Microvascular Disease After Renal Transplantation

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Key Words
Renal transplantation • Microvasculature • Retinal arterioles

Abstract
Background/Aims: Individuals who reach end-stage kidney disease (CKD5) have a high risk of vascular events that persists even after renal transplantation. This study compared the prevalence and severity of microvascular disease in transplant recipients and patients with CKD5. Methods: Individuals with a renal transplant or CKD5 were recruited consecutively from renal clinics, and underwent bilateral retinal photography (Canon CR5-45, Canon). Their retinal images were deidentified and reviewed for hypertensive/microvascular signs by an ophthalmologist and a trained grader (Wong and Mitchell classification), and for vessel caliber at a grading centre using a computer-assisted method and Knudtson’s modification of the Parr-Hubbard formula. Results: Ninety-two transplant recipients (median duration 6.4 years, range 0.8 to 28.8) and 70 subjects with CKD5 were studied. Transplant recipients were younger (p<0.001), with a higher eGFR (p<0.001), but were just as likely to have a moderate-severe hypertensive/microvascular retinopathy (46/92, 50%) as subjects with CKD5 (38/70, 54%; OR 0.84, CI 0.45 to 1.57, p=0.64), and had similar mean arteriole and venular calibres (135.1 ± 7.5 µm and 137.9 ± 14.9 µm, p=0.12; and 199.1 ± 17.8 µm and 202.4 ± 27.8 µm, p=0.36, respectively). Arteriole and venular caliber were not different in nine patients examined before and after transplantation (p=0.62 and p=0.11, respectively). Conclusions: Hypertensive/microvascular disease occurred just as often and was generally as severe in transplant recipients and subjects with CKD5. Microvascular disease potentially contributes to increased cardiac events post-transplantation.

Introduction

Cardiac death is 10 to 20 times more common in dialysis patients than in the general population [1]. The increased risk results from both the traditional vascular risk factors,
and non-traditional factors related to poor kidney function, such as chronic inflammation, anaemia, volume overload, and disturbed calcium-phosphate metabolism [2, 3].

Renal transplantation significantly prolongs life expectancy for dialysis patients and reduces their rate of cardiac death by improving renal function and halting the progression of cardiovascular disease [1, 4, 5]. However, cardiac disease is still the leading cause of death in transplant recipients [6], who have events at nearly 50 times the rate seen in the rest of the population [7]. Almost 40\% of older patients have an event, typically, a myocardial infarct or a new episode of congestive heart failure, within 36 months of transplantation [8].

Most studies of cardiac disease in endstage renal failure and transplantation focus on the consequences of macrovascular disease in the coronary arteries. However microvascular damage contributes to ischemic heart disease with normal coronary angiography, diastolic heart failure, and also to lacunar stroke, vascular dementia and renal failure progression [9-13].

Visualisation of the retinal microvasculature represents a surrogate for direct examination of the systemic small vessels, including those in the heart. Commonly-used methods include grading of retinal vascular signs such as hypertensive retinopathy and diabetic retinopathy, and measurement of arteriolar and venular caliber. Recent advances in the quantification of retinal vascular caliber mean that these measures are accurate and highly reproducible [14]. Any change to retinal vessel caliber closely parallels changes elsewhere in the body [9]. Furthermore, microvascular retinopathy, arteriolar narrowing and venular widening, all predict cardiac events in other high risk populations [15-18]. This study compared the prevalence and severity of retinal microvascular abnormalities and diabetic retinopathy in patients with a renal transplant or CKD5, in both a cross-sectional and smaller longitudinal series.

**Methods and Participants**

**Study design**

This comprised a cross-sectional, observational study of patients with a renal transplant or with CKD5 (estimated glomerular filtration rate [GFR] < 15 ml/min/1.73 m² based on the MDRD formula [19]) for at least 3 months; and a smaller longitudinal series study of 9 patients with CKD5 examined both before and after transplantation. Participants underwent retinal photography and their images were deidentified and graded for hypertensive/microvascular retinopathy and diabetic retinopathy, and vessel caliber was measured. Clinical and retinopathy features were compared between transplant recipients and patients with CKD5 in each study.

**Study participants**

Participants were recruited consecutively from the renal clinics of two metropolitan teaching hospitals one day a week over a period of 18 months. They were at least 18 years old, and were excluded from the study only if their retinal images could not be graded, usually because of cataract. Some patients with CKD5 have been described previously [20, 21].

