The effects of renal transplantation on diabetic retinopathy: Clinical course and visual outcomes

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Purpose: To elucidate the clinical course of diabetic retinopathy (DR) after renal transplantation (RT) in a hospital based cohort. Design: Retrospective study. Materials and Methods: A total of 56 eyes of 28 patients, who had DR and end stage renal disease (ESRD) due to diabetes and had undergone RT, were included in this study. Diagnosis and management of DR was carried out according to early treatment of diabetic retinopathy study (ETDRS) guidelines. DR outcome was defined as worsening if there was >2 step increase in the grade of DR or need for intervention such as laser (macular or pan retinal) or vitreoretinal surgery, improvement for <2 step change while stabilization was defined if DR remained within these two limits. Results: The mean age of the patients were 48.9 years. The mean duration of diabetes in the study group was 12.7 years. The patients were followed-up for a mean period of 52.2 ± 43.6 months. The pre-transplant mean Best corrected visual acuity (BCVA) was 0.4876 log MAR units and post-transplant mean BCVA was 0.4858 (P = 0.05). However, there was a significant visual improvement in first 20 months of renal transplant (P = 0.03). Worsening of DR was noted in 16 (32%) eyes whereas improvement was seen in 4 (8%). However, majority of eyes 30 (60%) had stable retinopathy at the final follow-up. Conclusions: RT stabilized the retinopathy status in the majority of patients although in a minor subset the disease course was unpredictable.

Key words: Diabetic retinopathy, renal transplant, visual outcome

Diabetic retinopathy (DR) develops in nearly all persons with type 1 diabetes and in more than 77% of those with type 2 diabetes, who survive for over 20 years with the disease.[1] Diabetes mellitus is also a main cause of end stage renal disease (ESRD) in developing countries.[2] After 15 years of having the disease, nephropathy develops in approximately 30-40% of persons with type I[3] and 30.3% of type II diabetes mellitus.[4]

Retinopathy often accompanies ESRD in diabetes.[5] There are conflicting evidences regarding the effect of restoration of renal function and progression or deterioration of diabetic retinopathy. The restoration of renal function is achieved by renal replacement therapy, which includes hemodialysis, continuous ambulatory peritoneal dialysis (CAPD) and renal transplantation (RT).

As compared to dialytic modalities of renal replacement therapy, RT in diabetic ESRD gives a markedly better quality as well as quantity of life.[6] There are studies to show improvement, stabilization or deterioration of retinopathy after RT.[7-15] However, all these studies recruited fewer subjects and had a shorter follow-up. There are very few studies, which particularly describe the clinical course of DR after renal transplant over a longer period of time. We report a hospital-based cohort of 56 subjects with diabetes who were evaluated, pre- and post-transplant, and subsequently had a mean follow-up of 52 months. The aim of the study was to elucidate the DR status and progression after RT.

Materials and Methods

Between 1998 and 2010, 56 eyes of 28 patients, who had DR and ESRD due to diabetes and had undergone RT, were included in this study. All patients were at least evaluated once before they underwent RT for ESRD due to diabetes and also had a post-renal transplant evaluation. The study was approved by the Institutional Review Board and a written consent was taken as per the Helsinki Declaration. Blind eyes (3 Phthisis bulbi and 3 enucleated) were excluded. Thus, finally 50 eyes were considered for the analysis.

A detailed history regarding the duration of diabetes, any previous treatment for retinopathy, a history of dialysis and treatment for diabetes (insulin or oral anti-hypoglycemic agents) were taken. Any history or treatment for associated medical conditions such as neuropathy, ischemic heart diseases, and hypertension were also noted. A baseline blood pressure (BP) measured in the supine position along with blood urea and serum creatinine were also measured which was repeated at each visit.

On each visit, a comprehensive eye examination was carried out including the best corrected visual acuity, intraocular pressure measurement with the Goldmann Applanation Tonometer and slit lamp examination. Fundus evaluation was carried out by dilated indirect ophthalmoscopy and slit lamp biomicroscopy using +78D lens by an experienced retinal specialist. Clinical cataract grading was carried out for all the eyes according to their morphological types.

