

Original Article

Ethnic differences in creatinine kinetics in a New Zealand end-stage kidney disease cohort

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SUMMARY AT A GLANCE

This retrospective study examined creatinine kinetics from a peritoneal dialysis population across four ethnic groups in New Zealand, and found that Pacific People had higher lean body mass and creatinine generation than other ethnic groups. This may explain why equations for predicting glomerular filtration rate in Black people may have increased accuracy in this population.

ABSTRACT:

Background: Recent data have suggested that glomerular filtration rate (GFR) is better predicted in New Zealand (NZ) Māori and Pacific People using the equations for Black people that predict higher GFR for any given serum creatinine. We hypothesized that this might be due to a higher rate of creatinine generation in NZ Māori and Pacific People.

Aim: To compare creatinine kinetics between different ethnic groups in a cohort of NZ peritoneal dialysis patients.

Methods: In this retrospective single-centre observational study, creatinine kinetics in 181 patients were determined from timed serum samples, peritoneal dialysate and urine collections between 1 October 2004 and 31 July 2011. Ethnicity was classified as Asian, NZ European, NZ Māori and Pacific People.

Results: A total of 799 samples from 181 patients were analysed: 194 in Asians, 127 in NZ Europeans, 268 in NZ Māori, 207 in Pacific People. Pacific People had the highest serum creatinine and lean body mass, and the highest creatinine generation rate at 1349 mg/day, compared with 1049 for Asians, 1186 for NZ Europeans and 1094 for NZ Māori ($P = 0.0001$). After adjustment for confounding factors, Pacific People had a greater creatinine generation by 140 mg/day compared with NZ Europeans ($P = 0.047$).

Conclusion: Pacific People on peritoneal dialysis in NZ have higher serum creatinine, lean body mass and creatinine generation than other ethnic groups. This is consistent with previous observations that equations for predicting GFR in Black people may have increased accuracy in some Australasian non-White non-Asian populations.

Chronic kidney disease (CKD) is a major global health problem that imposes a significant clinical and economic burden. The ability to accurately ascertain renal function enables clinicians to intervene appropriately to preserve renal function, and to initiate renal replacement therapy in a timely manner. Glomerular filtration rate (GFR) is a fundamental indicator of renal function, and is used with proteinuria to classify CKD into stages that correlate with increasing risk of adverse outcomes.¹ Several equations are in common clinical use for estimating GFR, and include the

Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Cockcroft–Gault equations. All of them predict renal function from serum creatinine, with variable adjustments for gender, age and ethnicity to account for the confounding effect of creatinine generation on the relationship between serum creatinine and GFR.

Creatinine-based estimating equations for GFR are likely to remain the standard for routine clinical use in the foreseeable future. The MDRD and CKD-EPI equations have

been developed with a high degree of statistical rigour and have a corresponding high degree of internal validity. However, just as important is the equations' external validity. Validation studies have been performed testing them in populations that are different from those in which they have been developed, and such studies often have shown poorer performance. Ethnicity (and its associated characteristics) is therefore an important effect modifier of the relationship between serum creatinine and GFR, indicating different creatinine kinetics across different ethnic groups. Previous researchers have attempted to improve the performance of estimating equations by introducing ethnic-specific modifications.²⁻⁸ A recent study examined these equations in a small cohort of CKD patients from Australia and New Zealand (NZ).⁹ The study had two findings of note. The first was that the performances of the MDRD and CKD-EPI equations were at best modest, and the second was that equations developed for Black people of African descent were most accurate for estimating GFR in non-White, non-Asian patients. These patients were almost exclusively NZ Māori and Pacific People, which strongly suggests different creatinine kinetics in these ethnic groups compared with White people.

Published studies involving Black people of African descent have shown that differences in skeletal muscle mass and diet are the main factors accounting for the observed ethnic differences in creatinine kinetics.¹⁰⁻¹² Of note, it is also well accepted that Pacific People in NZ also have a higher percentage of muscle mass compared with other local ethnic groups,¹³ supporting the plausibility of increased creatinine generation in this population. Surprisingly, the evidence is less convincing for NZ Māori despite the accepted dogma of this race as a Pacific People.

