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Implications and importance of skeletal muscle mass in estimating GFR at dialysis initiation

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Abstract

There is a trend towards “early” initiation of dialysis for renal replacement therapy. However, several observational studies showed an association of increased mortality at higher estimated GFR at dialysis initiation. This surprising result is due to errors in estimation of GFR. In malnourished patients with low muscle mass, serum creatinine based equations overestimate GFR. In patients with higher muscle mass, these equations underestimate GFR. Ultimately, this spurious association of higher prevalence of malnutrition in patients with higher eGFR compared with those with lower eGFR, leads to the appearance of increased mortality with “early” initiation of dialysis. Therefore, reliable equations that properly account for creatinine production are warranted to estimate GFR at initiation of dialysis. Until then, in those with extremes of nutrition, mean of measured urea and creatinine clearances might provide more accurate GFR estimation for initiation of dialysis than the currently available equations.

Introduction

The timing of initiation of dialysis has been controversial. There is little controversy that initiation of dialysis improves survival in those with advanced kidney failure with absolute indications such as uremic pericarditis, hyperkalemia, volume overload, metabolic acidosis. However, it has been advocated that dialysis should be initiated much earlier when the patient does not have uremic symptoms or signs. The rationale for this argument is that with progression of kidney failure, there is loss of appetite with consequent decrease in muscle mass and drop in serum albumin. Malnutrition as indicated by low serum albumin levels, low body mass index, low muscle and fat mass are strong predictors of mortality in dialysis patients. Hence, it is biologically plausible that initiation of dialysis is beneficial in those with indices of malnutrition such as progressive weight loss, serum albumin levels below 4.0 g/dL, serum transferrin levels below 200 mg/dL, and spontaneous dietary protein intake below 0.8 to 0.7 g/kg per day¹. Assuming that biological effects of dialytic clearances are

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equivalent to that of native kidney clearances and initiation of dialysis will reverse uremic malnutrition, many national guidelines^{2, 3} have recommended initiating dialysis when estimated GFR is about 10 ml/min/1.73 m². These recommendations have impacted clinical practice. The proportion of dialysis patients with estimated GFR > 10 ml/min per 1.73 m² has increased between 1996 and 2008 from 25% to 55% in diabetics and 16% to 48% in non-diabetics. In other words, more than 50% of all patients initiated on dialysis have an “early” start⁴.

The following discussion summarizes the controversies and data regarding the impact of nutritional status on GFR estimation in advanced CKD and the impact of timing of dialysis on nutritional status and outcomes.

Methods of estimating GFR

Glomerular filtration rate could be measured by the urinary clearance of exogenous or endogenous markers. The gold standard for measurement of GFR is inulin clearance. Inulin is an uncharged polyfructose molecule with an average molecular weight of ~5,000, is not metabolized in the body, not bound to plasma proteins, is filtered freely in glomeruli, and is neither reabsorbed nor secreted by the renal tubules. Other exogenous markers such as iothalamate could also be used to measure GFR. However, these exogenous markers need to be infused or injected with timed collection of urine samples to measure GFR. Hence, these are impractical for routine clinical use.

Therefore, endogenous markers that are filtered by the glomerulus such as creatinine, urea and cystatin C are used in clinical practice. Because these markers are endogenously produced, the factors that affect the production of these markers could potentially affect GFR estimation using these markers.

Creatinine and urea based measurement of GFR

Creatinine and urea are freely filtered by the glomerulus and hence are endogenous markers of kidney filtration. Apart from glomerular filtration, creatinine is also secreted by the tubule and hence urinary creatinine excretion is higher than its filtration. Hence, creatinine clearance calculated from timed urinary collection overestimates the GFR. As the proportion of tubular secretion to glomerular filtration of creatinine increases with advanced kidney disease, the overestimation of GFR is greater at lower levels of kidney function.

On the other hand, urea is absorbed by the tubule and hence the urinary excretion of urea is lower than the glomerular filtration. As a result, urea clearance underestimates GFR. In those with advanced kidney failure, the average of creatinine and urea clearances is used to correct for the over-estimation with creatinine clearance and underestimation with urea clearance.

Serum creatinine based estimates of GFR

Twenty-four hour urine collection is cumbersome and under-collection of urine is often a problem. Hence, estimation of GFR from single serum levels of creatinine is appealing.