DR was diagnosed based on the modified Klein classification[16] (modified early treatment DR study scales) and was graded as mild, moderate, severe, very severe, early proliferative diabetic retinopathy (PDR) or high-risk PDR. Patients underwent macular laser for clinically significant
macular edema and pan retinal photocoagulation was carried out for proliferative diabetic retinopathy. Vitreous surgery was carried out for eyes with vitreous hemorrhage or tractional retinal detachment. Patients having significant cataract underwent cataract extraction. Retinopathy was deemed stable if there was <2 step progression and was deemed unstable if >2 step progression.

Statistical Package for the Social Sciences - SPSS (version 14.0) was used for the statistical analysis. All the data were expressed as mean ± SD or as a percentage. The statistical significance was assumed at $P \leq 0.05$.

Results

Table 1 summarizes the demographic and base line characteristics of the study subjects before renal transplant. All subjects had diabetic nephropathy on presentation. The mean age of the patients was 48.9 years. The mean duration of diabetes in the study group was 12.7 years. The patients were followed-up for a mean period of 52.2 ± 43.6 months. Systemic factors, pre- and post-transplant, were compared based on years of successful post-renal transplant period [Table 2].

The base line metabolic factors of the patients were analyzed at pre and post-transplant. Irrespective of the duration of the transplant, the blood urea and serum creatinine were reduced after renal transplant ($P < 0.05$). Systolic BP also showed a significant reduction in 47-75 months follow-up quartile (160.3 ± 12.5 mmHg vs. 146.0 ± 3.4, $P = 0.0410$).

Fig. 1 shows the changes in visual acuity status in pre- and quartiles of post-transplant period. The pre-transplant mean best corrected visual acuity (BCVA) was 0.4857 log MAR units and post-transplant mean BCVA was 0.4858 ($P = 0.05$). However, there was a statistically significant visual improvement in first 20 months of renal transplant ($P = 0.03$).

Table 3 shows the lens status in pre- and post-renal transplant. At the pre-transplant visit, 44 (88%) eyes were phakic, 5 (10%) were pseudophakic and 1 (2%) was aphake. At the final follow-up, 27 (54%) eyes were phakic, 22 (44%) eyes were pseudophakic and aphakia was found in 1 (2%) eye. The proportion of pseudophakes was more than phakics in post-renal transplant as compared to pre-renal transplant (44% vs. 10% were pseudophakia, $P = 0.002$, and 52% vs. 88% were phakic, $P = 0.041$). The morphological type of cataract did not differ in the two groups.

Table 2: Relation of patient characteristics with duration of post-renal transplant

| Duration post-renal transplant (months) | ≤20 | 21-46 | 47-75 | >75 |
|----------------------------------------|-----|-------|-------|-----|
|                                       | Pre | Post  | $P$   | Pre | Post  | $P$   | Pre | Post  | $P$   | Pre | Post  | $P$   |
| Blood urea (mg/dl)                     | 104.8±13.7 | 35.6±12.3 | 0.018 | 114.4±21.8 | 36.1±8.1 | 0.018 | 113.8±31.3 | 42.0±9.3 | 0.018 | 108.7±32.8 | 39.3±15.5 | 0.01 |
| Serum creatinine (mg/dl)               | 6.1±1.2 | 0.78±0.54 | 0.018 | 5.9±1.5 | 1.1±0.3 | 0.018 | 5.7±2.4 | 1.0±0.4 | 0.018 | 5.9±2.8 | 1.1±0.3 | 0.01 |
| Systolic BP (mmHg)                     | 157.7±12.1 | 146.3±5.1 | 0.066 | 152.0±14.1 | 144.3±8.3 | 0.109 | 160.3±12.5 | 146.0±3.8 | 0.041 | 156.3±10.2 | 152.3±7.1 | 0.15 |
| Diastolic BP (mmHg)                    | 96.9±7.9 | 91.6±4.9 | 0.068 | 90.7±8.6 | 88.7±5.8 | 0.180 | 94.4±4.3 | 90.7±5.4 | 0.109 | 97.0±3.5 | 94.0±3.1 | 0.1  |