This study was approved by the Human Research Ethics Committee of Northern Health and Austin Health, and all participants provided signed, informed consent in accordance with the principles of the Declaration of Helsinki.

**Measurements**

Participants completed a structured questionnaire that included their medical details and vascular risk factors, underlying renal disease, date of transplantation, and current medication. Hypertension was defined as a resting blood pressure of ≥ 140/90 mm Hg, diabetes by a random glucose measurement of > 11.0 mmol/L, and dyslipidemia with a serum cholesterol ≥ 5.00 mmol/L, or in each case, a physician-based patient self-reported diagnosis. Laboratory test results (haemoglobin, blood glucose, lipids, and eGFR) were obtained from the patients’ electronic medical records.
Participants underwent bilateral retinal photography after dark adaptation or dilatation with 1% tropicamide using a nonmydriatic digital retinal camera (Canon CR5-45NM, Canon, Japan). At least one image was centered on the macula and another on the optic disc. Images were coded, reviewed for retinal hemorrhage, and graded independently for microvascular signs [22] and diabetic retinopathy [23] by an ophthalmologist and a trained observer. The final grade for any individual was determined by the changes in the more severely-affected eye.

Retinal vessel caliber in these images was measured by a trained grader at the Centre for Eye Research Australia (Melbourne, Australia) using a standardized method and a computer imaging program (University of Wisconsin, WI) described previously [14, 24]. The ‘Central Retinal Artery Equivalent,’ (CRAE) and the ‘Central Retinal Vein Equivalent’ (CRVE) were calculated from measures of the 6 largest vessels using a revision of Knudtson’s formula [25]. Measurements were highly reproducible with intraclass correlation coefficients of 0.99 (95% CI 0.98 – 0.99) for the CRAE and 0.94 (95% CI 0.92 - 0.96) for the CRVE.

Statistical analysis

Demographic data were compared using Fisher’s exact test or the unpaired t test. CRAE and CRVE measurements were categorized into quartiles, and the differences in features of individuals with calibers in the lowest and highest quartiles were compared using Fisher’s exact test or the unpaired t test. Characteristics from patients before and after renal transplantation were compared using the paired t test. Statistical analyses were performed using GraphPad (GraphPad Software, CA) A result was considered significant if the p value was less than 0.05, and where relevant, the odds ratio (OR) greater or less than 1, and the 95% confidence interval did not include 1.00.

Results

Clinical features in patients with a renal transplant or CKD5

The 92 transplant recipients comprised 60 (65%) men and 32 (35%) women with a median age of 52 years (range 22 – 78) (Table 1). Renal failure was due to glomerulonephritis (43, 47%), inherited disease (renal agenesis, reflux nephropathy, polycystic kidney disease, etc) (35, 38%), diabetic nephropathy (4, 4%), hypertensive or renovascular disease (2, 2%), and miscellaneous or unidentified causes (8, 7%). Their median time since transplantation was 6.4 years (range 0.4 – 28.8), and their mean eGFR was 46.7±19.3 ml/min/1.73 m². Twenty (22%) patients currently had CKD1-2, and 72 (78%) had CKD 3-5, including 57 (62%) with CKD 3, 11 (12%) with CKD4 and 4 (4%) with CKD5. The 70 patients with CKD5 had renal failure from glomerulonephritis (17, 24%), inherited disease (7, 10%), diabetic nephropathy (20, 29%), hypertensive or renovascular disease (12, 17%), and miscellaneous or unidentified causes (14, 20%).

Overall, patients with a renal transplant were younger (p<0.001), and had better renal function (p<0.001) than those with CKD5 (Table 1). They were just as likely to have hypertension (OR 1.13, 95%CI 0.47 to 2.71, p=0.83) but required fewer antihypertensive agents (p<0.01), and were less likely to have diabetes (OR 0.47, 95%CI 0.24 to 0.93, p=0.04).
Retinal abnormalities in patients with a renal transplant or CKD5

The prevalence of retinal hemorrhage was the same in transplant recipients (46, 50%) and patients with CKD5 (30, 45%) (OR 1.33, 95% CI 0.71 to 2.49, p = 0.43) (Table 2).