Given the heavy burden of CKD in NZ Māori and Pacific People,^{14,15} the ability to accurately assess their renal function is crucial. In this study, we aim to assess the presence and degree of differences in creatinine kinetics between various NZ ethnic groups to determine the need for ethnic-specific equations to estimate GFR from serum creatinine. We use retrospective data from a cohort of patients on peritoneal dialysis (PD), comparing creatinine kinetic parameters determined from measurements made for dose quantification under the steady-state assumption.

METHODS

Study design

In this research, we used data for the assessment of PD dose to model creatinine kinetics. The assessment of PD dose requires measurement of creatinine mass balance using serum, urine and dialysate samples, which is then combined with basic anthropometric data to allow the calculation of creatinine generation and clearance under the assumption of a steady state. We analysed these data in a retrospective observational study using a convenience sample of PD patients in our

centre. We compared creatinine kinetic parameters between ethnic groups using simple and more complex statistical techniques.

Setting and participants

The setting of our study is the Counties-Manukau District Health Board (DHB) in South Auckland, New Zealand. Counties-Manukau is a large urban district serving 491 270 at the end of the study period, 553 of whom were on dialysis (158 on PD, and 79 on home haemodialysis, the remainder on facility haemodialysis). The DHB's population can be summarily described as being young, multi-ethnic and socioeconomically disadvantaged (<http://www.cmdhb.govt.nz>).

We identified a study cohort of 181 patients using the PD management software used in our service (PatientOnLine®, Fresenius Medical Care Australia Pty Ltd (New Zealand Branch), Auckland, New Zealand). We included every patient with a complete assessment of PD dose between 1 October 2004 and 31 July 2011, and included all assessments from each patient. The study was granted ethics approval by the Northern X Regional Ethics Committee of the New Zealand Ministry of Health.

Data measurement and quantitative variables

The primary covariate of interest was self-determined ethnicity identified from patients' clinical records. The main measurements of interest were creatinine kinetic parameters: serum creatinine, measured creatinine clearance and measured creatinine generation. These were ascertained using 24 h collections of urine and peritoneal dialysate, with a single serum creatinine measurement at the end of the collection period. As such, calculations assume steady state and patients are routinely chosen for the assessment of PD dose at times when they are clinically stable with no acute medical illnesses. Under the steady-state assumption, conservation of mass means that creatinine generation is equal to creatinine removal, irrespective of dialysis dose. Specific creatinine kinetic formulas are detailed in Appendix I.

Creatinine assays were performed using the Jaffe method (Abbott Aeroset®, Ci8200 or Ci16200, Abbott Laboratories (N.Z.) Limited, Auckland, New Zealand), with a 1% within-assay and 3% between-assay coefficient of variation at the levels in this study. Assays were calibrated to isotope dilution mass spectroscopy for the majority of the period of observation.

We collected relevant descriptive data on key additional demographic and clinical variables from patients' clinical records: age, sex, primary kidney disease, estimated GFR at dialysis inception, late referral for nephrology predialysis care (defined as 3 months before dialysis inception), diabetes mellitus (none, type 1 and type 2), body mass index (BMI), comorbid conditions (coronary artery disease, peripheral vascular disease, cerebrovascular disease and chronic lung disease), smoking and country/state at dialysis inception.

Statistical analysis

Simple comparisons of data were made using the Kruskal-Wallis equality-of-populations rank test. Definitive comparisons were made using multivariate mixed models to account for lack of independence and internal correlation between repeated patient measurements, and to avoid clustering bias and distortion in estimates of

variability.^{16,17} We assumed different random effects for different patients. Analyses were conducted using Stata MP/12 (StataCorp, College Station, TX, USA).

