Brief Communication

Advanced Diabetic Nephropathy with "Clean" Eyes: An Extreme Phenotype

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Abstract

Introduction: It is generally accepted that renal and eye changes in diabetes are concordant. There are however a fair number of patients with diabetes who have end-stage renal disease (ESRD) without any of the typical eye changes. The present study highlights the discordance between retinopathy and nephropathy and describes a series of patients of long-standing diabetes undergoing renal transplant who had little or no evidence of retinopathy. **Methods:** All patients with ESRD undergoing renal transplants underwent comprehensive fundus evaluation including dilated indirect ophthalmoscopy, slit lamp biomicroscopy, and fundus photography. The patients' age, gender, physical parameters (body mass index and blood pressure), duration of diabetes, glycosylated hemoglobin (HbA1c), albumin creatinine ratio, and presence of diabetic peripheral neuropathy (DPN) were determined. Renal histopathology was reviewed, if available. **Results:** Five patients with diabetic nephropathy (DN) underwent renal transplant and had no evidence of diabetic retinopathy (DR) or up to two microaneurysms per fundus. All the patients were between 50 and 65 (mean ± standard deviation – 58.6 ± 4.67) years of age. The mean duration of diabetes was 16 ± 2.91 years. All had poor glycemic control with a mean HbA1c of 9.2 ± 0.837%. All had hypertension, macroalbuminuria, and DPN. **Conclusion:** There is a well-recognized association between retinopathy and nephropathy, in which nephropathy without retinopathy is rare but retinopathy without nephropathy is common. We have identified a subset of patients with kidney disease of sufficient severity to warrant renal transplant but who are protected from retinopathy. It is possible that there is an extreme phenotype of DN patients with unaffected eyes who carry genes protecting against DR.

Keywords: Advanced nephropathy, diabetic retinopathy, Indian, type 2 diabetes

Introduction

There is usually a concordance between eye and renal complications in patients with diabetes mellitus.[1] Although some studies have demonstrated the presence of severe retinopathy without nephropathy, the reverse, i.e., overt nephropathy without retinopathy is rare.[2] Two studies looked into the relationship between retinal and glomerular lesions, determined by renal biopsy in type 1 diabetic patients and concluded that discordance between retinopathy and nephropathy was more common than previously anticipated.[2,3] The observations were consistent with the hypothesis that there were divergences in some aspects of the pathogenesis of retinal and renal lesions. Nevertheless, the nature of the discordance between retinopathy and nephropathy in type 2 diabetes patients has not been clearly determined.[4] We looked at patients with diabetic nephropathy (DN) undergoing renal transplant between December 2016 and June 2017 and identified five patients who had little or no evidence of retinopathy. In this brief communication, we report these patients' clinical profiles and review the literature on the discordance between retinopathy and nephropathy.

Methods

All patients with ESRD undergoing renal transplant underwent comprehensive fundus evaluation including dilated indirect ophthalmoscopy, slit lamp biomicroscopy, and fundus photography. The patients' age, gender, physical parameters (body mass index [BMI] and blood pressure), duration of

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diabetes, glycosylated hemoglobin (HbA1c), albuminuria, and presence of diabetic peripheral neuropathy (DPN) were determined. Renal histopathology was reviewed, if available.

Results

Five patients with ESRD who underwent renal transplant were identified in the period December 2016–June 2017. They either had no evidence of diabetic retinopathy (DR) or up to two microaneurysms in each side as affirmed by the results of direct and indirect ophthalmoscopic examination. The clinical and biochemical findings of these five patients (four were male) are given in Table 1. All the patients were between 50 and 65 (mean ± standard deviation – 58.6 ± 4.67) years of age. The mean duration of diabetes was 16 ± 2.91 years, and the mean BMI was 24.4 ± 1.6 kg/m^2. All had poor glycemic control with a mean HbA1c of 9.2 ± 0.83%. All had hypertension (HTN) and were on multiple antihypertensive drugs. All had macroalbuminuria and DPN. The clinical characteristics of these five patients were similar with respect age, poor glycemic control, the presence of DPN, and HTN.

