	514.25±147.03
Group B	222.25±30.27	264.80±43.85
Group C	208.85±26.34	240.80±32.93
p-value1	0.0001*	0.0001*
p-value[2]		
Group A vs. Group B	0.0001*	0.0001*
Group A vs. Group C	0.0001*	0.0001*
Group B vs. Group C	0.80	0.68

ANOVA test, 2Tukey's Post hoc tests, *Significant

Table 3: Shows the comparison of HbA1C level among the groups after 3 months

Groups	**HbA1C (Mean±SD)**
Group A	7.87±0.89
Group B	6.72±0.34
Group C	6.74±0.38
p-value1	0.0001*
p-value[2]	
Group A vs Group B	0.0001*
Group A vs Group C	0.0001*
Group B vs Group C	0.99

ANOVA test, Tukey's Post hoc tests, *Significant

Table 4: Shows the comparison of HbA1C level among the groups from baseline to after 3

Groups	**Mean change in HbA1C (Mean±SD)**
Group A	2.80±0.91
Group B	0.66±0.17
Group C	0.59±0.07
p-value1	0.0001*
p-value[2]	
Group A vs Group B	0.0001*
Group A vs Group C	0.0001*
Group B vs Group C	0.89

steroids dose play a role in deciding the glycemic levels of the patient. So in our study also it was observed that the patients of Group a of Insulin having higher glycemic levels were also on higher doses of steroid with a mean of 7.00 as compared to Group B and Group C. It can be inferred that steroids do cause a higher incidence of NODAT when given in higher doses, however it didn't affect the drug efficacy in question in our study as the doses were maintained at the same level throughout the study period. Steroids have a role in incidence of NODAT but no role in drug efficacy when maintained at the same dose throughout study period. CNI doses were also comparable in all the three study groups and had no significant impact on the results of the study. mTOR use was only in a small fraction of patients (10%) but it was comparable in all the groups, so it didn't affect the results of the study. HbA1c was compared before and at the end of three months after treatment with respective drugs of the three study groups. In Group a of Insulin, mean HbA1c dropped from 10.67-7.87 after three months with reduction of 2.80. In Group B of Glimepiride, mean HbA1c dropped from 7.38-6.74 after three months with reduction of 0.66. In Group C of Linagliptin, mean HbA1c dropped from 7.33-6.74 with reduction of 0.59. This suggests that for our freshly diagnosed cases of

NODAT, all the three regimens of Insulin, Glimepiride and Linagliptin worked efficiently and brought out a significant drop in HbA1c levels. As per study done by Garcia C, Wallia A, Gupta S[16], intensive glycemic control using iv insulin was advocated in hospitalized patients and especially in the early post-transplant period. This was due to combined effect of higher doses of immunosuppression being used at this time along with impact of stress and inflammation. Published data by Boerner B, Shivaswamy V, Goldner W, Larsen J[17] recommended use of iv insulin infusion when patient is sick and hospitalized and to switch it over to basal bolus regime of multiple insulin injection including long acting and premeal short acting ones at the time of discharge. They even recommended to start oral hypoglycemia agent in cases of very well controlled mildly raised sugar patients. In our study, when NODAT was freshly diagnosed patients were randomized to the treatment groups as per the severity. Those presenting with uncontrolled hyperglycaemia or in sick complicated state, straight away insulin was started. That's why in Group A, the mean average FBS at the start of the study was 402.95 and mean average PPBS was 514.25 with HbA1c being 10.67. Insulin showed highest efficacy in terms of glycaemic control with an average reduction of HbA1c of 2.8 as compared to Group B and Group C. No major side effects were seen in Group A of Insulin and patients tolerated this treatment well.

