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Telomere Length of Recipients and Living Kidney Donors and Chronic Graft Dysfunction in Kidney Transplants

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Abstract

Background—A biological marker that would allow clinicians to determine the length of time an allograft will remain functional after transplantation would greatly aid the ability to stratify donors by risk and to use biologically “young” allografts in young recipients, maximizing the use of this rare resource. Telomere length (TL) has been proposed to be such a marker to determine the biological age of a tissue.

Methods—We genotyped DNA from 1805 recipients and 1038 living kidney donors for TL to determine the association of TL with acute rejection (AR), chronic graft dysfunction (CGD), and graft failure of kidney allografts. DNA was isolated from peripheral blood white blood cells and TL was measured in DNA using the multiplexed monochrome quantitative polymerase chain reaction assay.

Results—As has been previously shown, we found a significant association between log-transformed TL and donor age ($P=3.8\times10^{-4}$) and recipient age ($P=5.6\times10^{-8}$). Univariate and multivariate analysis did not show any significant associations between log-transformed TL in donor or recipient DNA with AR, CGD, or graft failure, although we did observe an association between donor chronological age and CGD ($P=0.018$).

Conclusion—Although older allografts have been shown to be at greater risk for AR and CGD, this does not appear to be associated with shorter TL. Different markers will need to be identified

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to determine how biological age impacts transplant outcome, such as age-related fibrosis or tubular atrophy and tubular loss.

Keywords

Telomere; Kidney; Transplant; Graft dysfunction

The identification of biomarkers that can measure the biological age of an allograft could aid in optimizing the allocation of the allograft to specific recipients to maximize the life of each transplanted organ. Older kidneys have been shown to be more susceptible to chronic graft dysfunction (CGD) and graft failure (GF) when compared with younger kidneys after transplantation (1, 2). Older kidneys have a faster progression of tubular atrophy and tubular loss when compared younger kidneys (3) as well as having an increased incidence of delayed graft function (4), and this is felt to be an intrinsic feature of the older donated kidney. This has become an important issue, as older kidney allografts are increasingly being used in transplantation along with the poorer outcomes associated with these older kidneys, especially when transplanted into young recipients (5). Cellular replicative senescence, due to aging, is thought to play an important role in loss of graft function and this senescence may be linked to telomere length (TL) (6). Additionally, it has been suggested that younger recipients have a higher risk of acute rejection (AR) events than older recipients (7, 8), although these results are controversial (9). This reduced risk for AR in older recipients may be due to an older immune system that is less responsive, resulting in a lower risk of AR. Progressively shorter TL in immune cells due to aging in recipients may be a reason reduced immune response potentially making TL a better predictor of AR than chronological age.

The aging of tissues and organs is a controlled biological process. Somatic cells have been shown to have a limited replicative capacity (10) and this is thought to be associated, in part, with the reduction in TL as chromosome replication occurs with each cell division (11). Telomeres consist of multiple copies (100s–1000s) of short (6 nucleotide) repeats at the end of all chromosomes, playing a protective role against chromosome deterioration. With every round of DNA replication in somatic cells, TL is reduced and this progressive shorting is thought to have a fundamental role in cell senescence. TL is thought to reflect the remaining replicative potential of a population of cells (10). TL is heritable and shortens throughout life, making TL a potential marker for the “biological age” of a tissue (12).

The analysis of TL as a predictive marker of transplant outcome has been previously reported. It has been shown that TL may be a marker of treatment-related mortality in hematopoietic stem cell transplantation (13). A study by Bansal et al. (14) found that reduced TL was associated with reduced kidney function, but the significance was lost after adjustment for age. A modest significance associating TL and variation in serum creatinine levels in transplanted kidneys has also been reported (15). Using senescence-associated β-galactosidase (SA-β-Gal) enzyme as a marker, donor age appeared to be the major determinant factor in replicative senescence, as seen in higher expression of SA-β-Gal in donor kidneys with chronic allograft nephropathy (16). It was found that TL was significantly shorter in SA-β-Gal–expressing cells. Additionally, ischemia-reperfusion

during transplantation of primate kidneys was associated with a more rapid decrease in TL (17). It has also been shown that TL shortens more rapidly in transplanted human liver allografts than in untransplanted livers resulting in a shorter than expected life for liver allografts, as would be predicted by the chronological age of the donor (18). Because of this progressive decrease in the TL, individuals who obtain a kidney from a donor with shorter than normal telomeres may be at greater risk for reduced graft survival and more susceptible to age associated disease, including allograft dysfunction.