Microvascular retinopathy. Seventy-nine (86%) transplant recipients and 53 (76%) patients with CKD5 had microvascular abnormalities (Figure 1) (OR 1.95, 95% CI 0.87 to 4.35, p = 0.11). Incidental abnormalities such as CMV retinitis were present in occasional patients. There was a trend for more mild changes in the transplant recipients (34%) than in patients with CKD5 (21%) (OR 2.1, 95% CI 1.01 to 4.18, p = 0.06), but there was no difference in the prevalence of moderate disease (49% and 53% respectively, OR 0.85, 95% CI 0.46 to 1.59, p = 0.64). Only one transplant recipient and one patient with CKD5 had a severe microvascular retinopathy.

Table 2. Comparison of retinal abnormalities in patients with a renal transplant or CKD5

| Retinal hemorrhage (%) | Renal transplant recipients (n=92) | CKD5 (n=70) | Odds ratio* |
|------------------------|-----------------------------------|------------|-------------|
| Any retinopathy (%)    | 79 (86)                           | 53 (76)    | 1.95 (0.87 to 4.35), 0.11 |
| Mild (%)               | 33 (34)                           | 15 (21)    | 2.1 (1.01 to 4.18), 0.06 |
| Moderate (%)           | 45 (49)                           | 37 (53)    | 0.85 (0.46 to 1.59), 0.64 |
| Severe (%)             | 1 (1.1)                           | 1 (1.4)    | 0.76 (0.05 to 12.34), 1.00 |
| Retinal vessel caliber | n=92                              | n=70       | Mean difference (μm)* |
| CRAE (mean, SD, μm)    | 135.1 (7.5)                       | 137.9 (14.9) | - 2.8 (-6.3 to 0.7), 0.12 |
| CRVE (mean, SD, μm)    | 199.1 (17.8)                      | 202.4 (27.8) | - 3.3 (-10.4 to 3.8), 0.36 |

Diabetes

| Any retinopathy (%) | Renal transplant recipients (n=21) | CKD5 (n=27) | Odds ratio * |
|---------------------|-----------------------------------|------------|-------------|
| Mild (21 - 31) (%)  | 4 (19%)                           | 18 (67%)   | 0.12 (0.03 to 0.45), <0.01 |
| Moderate (37 - 53) (%) | 3 (14%)                           | 7 (26%)    | 0.48 (0.11 to 2.12), 0.48 |
| Proliferative (>60) (%) | 0 (0%)                           | 6 (22%)    | 0.05 (0.00 to 0.97), 0.03 |

* (95% CI), p value

Fig. 1. Retinal images from patients post-transplantation: A. microaneurysms at 6 o’clock; and drusen at 2 o’clock; B. new vessels at the disc, hard exudate at macula; C. silver wiring; and D. infective emboli associated with immunosuppression after transplantation. Abnormalities are indicated with arrows.

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Transplant recipients with a moderate-severe retinopathy were not different from those with no retinopathy or only mild changes in terms of age, gender, hypertension, diabetes, smoking history, dyslipidemia, CKD stage, eGFR, time since transplant, haemoglobin level, diabetic retinopathy, or arteriolar or venular caliber (Table 3). However, notably, all four transplant patients with CKD5 had a moderate-severe microvascular retinopathy on examination (p=0.12).

**Retinal microvascular caliber.** Retinal arteriolar and venular caliber were not different in transplant recipients and patients with CKD5 (135.1±7.5 µm and 137.9±14.9 µm, p=0.12; and 199.1±17.8 µm and 202.4±27.8 µm, p=0.36, respectively) (Table 2). These calibers were less than those we have noted previously in CKD3 and 4 (Figure 2) [21].

When characteristics were compared between transplant recipients with arteriole caliber in the smallest and largest quartiles, there was no difference in age (p=0.45), gender (OR 1.24, 95%CI 0.34 to 4.49, p=1.00), hypertension (OR 1.58, 95%CI 0.24 to 10.4, p=1.00), diabetes (OR 1.58, 95%CI 0.41 to 5.96, p=1.00), smoking history (OR 0.84, 95%CI OR 0.26 to 2.68, p=1.00), dyslipidemia (OR 1.52, 95%CI 0.42 to 5.47, p=0.75), eGFR (p=0.69), duration