Haidinger M, Antlanger M, Kopecky C, Kovarik JJ, Säemann MD, Werzowa J[18] recommended treatment strategies for NODAT. They advocated the use of sulfonylurea with little proved efficacy in control of sugars. Hypoglycemia can be significantly increased with the use of these drugs especially in those with renal insufficiency. Repaglinide is sometimes been preferred in patients with reduced kidney function because of its shorter half-life, although it stimulates insulin secretion similar to sulfonylureas. In a small observational trial, Turk *et al.* concluded that repaglinide was modestly efficacious in kidney transplant recipients with NODAT[19]. There is paucity of data regarding the efficacy and safety of sulfonylurea in literature. No trial is available comparing sulfonylurea Glimepiride directly with other hypoglycemia drugs. We used sulfonylurea Glimepiride in freshly diagnosed NODAT cases where sugars were mildly raised of the level that mean average FBS was 222.25 and PPBS being 264.80 with HbA1c of 7.38 at the start of the study. This was comparable to the patients enrolled in Group C of Linagliptin. Dose of Glimepiride was adjusted as per the glycaemic level per patient wise. It was found that Glimepiride was effective in controlling sugars of NODAT patients with average HbA1c reduction of 0.66 by them at the end of three months. This was lower than what insulin achieved in Group A but comparable to effect of Linagliptin seen in Group C. The one thing which was concerning in this Group B of Sulfonylurea Glimepiride was the incidence of Hypoglycemia. It was seen in 5 patients which made a total of 25%. This was significantly higher than the 5% incidence of hypoglycemia seen in Group C of Linagliptin and in none of the patients of Group a of Insulin. Point to be noted here is the fact that hypoglycemia occurred in only those patients who had some form of renal dysfunction and higher baseline creatinine (mean average baseline serum creatinine being 1.54 in these patients).

Regarding Dipeptidyl-peptidase-4 (DPP-4) inhibitors they were shown to have relatively low risk of hypoglycaemia in non-transplant settings, are said to be weight neutral and can be used safely in patients who have only mild reductions in kidney function or if the dose is adjusted appropriately with more significant chronic kidney disease. Also as they do not affect immunosuppressant levels, DPP-4 inhibitors are increasingly used for treatment of NODAT without significant safety concerns identified[20,21]. A trial done by Werzowa J *et al*. concluded that Vildagliptin reduced 2-hour plasma glucose on OGTT as well as HbA1c in kidney transplant recipients with impaired glucose tolerance, as well as for NODAT in a randomized, double-blind, placebo-controlled, phase II trial[21]. Importantly, no differences in renal function or immunosuppressant levels were noted and adverse effects were not different between the two groups. Another DPP-4 inhibitor, sitagliptin, has also been studied by Boerner BP and Lane JT for safety and efficacy in a small case series and retrospective study[20,22]. Gueler I *et al.* suggested Vildagliptin to be efficacious for pretransplant diabetes or NODAT after heart transplant[23]. HbA1c was significantly reduced after 8 months of therapy, with no change in immunosuppressant levels or required change in immunosuppressant drug dose. Another study done by Debmalya Sanyal[24] concluded that linagliptin monotherapy is effective for glycemic control in NODAT, even on glucocorticoid and standard dose of tacrolimus. There was no alteration of tacrolimus drug levels or estimated glomerular filtration rate (eGFR) and minimal side effects, including weight gain and hypoglycemia. In our study, patients of Group C treated with Linagliptin showed decent recovery. We used DPP IV inhibitor Linagliptin in freshly diagnosed NODAT cases where sugars were mildly raised of the level that mean average FBS was 208.85 and PPBS being 240.8 with HbA1c of 7.33 at the start of the study. This was comparable to the patients enrolled in Group B of Glimepiride. It was found that Linagliptin was effective in controlling sugars of NODAT patients with average HbA1c reduction of 0.59 by them at the

end of three months. This was lower than what insulin achieved in Group A but comparable to effect of Glimepiride seen in Group B. Incidence of hypoglycemia was minimal and seen in only 1 patient (5%) who had the baseline serum creatinine as 1.6. The one thing important which was observed was the fact that 3 patients (15%) did not achieve adequate sugar control with Linagliptin alone. They had to supplemented with a second oral hypoglycemia agent at the end of three months for better control.