Table 1 Clinical characteristics of the study cohort at earliest assessment of peritoneal dialysis dose

Variable	
Number of patients	181
Vintage (days)	116 (71, 269)
Age (years)	57.9 (48.3, 65.9)
Gender	
Female	103 (57%)
Male	78 (43%)
Peritoneal dialysis modality	
Automated	26 (14%)
Continuous ambulatory	155 (86%)
Ethnicity	
NZ European/other	27 (15%)
NZ Māori	71 (39%)
Asian	37 (20%)
Pacific People	46 (26%)
Late referral	24 (13%)
Smoking	29 (16%)
Diabetes mellitus	109 (60%)
Primary renal disease	
Other	17 (9%)
Hypertension/ischaemic	10 (6%)
Glomerulonephritis	43 (24%)
Polycystic kidney disease	6 (3%)
Diabetic nephropathy	105 (58%)
Comorbid disease	
Coronary artery	52 (29%)
Peripheral vascular	24 (13%)
Cerebrovascular	15 (8%)
Lung	22 (12%)

Continuous variables are shown as median (25th, 75th percentile); categorical variables are shown as number (percentage). NZ, New Zealand.

RESULTS

Patient characteristics

We included 181 patients for analyses, with a total of 799 assessments of PD dose between them. We excluded three three assessments from final modelling because of clearly erroneous or missing data. The number of assessments for each patient ranged between one and 17, with an average of four assessments of PD dose per patient. Baseline patient characteristics (defined as those at the time of the earliest assessment) are summarized in Table 1.

Main results

Table 2 tabulates and compares creatinine kinetic parameters and relevant anthropometric and nutritional data, by ethnicity. Of note, there are higher residual renal clearances in subjects in the NZ European/other ethnic category, likely as a result of less diabetic nephropathy in this group compared with others.¹⁵ In contrast, there are reasonably similar peritoneal clearances between ethnic groups, reflecting the high proportion of patients on continuous ambulatory PD in NZ who are for the most part treated using a fixed dialysis prescription of 56 L per week.

Figures 1 and 2 illustrate and compare key creatinine kinetic parameters, by ethnicity. There was no difference between ethnic groups in terms of serum albumin or BMI, other than for Asians who were significantly smaller than other groups. Serum creatinine concentrations, creatinine generation and lean body mass were highest in Pacific People but similar across other ethnic groups. Creatinine clearance was highest in NZ Europeans but similar across other ethnic groups. After adjustment for age, sex, BMI, body surface area and lean body mass, Pacific People still had significantly

Table 2 Creatinine kinetic parameters and relevant anthropometric and nutritional data, by ethnicity