Discussion

In India, diabetes mellitus is one of the leading causes of end-stage renal disease (ESRD).[5] DR is commonly found in the majority of patients with DN.[6] Taft *et al*. examined 136 consecutive renal biopsy specimens from diabetes patients and showed that patients with moderate or advanced glomerulosclerosis were significantly more likely to have retinopathy than those with mild disease.[7] A large cross-sectional study of type 1 diabetes patients found a positive association between degree of retinopathy and level of albuminuria and also found that macroalbuminuria without retinopathy was rare (0.9%).[8] All our patients had macroalbuminuria. Chavers *et al*. examined renal biopsy specimens from 86 patients with type 1 diabetes and found a discordance of retinal and glomerular lesions; 1 of 19 patients (5.2%) without retinopathy had advanced mesangial lesions.[4] The prevalence of DR varies from 47% to 63% in type 2 diabetic patients with proteinuria.[9,10] John *et al*. studied patients with type 2 diabetes associated with nondiabetic renal disease and reported that only 12% of them showed evidence of retinopathy.[11] The standard medical opinion is that DN in the absence of DR should trigger a search for nondiabetic renal disease.[12] Our patients had unequivocal DN from the history and presence of proteinuria. Our patient characteristics were in concordance with the findings of Kanauchi *et al*. with regard to age, the HbA1c, BMI, HTN, and male preponderance for this rare phenotype.[12] However, the mean duration of diabetes of 16 ± 2.91 years was higher than reported by Kanauchi *et al*. at 10.8 ± 3.768 years. Previous studies have shown that age at diagnosis, duration of diabetes, high HbA1c levels, and arterial HTN were risk factors for the development of DR.[12-14] Interestingly, all of these risk factors were present in our patients, but without DR. It is generally recognized that DR can exist in the absence of DN, but DN, especially ESRD, is almost always associated with DR. A recent meta-analysis involving 2012 patients from 26 studies concluded that DR is useful in diagnosing or screening for DN in patients with type 2 diabetes and renal disease, and proliferative DR was recognized as a highly specific indicator for DN.[15]

Table 1: Summary of the five patients presented

Features	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	52	64	58	62	57
Sex	Male	Male	Male	Female	Male
Duration of diabetes (years)	12	20	16	17	15
HbA1c (%)	10.2	9.5	8.8	8.4	9.2
BMI (kg/m^2)	23.4	24	27	25.2	23.2
ACR (mg/g)	845	2534	795	2154	845
HTN	176/100	166/96	180/100	140/94	168/98
DPN	Y	Y	Y	Y	Y

BMI: Body mass index, ACR: Albumin creatinine ratio, HTN: Hypertension, DPN: Diabetic peripheral neuropathy, HbA1c: Glycosylated hemoglobin

Microvascular complications of the kidney do not always spill over to the retina. This suggests that the etiopathogenesis of the two complications are distinct from each other. It is also possible that some individuals with DN and ESRD are genetically protected from DR. Many genes have been implicated in the causation of DR and some protective genes have been identified. Marre *et al.* described that genotype II of the angiotensin-converting enzyme gene as a marker for a decreased risk of DN but not for DR.[16] Recently, Hu *et al*. suggested that the XbaI (2) allele of GLUT1 gene might be a genetic marker of type 2 diabetes with DN, and this genetic susceptibility is independent of its effect on the retina in Chinese patients.[17] Aldose reductase polymorphisms involving the *Z* = 2 and Z alleles of the (CA) n microsatellite located at the 5' end of the gene show protection.[18] A large number of vascular endothelial growth factor (VEGF) polymorphisms have been identified including some in a South Indian cohort.[19] Genes that reduce oxidative stress, for example, the GSTM1-null genotype may protect against DR.[20] A large number of candidate genes that may protect against DR have been proposed including those which reduce oxidative stress, inflammation, chemotaxis, and cell adhesion.[20]

Conclusion

There is a well-recognized association between retinopathy and nephropathy, in which nephropathy without retinopathy is rare but retinopathy without nephropathy is common. We have identified a subset of patients with DN who underwent renal transplant but were protected from retinopathy. It is possible that if an extreme phenotype, i.e., DN patients with unaffected eyes are studied, genes protecting against DR will be identified even from a small number of patients.

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Conflicts of interest
There are no conflicts of interest.

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