So in total, the three testing drugs of Conventional Insulin versus Sulfonylurea Glimepiride versus DPP IV Inhibitor Linagliptin were compared and analysed on various aspects. Standard and universally accepted methodology (ion-exchange chromatography) was used in estimating HbAlc and for other tests such as FBS, PPBS and serum creatinine also[25]. A strict quality control was ensured and samples were tested in assorted manner. Bias was tried to be avoided and minimized in the best possible manner. Finally modern statistical tools were used to bring out the most accurate results from our study.

CONCLUSION

Henceforth, like in Type II Diabetes Mellitus, treatment of NODAT should be individualized keeping in mind severity, associated comorbidities, existing renal dysfunction and expected compliance. Solid organ transplant be it kidney, liver, heart are the need of the hour and have been proved to be a game changer in management of some very common chronic health conditions. On one hand they open the world of better survival and quality of life of its patients but on the other hand it even predisposes them to acquire newer set of problems including NODAT and infections. Prevention is always better than cure. So in order to prevent NODAT, healthy lifestyle measures should be adopted including strict check on weight, regular exercises and controlled lipid profile. Immuno suppression should always be titrated as per patients need and over immunosuppression should be avoided especially with agents like steroids, CNI's and mTOR inhibitors. Treatment of NODAT has plentiful options like that of type II Diabetes. Starting from conventional Insulin to oral hypoglycaemic agents like Metformin, Sulfonylureas, DPP IV inhibitors, GLP I analogues and SGLT 2 inhibitors. Treatment should be individualized taking care of patients profile, severity, associated comorbidities and existing renal functions. Overall team effort is requires in managing NODAT with special emphasis on multi system care as diabetes in itself is a systemic disease affecting multiple body organs. Starting from neurological and cardiovascular assessment and regular surveillance, care of eye foot and skin should never be ignored. To conclude all transplant recipients should always work towards preventing NODAT, then suspect it and get it regularly evaluated and finally treat it with wholesome multidisciplinary approach and the best suited agent as well.

Limitations:

- Need of more large scale, longer duration randomized trials to compare these agents in a better way.
- Paucity of data exists on treatment modalities for NODAT and more active research on this remains the need of the hour with increasing available treatment options.

REFERENCES

1. Morris, P.J., 2004. Transplantation-a medical miracle of the 20th century. New Engl. J. Med., 351: 2678-2680.
2. Wolfe, R.A., V.B. Ashby, E.L. Milford, A.O. Ojo and R.E. Ettenger *et al.*, 1999. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. New Engl. J. Med., 341: 1725-1730.
3. RABBAT, C.G., K.E. THORPE, J.D. RUSSELL and D.N. CHURCHILL, 2000. Comparison of mortality risk for dialysis patients and cadaveric first renal transplant recipients in ontario, Canada. J. Am. Soc. Nephrol., 11: 917-922.
4. Ojo, A.O., J.A. Hanson, H.U. Meier-Kriesche, C.N. Okechukwu and R.A. Wolfe, 2001. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. J. Am. Soc. Nephrol., 12: 589-597.
5. Meier-Kriesche, H.U., F.K. Port, A.O. Ojo, S.M. Rudich and J.A. Hanson *et al.*, 2000. Effect of waiting time on renal transplant outcome. Kidney Int., 58: 1311-1317.
6. Brunkhorst, R., V. Lufft, B. Dannenberg, V. Kliem, G. Tusch and R. Pichlmayr, 2003. Improved survival in patients with type 1 diabetes mellitus after renal transplantation compared with hemodialysis. Transplantation, 76: 115-119.
7. Merion, R.M., V.B. Ashby, R.A. Wolfe, D.A. Distant, T.E. Hulbert-Shearon, R.A. Metzger, A.O. Ojo and F.K. Port, 2005. Deceased-donor characteristics and the survival benefit of kidney transplantation. JAMA, 294: 2726-2733.
8. Franke, G.H., J. Reimer, T. Philipp and U. Heemann, 2003. Aspects of quality of life through end-stage renal disease. Qual. Life Res., 12: 103-115.SS
9. Jofre, R., J. Lopez-Gomez, F. Moreno, D. Sanz-Guajardo and F. Valderrabano, 1998.