Serum creatinine level is a measure of creatinine production by the muscle and creatinine excretion by the kidney. Since, glomerular filtration is the primary mode of creatinine excretion, GFR could be estimated from serum creatinine levels provided the creatinine production is accounted for. Cockcroft-Gault formula was developed to estimate 24 hr creatinine clearances from serum creatinine using age, gender and body weight to account for creatinine production⁵.

Nonetheless, Cockcroft-Gault formula estimates creatinine clearance and not GFR. In the Modification of Diet in Renal Diseases (MDRD) study, GFR was measured with iothalamate clearances⁶. Levey et al used this dataset to derive regression equations of measured GFR with serum creatinine and other variables⁶. The most commonly used MDRD equation is the 4 variable formula which uses age, gender and race to account for creatinine production. More recently the CKD-EPI equation was developed to estimate GFR and this equation performs better than the MDRD equation at higher GFR levels⁷. Both the MDRD and the CKD-EPI equations use age, gender and race to account for creatinine production.

Influence of nutrition on timing of initiation of dialysis with GFR estimated from serum creatinine

Table 1 summarizes the data from observational studies regarding eGFR at the start of dialysis and subsequent outcomes. Surprisingly, most of these studies found that people who started dialysis early had worse survival compared to those who started late. This counter-intuitive finding might be because clinicians start sicker patients earlier on dialysis. On the surface, this explanation appears biologically plausible as there is a higher prevalence of malnutrition in those started early on dialysis.

Nonetheless, there is an alternate explanation for the observed early start of dialysis in malnourished patients. The fundamental assumption of the MDRD (and the CKD-EPI) equation is that age, gender and race account for creatinine production and therefore, at a given age, race, gender and serum creatinine level, the GFR is constant. In other words, as per the MDRD equation, all 65 year old white women with a serum creatinine of 1.5 mg/dl have a GFR of 35 ml/min/1.73 m² because they all have the same level of muscle mass. This assumption is unlikely to be valid.

In those with extremes of nutrition there is likely a systematic bias in estimation of GFR from serum creatinine with the MDRD equation. In malnourished patients with low muscle mass and low creatinine production, the serum creatinine at initiation of dialysis will be low. If age, sex, and race do not fully account for creatinine production and the MDRD estimate of GFR is inversely proportional to serum creatinine, the MDRD GFR will be expected to be higher than the measured creatinine clearance in patients with low creatinine production. For the same reasons, in patients with high creatinine production, the MDRD GFR will be lower than the measured creatinine clearance. The overestimation of GFR in patients with low creatinine production (malnourished patients) and *vice versa* in patients with high creatinine production (well-nourished patients) will result in a spurious association of higher

prevalence of malnutrition in patients with higher MDRD GFR compared with those with lower MDRD GFR.

This hypothesis was tested in the United States Renal Data System Dialysis Morbidity and Mortality Study in those with reported 24 hr creatinine clearances at initiation of dialysis⁸. Urinary creatinine was used as a surrogate marker of muscle mass. Malnutrition was defined as the presence of clinical diagnosis of malnutrition, serum albumin < 25th percentile (< 2.9 g/dl), or body mass index < 10th percentile (< 19.25 kg/m²). There was a systematic bias; in those with lower muscle mass, estimated GFR was higher than measured creatinine clearance and vice versa. Furthermore, each 5 ml/min/1.73 m² increase in eGFR at initiation of dialysis was associated with 21% higher odds of malnutrition (which was abolished by adjusting for creatinine production as indicated by urinary creatinine). Thus, these data suggest that a potential explanation for the observed association of higher eGFR at initiation of dialysis is because in those with malnutrition, eGFR is misleadingly high and in those with better nutrition, eGFR is misleadingly low.

Observational studies of measured creatinine clearances at the initiation of dialysis

Since the 24-h urinary excretion of creatinine reflects muscle mass, in those with advanced kidney failure and extremes of nutrition, measured creatinine clearances from 24-h urine collection are likely to be a less biased estimate of GFR. Indeed, the national guidelines recommend measuring 24-h creatinine clearance to assess GFR at initiation of dialysis as well as in individuals with variation in dietary intake or muscle mass, as these factors are not specifically taken into account in GFR prediction equations⁹.