The DeKAF Genomics study contains a large number of recipient/living donor pairs along with clinical outcomes (19). We hypothesized that the biological age of the allograft, as estimated using TL from peripheral blood DNA, would be more reflective of risk for transplant outcomes than the chronological age of the allograft. We investigated if TL, in either the recipient or the donor, is associated with kidney allograft outcome.

Results

Table 1 shows the demographics of the study cohort. There were no significant differences between the characteristics of the recipients or donors. TL was analyzed as a ratio of the amount of telomere sequence in the tested genome versus the amount of DNA associated with a single copy gene, in our case, albumin. The result is presented as a ratio between the telomere signal and the albumin signal (T/S). To correct for the skewed distribution of TL, found in both recipients and donors, log transformation was used to normalize both recipient and donor TL (LnTL) in the analysis. Mean TL for different ethnic groups for both recipients and donors is shown in Table 2. A significant difference was observed on LnTL between reported ethnic groups in recipients (P=0.0005 for white vs. non-white individuals) but not in donors (P=0.19 for white vs. non-white individuals), although the number of non-white donors is relatively small. There was also a significant difference between Caucasians and African American recipients, where African Americans had longer telomeres than Caucasians even after adjusting for age (P=0.003). As has been previously reported, there was a significant negative association between donor LnTL and donor age ($P=3.8\times10^{-4}$) and recipient LnTL and recipient age ($P=5.6\times10^{-8}$). No significant difference was observed on LnTL between gender (P=0.51 and 0.38 for recipients and donors, respectively). The mean LnTL for AR, CGD, and GF in both recipients and donors is found in Table 3. Univariate analysis of AR, CGD, and GF associated with either age at transplantation or race is shown in Table 4. Donor chronological age was associated with AR (P=0.041; hazard ratio [HR], 1.15) and CGD (P=0.018; HR, 1.22) but not with GF. Recipient age was not associated with any of the outcomes. Recipient race (white vs. non-white) was significant for CGD (P=0.006; HR, 0.6) and both recipient (P=0.025; HR, 0.65) and donor (P=0.031; HR, 0.44) race were significant for GF. Univariate and multivariate association of either recipient or donor LnTL with AR, CGD, or GF was not significant (Table 5).

Discussion

The use of TL has been proposed as a candidate marker of biological age for tissues and organs, including kidney allografts (3, 12, 20). This is because of the strong association between TL and chronological age and individuals who inherit a longer than average TL

have been shown to have increased lifespans (21). This association has also been confirmed in animal models (22, 23). TL has also been associated with disease states including coronary artery disease (24, 25) and cardiovascular aging (26), which have both been associated with shortened TL. Additionally, smoking, obesity (27), type 2 diabetes (28), and even short sleep duration (29) have been associated with accelerated telomere shorting, all of which are risk factors for disease. There was also a significant difference between ethnicities, where we found that African Americans had longer telomeres than Caucasians even after adjusting for age. This difference has been previously reported (30) and may explain some differences in disease risk between different populations.

It has been previously shown that there is a negative correlation between TL and chronological age in kidney tissue (15). In this report, TL was associated with serum creatinine at 12 months after transplantation but only explained 6.6% of the variation in serum creatinine. Individuals with coronary heart disease also show an association between reduced kidney function and shorter TL as well as a more rapid shorting of TL, although this may also be explained by age alone (14). TL may also play a role in the progression of chronic kidney disease (31). It has also been reported that ischemia-reperfusion in kidneys is associated with accelerated telomere shortening (32).

Although TL has been hypothesized as a good candidate marker for “biological age,” published associations between TL and transplant outcome have been weak. Our data confirm this lack of association between TL in peripheral blood and transplant outcome. TL in kidney tissue or other markers will need to be identified as surrogates for biological age of the donor kidney. It is important to note that TL loss differs with different tissues in the kidney, where the telomere loss in medulla is less than that found in the cortex (33). There was a reported association between cyclin-dependent kinase inhibitor 2A expression levels and chronological age and has been proposed as a potential biomarker to ascertain the biological age of a kidney (3, 15). Other potential markers include p21 and other proteins associated with regulation of the cell cycle (34).

Current methods used in the determination of TL have limitations. Assays measuring TL provide an average for the entire genome when compared with a single copy gene control (e.g., albumin). This does not provide differences in the TL for specific chromosomes. It could be that there is an important “transplant event risk” gene on a specific chromosome and if linked to a shorter TL, even when the other chromosomes had a longer TL, would increase risk for an adverse outcome. Unfortunately, current methods to determine TL cannot differentiate between TLs of different chromosomes. Another limitation is that TL was determined in peripheral lymphocytes and not in the kidney. It may be that rate of TL shorting differs in different tissues.