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**Table 3.** Clinical features in patients with a renal transplant and moderate-severe or no-mild microvascular retinopathy

| Renal transplant recipients (n=92) | Moderate or severe microvascular retinopathy (n=46) | No or mild microvascular retinopathy (n=46) | OR* |
|-----------------------------------|-----------------------------------------------|------------------------------------------|-----|
| Age (median, range, years)        | 54.5 (22 – 71)                                | 50 (24 – 78)                             | 0.74|
| Male gender (%)                   | 32 (70)                                       | 28 (61)                                  | 1.47 (0.62 to 3.48), 0.51 |
| Hypertension (%)                  | 42 (91)                                       | 37 (80)                                  | 2.55 (0.73 to 8.99), 0.23 |
| Diabetes (%)                      | 9 (20)                                        | 12 (26)                                  | 0.69 (0.26 to 1.84), 0.62 |
| Smokers (%)                       | 21 (46)                                       | 18 (39)                                  | 1.31 (0.57 to 2.99), 0.67 |
| Dyslipidemia (%)                  | 38 (83)                                       | 33 (72)                                  | 1.87 (0.69 to 5.07), 0.32 |
| eGFR (mean, SD, ml/min/1.73m²)    | 44.7 (20.3)                                   | 48.6 (18.6)                              | 0.34|
| Time since transplant (mean, SD, months) | 105.0 (105.8)               | 107.2 (99.2)                             | 0.92|
| Haemoglobin (mean, SD, g/dL)      | 123.4 (25.2)                                  | 132.7 (18.3)                             | 0.046|
| Diabetic retinopathy (%)          | 3 (33%)                                       | 1 (9%)                                   | 5.50 (0.46 to 65.16), 0.27 |

Retinal vessel caliber | Mean difference (µm). *
| CRAE (mean, SD, µm) | 134.4 (7.1) | 135.7 (7.9) | -1.3 (-4.4 to 1.8), 0.41 |
| CRVE (mean, SD, µm) | 200.7 (17.8) | 197.5 (17.8) | 3.2 (-4.2 to 10.6), 0.39 |

* (95% CI), p value

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of transplant (p=0.26), or haemoglobin level (p=0.84).

Likewise, when characteristics were compared between transplant recipients with venular caliber in the smallest and largest quartiles, there was no difference in age (p=0.11), gender (OR 0.52, 95%CI 0.14 to 1.93, p=0.51), hypertension (OR 0.16, 95%CI 0.02 to 1.53, p=0.19), diabetes (OR 1.32, 95%CI 0.31 to 5.71, p=1.00), smoking history (OR 0.57, 95%CI 0.17 to 1.91, p=0.54), dyslipidemia (OR 1.68, 95%CI 0.40 to 6.97, p=0.72), eGFR (p=0.94), duration of transplant (p=0.52) or haemoglobin level (p=0.36).

Retinal microvascular abnormalities and caliber before and after renal transplantation. Nine patients, comprising 8 males and a female, with a median age of 55 years (range 20 – 76) were studied before and after renal transplantation (Table 4). At recruitment, 8 (89%) patients had hypertension, 3 (33%) had diabetes, 7 (78%) were former smokers, 6 (67%) had dyslipidemia, and 8 (89%) were undergoing dialysis. Patients had a second set of retinal photographs 2.6 years later (median, range 1.5 to 4.1), 9 months (median, range 5-32) after the transplant. At this time, their median eGFR was 47 ml/min/1.73 m² (range 19 – 57).

Pre-transplant, retinal images were graded as having no microvascular change in 2 individuals, mild changes in 4, moderate in 2 and severe in one. Post-transplantation, the changes were graded mild in 3 and moderate in 6.

Post-transplantation, retinal arteriole caliber increased in 4 individuals and decreased in 5, but overall the mean caliber was not different from before transplantation (128.8 ± 13.1 µm and 130.5 ± 9.6 µm respectively, p=0.62). After transplantation, retinal venular caliber increased in 5 individuals and decreased in 4, but the mean venular caliber was also not different from before transplantation (187.8 ± 20.3 µm and 199.9 ± 14.5 µm, p=0.11). The reason for this inconsistency warrants further examination.
Diabetic retinopathy. Retinal images from all 92 transplant recipients and 67 patients with CKD 5 were gradeable for diabetic retinopathy. Both diabetes (OR 0.47, 95% CI 0.24 to 0.93, p=0.04) and diabetic retinopathy (OR 0.12, 95% CI 0.03 to 0.45, p<0.01) were less common in transplant recipients than in patients with CKD5 (Tables 1, 2). The retinopathy was also milder in the transplant recipients, since only one (5%) transplant recipient but 11 (41%) with CKD5 had moderate- proliferative diabetic changes (OR 0.07, 95% CI 0.01 to 0.62, p<0.01).