Variable	Asian	NZ European	NZ Māori	Pacific People
Number of assessments	194	127	268	210
Serum creatinine* (μmol/L)	830 (670, 1010)	789 (528, 977)	790 (630, 990)	910 (638, 1160)
Creatinine clearance (peritoneal)* (L/week per 1.73 m ²)	44.8 (37.7, 50.5)	40.3 (35.0, 47.8)	42.6 (37.3, 47.9)	43.2 (38.6, 51.0)
Creatinine clearance (renal)* (L/week per 1.73 m ²)	21.5 (5.0, 36.7)	38.1 (9.3, 62.8)	18.6 (3.8, 40.9)	20.1 (0.9, 41.2)
Measured creatinine generation* (mg/day)	1049.4 (898.6, 1295.5)	1185.9 (1029.3, 1375.1)	1094.1 (881.7, 1443.4)	1349.0 (1113.4, 1679.6)
Predicted creatinine generation* (mg/day)	1015.0 (858.0, 1255.0)	1223.6 (1051.9, 1375.4)	1320.5 (1031.0, 1522.2)	1355.0 (1088.9, 1599.6)
Measured lean body mass* (kg)	37.9 (33.5, 45.1)	41.9 (37.3, 47.4)	39.2 (33.0, 49.4)	46.6 (39.8, 56.2)
Predicted lean body mass* (kg)	36.9 (32.3, 43.9)	43.0 (38.0, 47.4)	45.8 (37.4, 51.6)	46.8 (39.0, 53.9)
Body surface area* (m ²)	1.71 (1.62, 1.88)	1.97 (1.87, 2.03)	1.90 (1.74, 2.04)	1.97 (1.87, 2.04)
Volume of distribution for urea* (L)	34.7 (30.0, 40.2)	40.0 (38.3, 43.0)	39.4 (34.6, 44.4)	40.6 (35.9, 46.6)
Height* (m)	1.66 (1.59, 1.72)	1.68 (1.66, 1.72)	1.67 (1.59, 1.74)	1.68 (1.65, 1.74)
Weight* (kg)	68.7 (57.4, 77.0)	85.1 (73.9, 93.3)	82.0 (68.3, 92.3)	84.7 (77.3, 92.3)
Body mass index* (kg/m ²)	24.2 (22.2, 28.3)	29.0 (25.9, 33.8)	29.1 (25.7, 33.5)	29.3 (26.8, 32.7)
Serum albumin (g/L)	36 (34, 38)	37 (35, 39)	36 (33, 39)	36 (33, 39)
Kt/V*	2.1 (1.8, 2.4)	2.1 (1.7, 2.6)	1.9 (1.7, 2.3)	2.0 (1.7, 2.4)

*Kruskal–Wallis equality-of-populations rank test *P*-value < 0.05, indicating a significant difference within each parameter, by ethnicity. Continuous variables are shown as median (25th, 75th percentile). NZ, New Zealand.

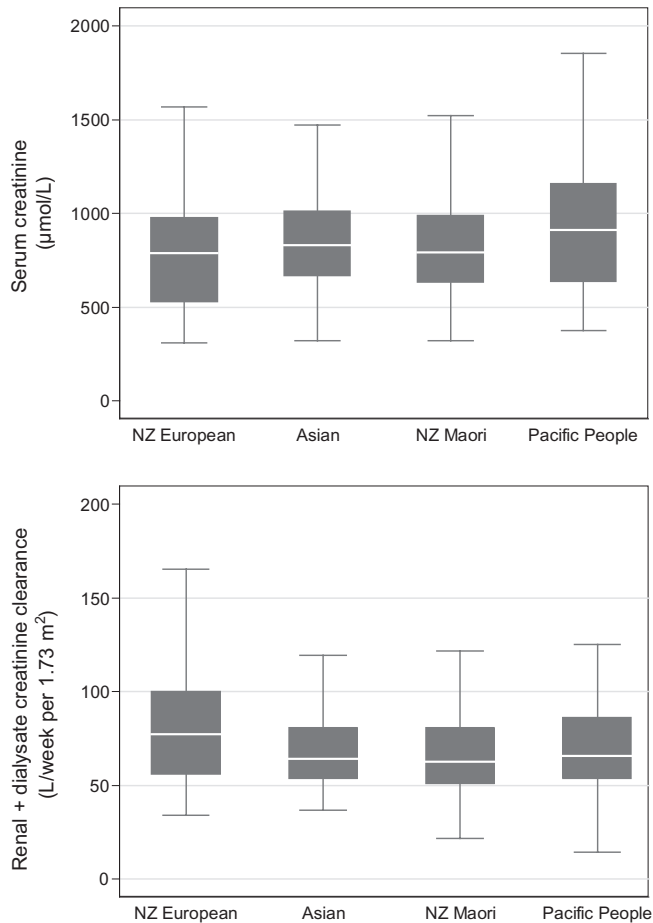


Fig. 1 Serum creatinine and creatinine clearance for the study cohort, by ethnicity (the horizontal bar near the middle of the box represents the median, the bottom and top of the box, the 25th to 75th percentile, and the whiskers, 1.5 times the interquartile range). Differences by ethnic group were statistically significant for serum creatinine (Kruskal–Wallis equality-of-populations rank test, *P*-value 0.0005), and for creatinine clearance (Kruskal–Wallis equality-of-populations rank test, *P*-value 0.003). NZ, New Zealand.