In conclusion, we show that there is no significant association between LnTL and kidney allograft outcome. Possibly, TL along with other biomarkers of biological age may create a profile that provides a better estimate of biological age along with an association with transplant outcome, but, for the present, chronological age appears to be the best indicator of allograft biological age.

Materials and Methods

Clinical Information

Research subjects were part of the DeKAF Genomics study (19). Subjects enrolled at the time of transplantation were part of a multicenter prospective study of kidney allograft recipients and donors. Patients were consented for participation at the time of or soon after transplantation. All kidney transplant recipients undergoing a kidney or simultaneous pancreas–kidney transplant were eligible. The institutional review boards at each of the study sites approved this study. Immunosuppression and AR treatment were center specific. Clinical data were collected at the time of transplantation and regularly until allograft failure and maintained in a central database. AR was defined by the treating physician. CGD was defined as an increase in serum creatinine after 3 months after transplantation, which resulted in a biopsy. As we have previously published, this CGD phenotype has both chronic changes and concomitant inflammatory changes on biopsies (35). GF was defined as a return to dialysis.

TL Measurement

Genomic DNA was isolated from peripheral blood white blood cells, obtained with consent. TL was measured on DNA from 1913 kidney recipients and 1038 living kidney donors. The multiplexed monochrome quantitative polymerase chain reaction (PCR) assay was adapted from the established published method measuring both TL and albumin in the same well (36). The telomere primers were *telg* [5′-ACACTAAGGTTTGGGTT-TGGGTTTGGGTTTGGGTTAGTGT-3′] at a final concentration of 900 nM and *telc* [5′-TGTTAGGTATCCCTATCCCTATCCCTATCCCTATCCCTA-ACA-3′] at a final concentration of 500 nM. Albumin was used as a single copy gene, and the primers were *Albugcr2* [5′-cggcggcgggcggcgcgggctgggcggCCATGCTTTTCAGCTCTGCAAGTC -3′] at a final concentration of 700 nM and *Albdgcr2* [5′-gcccggcccgccgcgcccgtcccgccgAGCATTAAGCTCTTTGGCAACGTAGGTTTC-3′] at a final concentration of 500 nM.

The final reactions contained 1 × SYBR Green 1 Master Mix, which includes Taq polymerase and dNPTs (Roche Applied Science, Indianapolis, IN) and 100 ng DNA (5 ng/μL) per 20 μL reaction. All samples were run in duplicate. A standard curve was assayed with samples at concentrations of 23.30, 11.65, 5.83, 2.91, 1.46, 0.73, 0.36, and 0.18 ng/μL reference DNA from HeLa cancer cells to quantify the number of target templates in the DNA relative to the number of reference templates in the DNA. Three control samples consisted of a father, mother, and daughter CEPH trio (Coriell Institute for Medical Research, Camden, NJ) assayed in duplicate. Each plate assayed contained a standard curve and controls.

Each plate was assayed on a Roche Lightcycler 480 Real-time PCR machine in a 96-well PCR plate using a multiplexed thermocycling protocol (Roche Applied Science). The telomere segment was amplified in the initial set of amplification cycles and the albumin gene was amplified in the second set of cycles. The thermal cycling consisted of Hotstart (95°C for 15 min, 1 cycle), 2 cycles of 94°C for 15 s followed by 49°C for 1 min, 4 cycles of

94°C for 15 s followed by 59°C for 30 s, 25 cycles of 85°C for 15 s followed by 59°C for 30 s with a single acquisition, and 1 cycle of 59°C to 95°C at 4.4°C/s. The single copy gene cycling was 35 cycles at 94°C for 15 s, 84°C for 10 s, 85°C for 15 s, and 1 cycle of 59°C to 95°C at 4.4°C/s.

Quality Control

Quality control in the multiplexed monochrome quantitative PCR assay was based on Minimum Information for Publication of Quantitative Realtime PCR Experiments guidelines (37) and previous published methods (38). If the mean squared error of the points on the standard curve was more than 5%, the plate was reassayed. Three CEPH control samples were included in each plate assayed. An average normalizing factor was determined by dividing the in-plate CEPH control telomere signal/single copy gene signal (T/S) by the average T/S measurement from the same controls over 10 assayed plates. The sample T/S measurement was then corrected by multiplying it with the average normalizing factor. If their T/S values were outside of 7% coefficient of variation, the sample was reassayed. The two closest values were then chosen and reported. With this assay, the mean coefficient of variation was 3.3% (SD=2.7; 0%–29.9%).

