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Trajectories of eGFR decline over a four year period in an Indigenous Australian population at high risk of CKD-the eGFR follow up study

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ABSTRACT

Being able to estimate kidney decline accurately is particularly important in Indigenous Australians, a population at increased risk of developing chronic kidney disease and end stage kidney disease. The aim of this analysis was to explore the trend of decline in estimated glomerular filtration rate (eGFR) over a four year period using multiple local creatinine measures, compared with estimates derived using centrally-measured enzymatic creatinine and with estimates derived using only two local measures.

Method: The eGFR study comprised a cohort of over 600 Aboriginal Australian participants recruited from over twenty sites in urban, regional and remote Australia across five strata of health, diabetes and kidney function. Trajectories of eGFR were explored on 385 participants with at least three local creatinine records using graphical methods that compared the linear trends fitted using linear mixed models with non-linear trends fitted using fractional polynomial equations. Temporal changes of local creatinine were also characterized using group-based modelling. Analyses were stratified by eGFR (< 60; 60–89; 90–119 and ≥ 120 ml/min/1.73 m^2) and albuminuria categories (< 3 mg/mmol; 3–30 mg/mmol; > 30 mg/mmol).

Results: Mean age of the participants was 48 years, 64% were female and the median follow-up was 3 years. Decline of eGFR was accurately estimated using simple linear regression models and locally measured creatinine was as good as centrally measured creatinine at predicting kidney decline in people with an eGFR < 60 and an eGFR 60–90 ml/min/1.73 m^2 with albuminuria. Analyses showed that one baseline and one follow-up locally measured creatinine may be sufficient to estimate short term (up to four years) kidney function decline. The greatest yearly decline was estimated in those with eGFR 60–90 and macro-albuminuria: -6.21 (-8.20, -4.23) ml/min/1.73 m^2.

Conclusion: Short term estimates of kidney function decline can be reliably derived using an easy to implement and simple to interpret linear mixed effect model. Locally measured creatinine did not differ to centrally measured creatinine, thus is an accurate cost-efficient and timely means to monitoring kidney function progression.

1. Introduction

The ability to accurately estimate the rate of decline of kidney function over time is of paramount importance to ensure a timely and adequate intervention for individuals at high risk of progressing to end stage kidney disease (ESKD). Prediction of the rate may be affected by several factors, including the nature of progression (linear or non-linear) and the source of the serum creatinine result. The identification

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of a model predictive of decline in kidney function is of particular importance in Australian Aboriginal and Torres Strait Islander peoples (hereafter respectfully referred to as Indigenous), among whom the age-adjusted incidence of ESKD requiring renal replacement therapy (RRT) is 6–7 times higher than the non-Indigenous Australian population [1].

The use a of simple linear regression model to predict eGFR levels over time has both methodological and clinical benefits, as the slope of the regression model can be interpreted as the change in eGFR over a given time period. Previous research has focussed on whether eGFR decline can be better estimated using a non-linear model or models where the decline might accelerate or decelerate from a certain point in time [2,3]. The identification of a model that performs well universally has been challenging since rates and trajectories of progression vary between individuals and across ethnicities [4].

The use of routinely and locally analysed creatinine measures as opposed to centrally analysed samples has a clear practical and economic advantage in multi-site longitudinal research studies and in providing timely clinical information to health providers.

This analysis is an extension to published work on the progression of kidney disease in Indigenous Australians: The eGFR Follow-up study [5]. Our previous analysis included participants who had both baseline and follow-up enzymatic creatinine centrally measured (67%) or baseline and follow-up creatinine locally measured (30.4%), thus involved assessment at 2 time points only. Local creatinine was also measured at several other occasions during the follow-up. The aim of this work was to explore the absolute decline and the trend of decline in eGFR over a four year period for participants with at least three local creatinine measures, thus establishing if the trend of decline is linear or non-linear. Further aims were to compare kidney function decline estimated using enzymatic creatinine with decline estimated using local creatinine measurements only, and to establish if a baseline and at least one follow-up creatinine measure over a four year period were sufficient to estimate the decline.