higher creatinine generation (Table 3). Consistent with studies in other populations, there was only a weakly positive relationship between lean body mass and serum albumin, reflecting the limited role of this parameter as a nutritional index.^{18–21}

Figure 3 shows mean adjusted creatinine generation and clearance as a function of serum creatinine from the main-effects model, comparing Pacific People with other ethnicities.²²

DISCUSSION

Our study has demonstrated that there are important differences in creatinine kinetics between ethnicities in NZ: Pacific People in our study had higher creatinine generation and serum creatinine than other ethnic groups for the same creatinine clearance. This was not observed to be the case

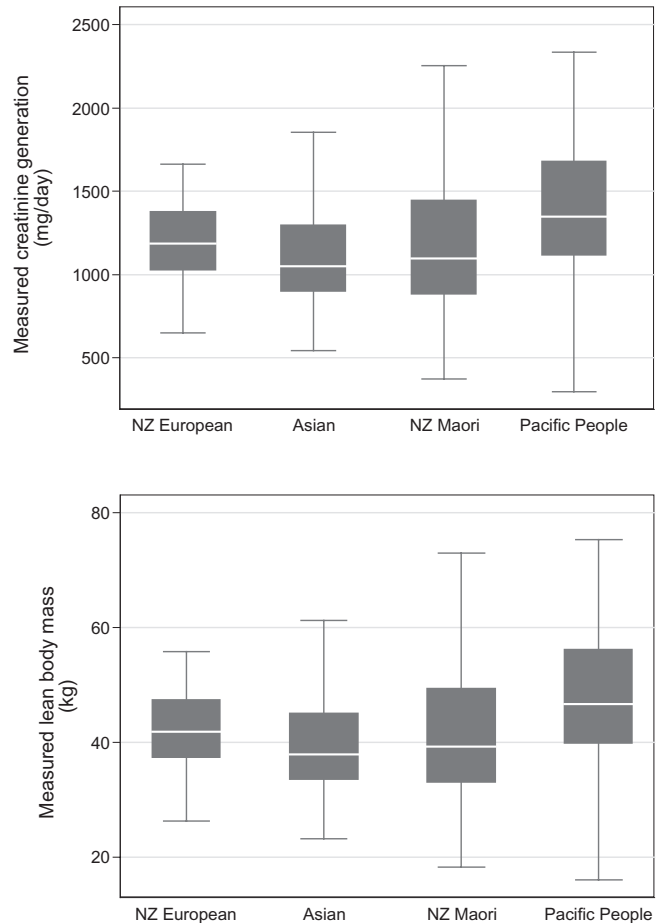


Fig. 2 Measured creatinine generation and lean body mass for the study cohort, by ethnicity (the horizontal bar near the middle of the box represents the median, the bottom and top of the box, the 25th to 75th percentile, and the whiskers, 1.5 times the interquartile range). Differences by ethnic group were statistically significant for creatinine generation and lean body mass (Kruskal–Wallis equality-of-populations rank test, *P*-value 0.0001). NZ, New Zealand.

for NZ Māori patients. The implication of this finding is that the use of MDRD and CKD-EPI equations for estimating GFR may underestimate true GFR in Pacific People. This hypothesis is consistent with the findings of a previous study comparing estimated with measured GFR in an ethnically diverse Australian and NZ cohort.⁹ Of note, the creatinine generation in this current study remained significantly greater among Pacific People even after adjustment for sex, BMI, age and serum albumin, meaning that increased creatinine generation was independent of these factors in the studied cohort.