Discussion

Cardiovascular disease is a leading cause of morbidity and death in the transplant population [7]. Heart failure is one of its commonest manifestations [8], and often has a microvascular origin. The studies described here demonstrate that hypertensive/ microvascular abnormalities, including the vessel narrowing found in patients with CKD5 [20, 21], are also present after transplantation. In contrast, diabetes and diabetic microvascular retinopathy are less common and less severe.

These cross-sectional and longitudinal studies compared the prevalence and severity of microvascular and diabetic retinopathy after transplantation and in patients with CKD5. We have shown previously that retinal microvascular disease and diabetic retinopathy are increased in CKD5 [20], and that retinal small vessels narrow progressively as renal function deteriorates from CKD1-2 through to CKD5 [21].

Both these studies examined patients for features of mild, moderate and severe hypertensive/ microvascular retinopathy and for small vessel calibre. Mild retinopathy included generalized or focal arteriolar narrowing, silver wiring, and arteriovenous nicking. Moderate features were hemorrhage, microaneurysms, cotton wool spots and exudates, and severe retinopathy was characterized by optic disc swelling. However these abnormalities are not permanent, and hemorrhage, exudates and papilledema may resolve, and small vessel caliber, even in CKD5, can increase in response to stressors such as dialysis [26]. Improvements in small vessel damage could occur post-transplantation because of better blood pressure control and resolution of renal failure-induced inflammation.

When the microvascular abnormalities in transplant recipients were compared with those in patients with CKD5, retinal hemorrhage was just as common. Retinal hemorrhage is a feature of both hypertensive and diabetic retinopathy, and is increased in renal failure. Most hemorrhages were small and none substantially affected vision.

There was also a trend to an increase in mild microvascular retinopathy in transplant recipients compared with CKD5 but no difference in the prevalence of moderate retinopathy. Thus, overall, microvascular retinopathy was at least as common in transplant recipients as in patients with CKD5, despite transplant patients being younger, and having better renal function, less severe hypertension, and less diabetes. This study did not identify the determinants of moderate retinopathy, but interestingly, all four transplant recipients with CKD5 had at least moderate small vessel disease.

The mean caliber of retinal arterioles and venules were also not different in transplant recipients and patients with CKD5, despite transplant patients having renal function equivalent to CKD3 [21].

The lack of improvement in microvascular change with renal transplantation was confirmed where nine patients were followed before and after their transplants. Again, most transplant recipients had renal impairment equivalent to CKD3 but their vessel caliber was less than expected for this level of function [21]. The change in caliber post-transplantation varied in individual patients, increasing in some and decreasing in the others. However, even where the caliber increased post-transplantation, in only two individuals was it comparable to that in other patients with equivalent renal function [21].

Thus, both cross-sectional and longitudinal studies suggest that the small vessel abnormalities and reduced caliber seen in CKD5 are not reversed by renal transplantation.
The appearance of the retinal microvasculature represents a surrogate for systemic small vessel appearance and suggests that cardiac small vessel abnormalities will also not normalize post-transplantation. This potentially explains why, despite prospective transplant recipients being screened for coronary artery disease prior to surgery, their likelihood of cardiac events, especially heart failure, remains high.

Diabetes and diabetic retinopathy were both less common and less severe in transplant recipients. The reduced prevalence of diabetes in this population largely depends on the selection criteria for transplantation. Many previous studies have shown that diabetic retinopathy is unchanged or improves after transplantation [27]. Proliferative retinopathy was uncommon in our transplant recipients probably because they were typically younger, and had better-controlled diabetes and blood pressure.

The major strengths of these studies were that they used standardized methods to assess microvascular and diabetic retinopathy, and a highly robust measure of small vessel caliber, and that they examined a large cross-sectional population and confirmed the results in a smaller longitudinal series. The studies’ major weakness was their observational nature.

**Conclusion**

In conclusion, the systemic small vessel disease seen in end-stage renal failure does not normalize after renal transplantation, and potentially contributes to the increased cardiac events in this population.

**Disclosure Statement**

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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