When measured creatinine clearances were used, higher estimated GFR at initiation of dialysis was not associated with increased mortality in the US Renal Data System Dialysis Morbidity and Mortality Study¹⁰. Similarly, in the Netherlands Cooperative Study on the Adequacy of Dialysis, higher GFR estimated from serum creatinine was associated with increased mortality but measured GFR (mean of creatinine and urea clearance) was not associated with increased mortality¹¹. These data suggest that increased mortality associated with higher MDRD GFR at start of dialysis is an artifact induced by the error in estimation of GFR in those with malnutrition.

Interventional trial of timing of dialysis

The above interpretation is supported by the results of Initiating Dialysis Early and Late (IDEAL) study¹², a controlled trial of 828 adults, randomized either to early start (Cockcroft–Gault equation estimated creatinine clearance between 10.0 to 14.0 ml per minute) or late start (estimated clearance between 5.0 to 7.0 ml per minute). In that study, median time to the initiation of dialysis was 1.8 months in the early-start group and 7.4 months in the late-start group. As a result of symptoms 76% of the patients in the late-start group initiated dialysis when the estimated GFR was above the target of 7.0 ml per min. There were no differences in mortality between the two groups over 3.6 years of follow-up

indicating that early start of dialysis conferred neither a survival advantage nor a disadvantage.

Methods of accounting for muscle mass in GFR estimation with serum creatinine

As discussed above, in those with advanced kidney failure and extremes of nutrition, timed collection of urine for measurement of urea and creatinine clearances and using the average of those two clearances might be more reliable than using the MDRD equation to estimate GFR. Nonetheless, equations to predict GFR with single measurement of serum creatinine that also account for creatinine production remain attractive. Since muscle mass and body weight are correlated, equations that incorporate body weight might provide better estimates of GFR in advanced CKD. Macdonald et al, developed a GFR prediction equation that includes bio-impedance measurement to account for skeletal muscle mass ¹³, and Taylor et al developed an equation that includes lean body mass measured with dual-energy X-ray absorptiometry (DEXA) ¹⁴. However, as bio-impedance and DEXA are not widely used in clinical practice, the utility of these equations for routine clinical are unclear.

Summary and conclusions

As age, gender and race are unlikely to capture the variations in muscle mass, the use of equations that use only these demographic variables to account for creatinine production result in misleading estimates of GFR and erroneous conclusions. In those with more advanced kidney disease and extremes of nutrition, mean of urea and creatinine clearances might be better tools to guide the decision on initiation of dialysis. GFR estimating equations that more precisely account for muscle mass need to be developed. The role of cystatin C in estimating GFR in more advanced kidney disease and extremes of nutrition remains to be defined.

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Table 1

Observational studies of timing of dialysis

Author/Year	Country	N	GFR estimation method	Finding
Korevaar et al. (2001) ¹⁵	Netherlands	253 patients	Mean of measured creatinine and urea clearances	Late start of dialysis associated with increased mortality
Traynor et al. (2002) ¹⁶	Scotland	275 patients	Cockcroft and Gault formula	Early start associated with increased mortality
Beddhu et al. (2003) ¹⁰	United States	2920 patients	MDRD equation, Cockcroft-Gault formula, reciprocal of serum creatinine and measured creatinine clearances	Higher GFR estimated from serum creatinine associated with increased mortality but not with measured creatinine clearances
Sawhney et al. (2009) ¹⁷	Scotland and Canada	7299 patients	MDRD equation	Higher MDRD GFR associated with increased mortality
Stel et al (2009) ¹⁸	European countries	11,472 patients	MDRD equation	Higher MDRD GFR associated with increased mortality
Lassalle et al (2010) ¹⁹	France	11,685 patients	MDRD equation	Higher MDRD GFR associated with increased mortality
Hwang et al (2010) ²⁰	Taiwan	23,551 patients	MDRD Equation	Higher MDRD GFR associated with increased mortality
Wright et al (2010) ²¹	United States	896,546 patients	MDRD Equation	Higher MDRD GFR associated with increased mortality
Clark et al (2011) ²²	Canada	25,910 patients	MDRD Equation	Higher MDRD GFR associated with increased mortality
Rosansky et al (2011) ²³	United States	81,176 patients	MDRD Equation	Higher MDRD GFR associated with increased mortality
Grootendorst et al (2011) ¹¹	Netherlands	569 patients	MDRD equation and mean of measured urea and creatinine clearances	Higher MDRD GFR associated with increased mortality but not measured GFR