The most likely explanation for our observations is inter-ethnic differences in skeletal muscle mass, which would be expected to result in differential rates of creatinine production. In our study, Pacific People had higher measured lean body mass than other ethnic groups despite a similar BMI, with NZ Māori and NZ Europeans being similar. Skeletal

Table 3 Table of coefficients relating the change in creatinine generation (mg/day) to predictive variables in the model, fully adjusted for other variables in the table

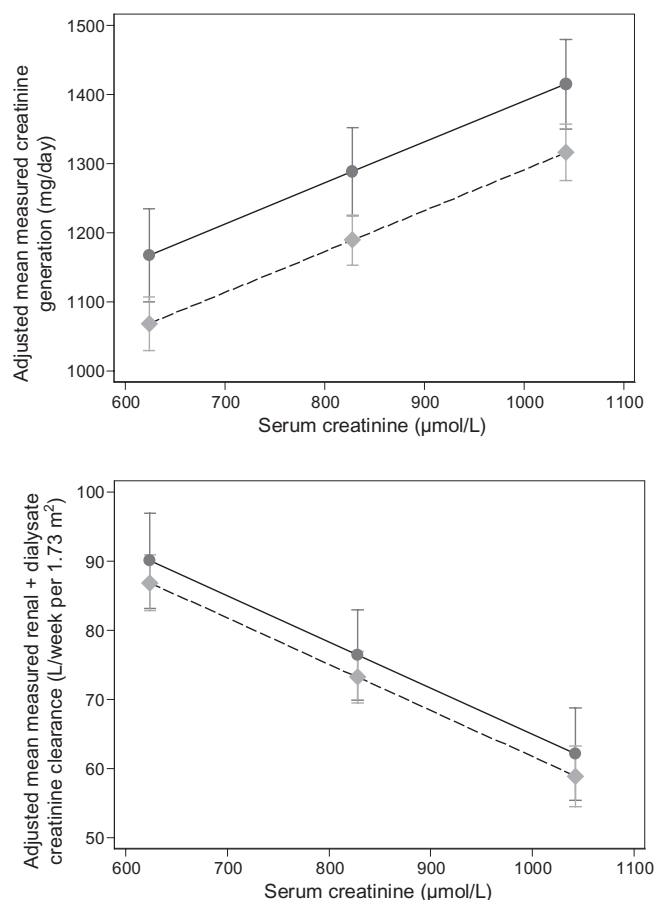
Predictor	Coefficient	95% confidence intervals	P-value
Sex			
Male	0 (Ref)	—	—
Female	-436.2	(-524.4, -347.9)	<0.0005
Body mass index (kg/m²)			
<25	0 (Ref)	—	—
25–30	234.1	(157.9, 310.4)	<0.0005
>30	361.1	(272.9, 449.4)	<0.0005
Age (years)			
<50	0 (Ref)	—	—
50–65	-120.3	(-210.6, -30.0)	0.009
>65	-297.1	(-402.2, -192.0)	<0.0005
Ethnicity			
Asian	10.3	(-135.2, 155.9)	0.9
NZ European	0 (Ref)	—	—
NZ Māori	-21.9	(-153.5, 109.6)	0.7
Pacific People	140.9	(0.5, 281.4)	0.047
Serum albumin (g/L)			
<35	0 (Ref)	—	—
35–37	27.9	(-24.9, 80.8)	0.3
>37	28.6	(-25.1, 87.1)	0.3

The coefficients can be interpreted as the change in creatinine generation per unit change in the predictive variable. For example, we are 95% confident that the creatinine generation is between 30 and 210.6 mg/day lower in those aged 50–65 years relative to those aged less than 50 years. NZ, New Zealand.

muscle mass has been well studied within the NZ population using definitive techniques. These studies show greater skeletal muscle in Pacific People than other ethnic groups (both in absolute terms and as a percentage of body weight), with NZ Māori and NZ Europeans being similar.¹³ This suggests that skeletal muscle mass is a causal link that results in higher creatinine generation and serum creatinine levels in Pacific People. Another contributing factor may be dietary habits, as Pacific People are known to consume more protein calories than other ethnic groups.^{23,24} Overall, our findings in Pacific People reflect the findings in similar studies of African American populations.^{10,25}