Statistical Analysis

LnTL was used for all analysis. Separate survival analysis was conducted for donor and recipient LnTL. In both donor and recipient groups, separate Cox proportional hazards models were used to investigate the association of TL with time to CGD, time to AR, or time to GF or patient death, stratifying by transplant center. Both univariate and multivariate analyses were done, with LnTL as a continuous variable. Multivariate analysis included donor age at transplantation and race (white vs. non-white) for donor analysis or recipient age at transplantation and race (white vs. non-white) for recipient analysis. Alternatively, the LnTL was divided into quartiles to check for potential nonlinear functional form, but the association with outcomes was similar (data not shown).

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Table 1

Donor and recipient characteristics

	Recipient (n=1805)	Donor[b] (n=1038)
Age in years, mean (SD)	49.8 (14.2)	43.6 (11.4)
Sex, n (%) female	698 (38.7)	413 (40.3)
Body mass index, mean (SD)	28.3 (5.7)	27.7 (4.6)
Race, n (%)		
Black	326 (18.1)	53 (5.1)
Caucasian	1369 (75.8)	951 (91.6)
Asian	64 (3.6)	14 (1.4)
Other	46 (2.5)	20 (1.9)
TL as T/S, mean (SD)	0.73 (0.65)	0.65 (0.39)
GF or death, n (%)	144 (8.0)	66 (6.4)
AR, n (%)	194 (10.8)	169 (16.3)
CGD, n (%)[a]	176 (14.2)	125 (14.1)

[a] 1423 recipients/886 donors had CGD measure.

[b] GF, AR, and CGD information for corresponding recipients.

Table 2

Distribution of TL by ethnicity

Ethnicity	n	Mean LnTL	SD
Recipient			
Asian	65	0.76	0.30
African American	340	0.80	0.76
Hawaiian/Pacific Islander	2	0.45	0.01
Multiracial	14	1.33	2.53
Native American	32	0.92	1.52
White	1460	0.71	0.55
Donor			
Asian	14	0.58	0.15
African American	52	0.68	0.26
Hawaiian/Pacific Islander	13	0.85	0.84
Multiracial	5	0.73	0.34
White	941	0.65	0.39

Table 3

Mean LnTL for events and nonevents

Event type	Events LnTL (SD)	Nonevents LnTL (SD)
Recipients		
AR	0.78 (0.87)	0.73 (0.62)
CGD	0.81 (0.94)	0.74 (0.65)
GF or death	0.71 (0.55)	0.73 (0.66)
Donors		
AR	0.64 (0.40)	0.65 (0.38)
CGD	0.61 (0.21)	0.66 (0.43)
GF or death	0.61 (0.20)	0.65 (0.40)

Table 4
Univariate analysis with sample characteristics

Trait	AR	CGD	GF or death
Recipient			
Age at transplantation[a]			
HR (95% CI)	0.98 (0.89–1.07)	0.93 (0.85–1.02)	0.90 (0.93–1.17)
P	0.61	0.14	0.46
Race (white vs. non-white)			
HR (95% CI)	0.97 (0.66–1.42)	0.60 (0.42–0.87)	0.65 (0.44–0.95)
P	0.88	0.006	0.025
Donor			
Age at transplantation[a]			
HR (95% CI)	1.15 (1.01–1.32)	1.22 (1.03–1.43)	0.89 (0.71–1.11)
P	0.041	0.018	0.30
Race (white vs. non-white)			
HR (95% CI)	0.93 (0.51–1.73)	0.82 (0.39–1.71)	0.44 (0.21–0.93)
P	0.81	0.59	0.031

[a]Age was rescaled by every 10 years.

CI, confidence interval.

Table 5

Association between LnTL and events

Event	Univariate	Multivariate
Recipient		
AR		
HR (95% CI)	1.10 (0.80–1.50)	1.08 (0.78–1.49)
P	0.57	0.63
CGD		
HR (95% CI)	1.18 (0.85–1.65)	1.10 (0.78–1.55)
P	0.31	0.56
GF or death		
HR (95% CI)	0.81 (0.53–1.23)	0.78 (0.51–1.20)
P	0.32	0.26
Donors		
AR		
HR (95% CI)	0.89 (0.59–1.36)	0.90 (0.59–1.37)
P	0.60	0.62
CGD		
HR (95% CI)	0.81 (0.48–1.37)	0.80 (0.47–1.36)
P	0.43	0.41
GF or death		
HR (95% CI)	0.92 (0.43–1.99)	0.89 (0.40–1.88)
P	0.83	0.71

Univariate model: event-log(telomere). Multivariate model: event-log (telomere)+age+race (white vs. non-white). Both analyses stratified by units.

CI, confidence interval.