2. Methods

Details of the eGFR study have been given elsewhere. In brief the baseline eGFR study comprised a cohort of 656 Indigenous Australian participants recruited between 2007 and 2011, with the majority of baseline data collected from 2009 to 2011 and follow-up data collected between 2012 and 2014, all laboratories were using IDSM methods since commencement of the study [6]. Participants were recruited from twenty sites in urban, regional and remote Australia across five strata of health, diabetes and kidney function. The aim of the baseline eGFR study was to assess the accuracy of GFR estimating equations in Indigenous Australians. The eGFR Follow-up study was a longitudinal extension of the eGFR study and details of the methods have been previously described [6].

2.1. Laboratory methods

Serum creatinine assays were performed at each regional centre as part of standard clinical care. The creatinine assay at each centre was performed in an accredited laboratory using an assay with claimed traceability to the Isotope Dilution Mass Spectrometry reference method. In addition, serum creatinine was measured in all samples at a central laboratory, using Roche enzymatic method on a Beckman-Coulter DxC 800 analyser (Fullerton, CA, USA). Details of the analytic methodology on how the reference measured GFR (mGFR) was derived has been given elsewhere [6,7]. Measures of eGFR were calculated using the CKD-EPI formula [8].

2.2. Participants

Indigenous Australians were eligible for participation in this analysis if they were aged 18 years and older and had provided a blood sample for baseline creatinine and urine ACR and at least two blood samples for follow-up creatinine. Participants with a follow-up time $<$ 6 months were excluded.

2.3. Outcome definition

For robustness, the analysis investigating the trends of decline over time used data from participants who had at least three locally-assayed creatinine measures over time; the median follow-up was 3 years and all follow-up was truncated at 4 years. Participant follow-up time was censored at the time point an eGFR of $<$ 15 ml/min/1.73 m^2 was reached or RRT initiated. Participants had up to eleven measures of creatinine; however, since data were sparse from the seventh measure we included only follow-up information up to and including the sixth measurement.

The outcome of eGFR change (CKD-EPI, ml/min per 1.73 m^2 per year) was calculated as (eGFR at follow-up – eGFR at baseline). The follow-up time was calculated as the time between the baseline date and the index follow-up creatinine measurement date (range, 0–4.0 years).

The analysis comparing decline estimated using local creatinine with decline estimated using centrally measured creatinine was carried out using a subset of participants that had baseline and one follow-up measure of both central and local creatinine.

3. Statistical analyses

Bland and Altman plots and paired *t*-tests were used to explore the agreement between measured baseline GFR and baseline GFR calculated using centrally measured creatinine and the agreement between measured baseline GFR and baseline GFR calculated using locally measured creatinine. Bias, precision and accuracy were computed for the locally derived values as compared to mGFR. Bias, precision and accuracy were computed for the centrally derived values as compared to mGFR have been reported elsewhere [7]. Bias was defined as the median absolute difference between the reference GFR and the estimated GFR (i.e. mGFR– eGFR), and percentage bias as the median percentage difference relative to mGFR Accuracy was defined as the percentage of eGFR values that fell within 30% of their corresponding mGFR value, and precision as the interquartile range of the absolute differences. Confidence intervals were calculated using the binomial exact method for proportions.

The absolute change in eGFR over time was estimated using linear mixed regression models where the outcome eGFR was regressed on follow-up time. Individual and grouped trajectories of eGFR over time were explored using graphical methods that compared the linear trends fitted using linear mixed models with non-linear trends fitted using fractional polynomial equations. All the mixed models included a random effect for participant and one for time to allow for correlation of measurements repeated within the same individual and used a flexible unstructured matrix for the variance and covariance. All the analyses were stratified by baseline eGFR ($<$ 60; 60–89; 90–119 and $\geq$ 120 ml/min/1.73 m^2) and albuminuria categories (A1 $<$ 3 mg/mmol; A2, 3–30 mg/mmol; A3, $>$ 30 mg/mmol). For statistical power reasons, in some of the analyses the eGFR groups 90–119 ml/min/1.73 m2 and $\geq$ 120 ml/min/1.73 m^2 were pooled into one group: eGFR $\geq$ 90 ml/min/1.73 m^2. The potential confounding effects of age, gender and baseline eGFR were also explored by including these factors as fixed terms in the mixed models.

As an alternative to the use of categories of baseline eGFR and albuminuria suggested by clinical guidelines, we also explored a method of differentiating groups of individuals according to change in renal function over time. For this purpose, temporal changes in eGFR during follow-up were characterized using group-based modelling (GBM), a statistical approach based on latent class analysis which identifies and clusters individuals' trajectories into distinctive groups [9].

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