Our observations suggest the need for ethnic-specific equations for estimating GFR in Pacific People. To illustrate, Figure 3 shows the 4–5% difference in creatinine clearance between Pacific People and other ethnic groups at any given level of serum creatinine. Assuming a similar difference in CKD populations, it is likely that failure to take this into account would result in differential decision making in Pacific People, potentially leading to undesirable consequences such as over-diagnosis of CKD and early initiation of renal replacement therapy. A case can therefore be made for further research into the estimation of GFR in Pacific People, with a view to ethnic-specific estimating equations.

As for any observational study, there are several limitations to our research. First, non-compliance with either PD or the urine and dialysate collections for assessment of PD

**Fig. 3** Predictive margins with 95% confidence intervals for creatinine generation and creatinine clearance from the main-effects statistical model, comparing Pacific People with other ethnicities. —●— Pacific People; - - -◇- - Other.

dose leads to spurious estimates of creatinine generation. If all urine and dialysate collections are done correctly after a period of non-compliance (i.e. compliance is resumed), there is a temporary increase in creatinine excretion over the baseline leading to overestimation of creatinine generation. If urine and dialysate collections are incomplete after a period of compliance, the opposite occurs. The discrepancy between predicted and measured creatinine generation that we observed in NZ Māori is consistent with either a genuinely lower rate of creatinine generation in this ethnic group, or alternatively non-compliance during the period of assessment^{26,27} (acknowledging the inaccuracy of this index as a measure of non-compliance^{28–30}). As importantly, our study did not include direct body composition and skeletal muscle mass measurements to corroborate our findings relating to creatinine generation. Available literature does support our hypothesis, however, with data from a North American cohort showing both increased BMI and also survival on dialysis in Pacific People within Network 17.^{31–33} This implies that the higher skeletal muscle mass in Pacific People is preserved after the onset of end-stage kidney disease. Finally,

there are additional novel factors above and beyond body composition and nutrition such as inflammation that may also influence creatinine kinetics or confound its assessment.^{34,35} We were unable to study these factors further in this particular research.

This study demonstrates the presence of differences in creatinine kinetics between various ethnic groups in a NZ dialysis population, with Pacific People having higher creatinine generation likely secondary to higher skeletal muscle mass. This observed difference is likely to be related to previously known differences in body composition and possibly dietary habit. Our study suggests further study to ensure the validity of commonly used estimating equations for GFR in this population, and perhaps the need for ethnic-specific equations.

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APPENDIX I

The following methods pertain to calculations in this research, and are those used in the proprietary peritoneal dialysis management software, PatientOnLine®.^{26,27} The serum creatinine concentration is corrected for protein concentration and expressed per unit of plasma water (CpCr). Body weight (Wt) is calculated in kg, and age is calculated in years. Solute clearances are normalized to body water (V) estimated by the Watson formula,³⁶ or normalized to 1.73 m² body surface area calculated by the Dubois formula.³⁷

The measured renal and peritoneal creatinine clearances are calculated as first-order clearances from 24 h urine and dialysate collections, KrCr and KpCr. They are summed over 24 h to give KprCrT (L/day). Metabolic degradation of creatinine in the gut lumen is also calculated as a first-order clearance mechanism (KgCr) in accordance with $1.44 \times [0.0264 \times (V/0.58)]$.^{38,39} This is summed over 24 h to give KgCrT (L/day).

Measured creatinine generation rate (mg/day) is calculated in accordance with:

$$KprCrT \times CpCr + KgCrT \times CpCr$$

Lean body mass is estimated from creatinine kinetics;^{40,41} predicted creatinine production (mg/day) is estimated by the Cockcroft–Gault formula:^{27,38,42}

$$[28 - 0.20 \times \text{age}] \times \text{Wt} \quad (\text{male})$$

$$[24 - 0.17 \times \text{age}] \times \text{Wt} \quad (\text{female})$$