BP: Blood pressure, mg/dl: Milligram per deciliter, mmHg: Millimeter of mercury, IOP: Intraocular pressure, IHD: Ischemic heart disease, CI: Confidence interval
The mean intraocular pressure at the pre-transplant visit was 15 mm Hg and the mean intraocular pressure at the final follow-up was 14.2 mmHg. Table 4 shows the DR status among the subjects. At the pre-transplant visit, mild, moderate, severe, and very severe non proliferative diabetic retinopathy (NPDR) were present in 4 (8%), 8 (16%) 1 (2%) and 1 (2%) eyes respectively. Four (8%) eyes had PDR and 7 (14%) eyes had high-risk PDR at the pre-transplant visit. However, majority of the patients 25 (50%) were post-laser or post-surgery status. At post-transplant follow-up the number of eyes which had mild, moderate, severe, and very severe NPDR were 3 (6%), 3 (6%), 1 (2.0%), and 0 (0.0%) respectively. The number of eyes with PDR and high-risk PDR were 0 and 1 (2%) respectively. At final follow-up 27 (54%) eyes had stable retinopathy, post-laser and surgery. Thirteen (26%) eyes of the post-laser/surgery group had unstable retinopathy whereas 4 (8%) eyes of the same group showed improvement in their retinopathy status.

The DR status in pre- and post-renal quartiles in transplants are showed in Fig. 2. There was an initial worsening of the DR status until the 2nd quartile post-transplant (21-46 months). However, by the last quartile (>75 months) 80% showed stabilization of DR (post-surgery/laser).

The overall change in the retinopathy status after renal transplant is elucidated in Fig 3. A change in retinopathy status >2 steps was considered significant. Worsening of DR was noted in 16 (32%) eyes, whereas improvement was seen in 4 (8%). However, majority of eyes 30 (60%) had stable retinopathy at the final follow-up.

During the study period, patients underwent various interventional procedures such as laser photocoagulation, cataract surgery, and vitreous surgery. Fig. 4 shows the distribution of these interventions after renal transplant. Cataract surgery was required in 17 (34%) eyes. Cataract surgery was performed along with vitreous surgery in one eye. Laser treatment in the form of either grid laser or pan retinal photocoagulation was required in 10 (20%) eyes. Among these focal/grids was required in 6 (12%) eyes. Pan retinal photocoagulation was required in 4 (8%) eyes. Vitrectomy surgery was carried out in 4 (8%) eyes. Vitreous hemorrhage was the cause for surgery in two eyes whereas tractional retinal detachment necessitated surgery in two eyes.

### Table 3: Lens status of study subjects in pre- and post-transplant period

| Lens status    | Pre-transplant n (%) | Post-transplant n (%) | P     |
|----------------|----------------------|-----------------------|-------|
| Phakia         | 44 (88.0)            | 27 (52.0)             | 0.041 |
| Pseudophakia   | 5 (10.0)             | 22 (44.0)             | 0.002 |
| Aphakia        | 1 (2.0)              | 1 (4.0)               | 1.000 |

### Table 4: Diabetic retinopathy status in study subjects

| Diabetic retinopathy | Pre-transplant n (%) | Post-transplant n (%) | P     |
|----------------------|----------------------|-----------------------|-------|
| Mild NPDR            | 4 (8.0)              | 2 (4.0)               | 0.688 |
| Moderate NPDR        | 8 (16.0)             | 4 (8.0)               | 0.388 |
| Severe NPDR          | 1 (2.0)              | 1 (2.0)               | 1.000 |
| Very severe NPDR     | 1 (2.0)              | 0 (0.0)               | 1.000 |
| PDR                  | 4 (8.0)              | 0 (0.0)               | 0.125 |
| High risk PDR        | 7 (14.0)             | 2 (4.0)               | 0.180 |
| Post-treatment (laser/surgery) stable | 25 (50.0) | 27 (54.0) | 0.890 |
| Post-treatment (laser/surgery) unstable | 0 (0.0) | 10 (20.0) | 0.002 |
| Post-treatment (laser/surgery) improvement | 0 (0.0) | 4 (8.0) | 0.125 |

NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

**Figure 2:** Diabetic retinopathy status after renal transplant during follow-up period

**Figure 3:** Change in diabetic retinopathy status in study subjects in post-transplant period
Discussion

In India, chronic glomerulonephritis and diabetes are the top two causes for ESRD[2] Diabetic nephropathy is the leading cause of ESRD in patients aged more than 40 years[2] hemodialysis, CAPD, and RT are the main modalities of treatment for such patients.