Changes in quality of life after renal transplantation. Am. J. Kidney Dis., 32: 93-100.
10. Overbeck, I., M. Bartels, O. Decker, J. Harms, J. Hauss and J. Fangmann, 2005. Changes in quality of life after renal transplantation. Transplant. Proc., 37: 1618-1621.
11. Balaska, A., P. Moustafellos, S. Gourgiotis, D. Pistolas, E. Hadjiyannakis, V. Vougas and S. Drakopoulos, 2006. Changes in health-related quality of life in Greek adult patients 1 year after successful renal transplantation. Exp. Clin. Transplant., 4: 521-524.
12. Cosio, F.G., T.E. Pesavento, K. Osei, M.L. Henry and R.M. Ferguson, 2001. Post-transplant diabetes mellitus: Increasing incidence in renal allograft recipients transplanted in recent years. Kid. Int., 59: 732-737.
13. Davidson, J., A. Wilkinson, J. Dantal, F. Dotta and H. Haller *et al.*, 2003. New-onset diabetes after transplantation: 2003 international consensus guidelines1. Transplan., 75: 3-24.
14. Boerner, B.P., V. Shivaswamy, C.V. Desouza and J.L. Larsen, 2011. Diabetes and cardiovascular disease following kidney transplantation. Curr. Diabetes Rev., 7: 221-234.
15. Mathew, J.T., M. Rao, V. Job, S. Ratnaswamy and C.K. Jacob, 2003. Post-transplant hyperglycaemia: A study of risk factors. Nephrol. Dialys. Transplant., 18: 164-171.
16. Joss, N., C.E. Staatz, A.H. Thomson and A.G. Jardine, 2007. Predictors of new onset diabetes after renal transplantation. Clin. Transplant., 21: 136-143.
17. Garcia, C., A. Wallia, S. Gupta, K. Schmidt and S. Malekar-Raikar *et al.,* 2013. Intensive glycemic control after heart transplantation is safe and effective for diabetic and non-diabetic patients. Clin. Transplant., 27: 444-454.
18. Shivaswamy, V., B. Boerner and J. Larsen, 2015. Post-transplant diabetes mellitus: Causes, treatment and impact on outcomes. Endocr. Rev., 37: 37-61.
19. Haidinger, M., M. Antlanger, C. Kopecky, J.J. Kovarik, M.D. Säemann and J. Werzowa, 2015. Post-transplantation diabetes mellitus: Evaluation of treatment strategies. Clin. Transplant., 29: 415-424.
20. Türk, T., F. Pietruck, S. Dolff, A. Kribben and O.E. Janssen *et al.*, 2006. Repaglinide in the management of new-onset diabetes mellitus after renal transplantation. Am. J. Transplant., 6: 842-846.
21. Boerner, B.P., C.D. Miles and V. Shivaswamy, 2014. Efficacy and safety of sitagliptin for the treatment of new-onset diabetes after renal transplantation. Int. J. Endocrinol., Vol.2014.10.1155/2014/617638.
22. Werzowa, J., M. Hecking, M. Haidinger, F. Lechner and D. Döller *et al.,* 2013. Vildagliptin and pioglitazone in patients with impaired glucose tolerance after kidney transplantation. Transplantation, 95: 456-462.
23. Lane, J.T., D.E. Odegaard, C.E. Haire, D.S. Collier, L.E. Wrenshall and R.B. Stevens, 2011. Sitagliptin therapy in kidney transplant recipients with new-onset diabetes after transplantation. Transplantation, 92:
24. Gueler, I., S. Mueller, M. Helmschrott, C.U. Oeing and C. Erbel, 2013. Effects of vildagliptin (Galvus®) therapy in patients with type 2 diabetes mellitus after heart transplantation. Drug Des. Devel. Ther., 7: 297-303.
25. Sanyal, D., S. Gupta and P. Das, 2013. A retrospective study evaluating efficacy and safety of linagliptin in treatment of nodat (in renal transplant recipients) in a real world setting. Indian J. Endocrinol. Metab., 17: 203-205.