We report the DR status in a cohort of subjects with diabetes, with both nephropathy and retinopathy at baseline, who underwent renal transplant. The cohorts had a longer duration of diabetes, deranged renal profile (blood urea and creatinine) and were also hypertensive.

We found that after renal transplant, the biochemical profile (serum urea and creatinine) normalized early and remained so even >75 months post-transplant. However, post-transplant, the decline in the BP was not clinically significant. This was in accordance to a study carried out earlier by Zoungas et al.[17] which compared the various biochemical factors in the pre- and post-transplant period. This finding was similar to a study carried out by Fiorina et al.[18] earlier which looked into various cardiovascular parameters in the pre- and post-transplant period.

Chow et al.[19] studying the effect of renal and pancreatic transplant on the status of retinal transplant found a stable visual acuity in the follow-up period. Our study, which had a mean follow-up of 52 months agreed on this finding with the mean BCVA of 0.4858 as compared to 0.4876 in the pre-transplant period.

After renal transplant, 44% of the subjects underwent cataract surgery. The use of systemic steroids in the post-transplant period could be a major cause in the increase of cataracts. Mittal et al.[12] also found an increase in cataract, which was attributed to the use of steroids in the post-transplant period.

At the post-transplant follow-up period, most of our patients (60%) had a stable retinopathy. In 32% of the patients, the retinopathy worsened for which additional treatment like laser/surgery was carried out. The DR status improved only in 8% of our subjects. Mittal et al.[12] also found stabilization in 90% of patients post-RT. Only in 10% did the retinopathy worsen. This difference could be attributed to a less duration of follow-up in their study (12 months as compared to 52 months in our study). Chow et al.[19] also reported a stabilization in 76% of his cases in DR patients post SPK transplant. Several studies have reported stabilization of retinopathy in up to 75% of successful SPK transplant recipients.[7,13]

Table 5 documents the comparison of our results with the results of previous studies.

We found an initial worsening of DR status till 2nd quartile post-transplant (21-46 months). However, by last the quartile (>75 months) 80% showed stabilization of DR (post-surgery/laser). Similar to our study, Ramsay et al.[14] and Zech et al.[15] also reported the early worsening of DR. It is possible that sudden normalization of glycemic status and abrupt change in osmolarity post a long-term poor glycemic controlled to micro vascular changes leading to additional bleeding. The current study has few limitations. Biggest limitation is its retrospective nature with a variable follow-up. Furthermore, being a retrospective study it is difficult to characterize relative contributions of various factors such as systemic control, renal transplant and treatment effects on final visual, and retinopathy status. Absence of pre- and post-transplant Hb A1C levels and absence of fundus photographic and angiographic documentation (fundus fluorescein angiography was not carried out in any patients because of impaired renal status) are other major limiting factors.

In conclusion, RT stabilized the retinopathy status in the majority of patients although in a minor subset the disease course was unpredictable. It has to be remembered that apart from maintaining a proper glycemic control, other systemic co-morbid factors have a bearing on the retinopathy and hence, should be adequately controlled. These co-morbid factors such as hypertension, lipid profile, and also pre-existing retinopathy status have a profound bearing on the final outcome. All patients should undergo complete ophthalmic work up pre-transplant and should undergo laser photocoagulation if required in the pre-transplant period in order to minimize chances of worsening of retinopathy in the post-transplant period.

Table 5: Comparison with published studies

| Studies | Transplant Number of eyes (%) | Stable (%) | Progression (%) | Improvement (%) |
|---------|-------------------------------|------------|-----------------|----------------|
| Chow et al. 1999 | P+R 82 | 75 | 11 | 14 |
| Pearce et al. 2000 | P+R 33 | 96 | 4 | 0 |
| Mittal et al. 2005 | R 40 | 90 | 10 | 0 |
| Present study | R 50 | 60 | 32 | 8 |

Figure 4: Therapeutic intervention in study eyes

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