Normalising the peritoneal dialysis dose – have we got it right?

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Commentary on: A single weekly Kt/Vurea target for peritoneal dialysis patients does not provide an equal dialysis dose for all.
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Abstract

How the dialysis dose is normalized is just one of several assumptions that clinicians need to take into account when prescribing peritoneal dialysis. *El-Kateb et al*. confirm that estimating the volume of urea distribution is associated with significant error and show that energy expenditure is not linearly related to volume, such that there is a potential need for a higher dialysis prescription in smaller, more active individuals. Although this should be born in mind, this is not the patient group that causes the greatest clinical concern, at least in the short term.

Rightly or wrongly, peritoneal dialysis guidelines have adopted the urea kinetic modelling approach, (Kt/V), originally developed for haemodialysis, to measure and set standards for adequacy of treatment.[1] There are many potential flaws in this approach, including the emphasis on small solute clearance and the fact that the largest study investigating the benefits of increasing peritoneal dialysis dose and thus informing practice, the ADEMEX trial, actually used creatinine clearance as its intervention target.[2] However here we will focus on the issue of how the dose should be normalized to account for patient specific attributes – usually size. The current approach is simple: urea is assumed to be distributed uniformly in the body water, so to determine clearance its removal is divided by the volume of distribution. More of a problem is the estimate of this volume, which has up to a 25% error when using the Watson formula,[3] especially in obese or malnourished patients, a concern to which we will return.

There are many, however, that question validity of the urea kinetic model, arguing that dialysis should be scaled not to volume of distribution but measures of metabolic activity, either by using a metric that is more closely aligned to this – for example body surface area (BSA) or an estimate of metabolic rate and energy expenditure. One of the arguments for this is the observation of differential effects of increasing the dialysis dose by gender in the HEMO study, the suggestion being that the relative benefit for women reflected a need for more dialysis due to their relatively higher metabolic rate for a given volume of distribution, [4], *see figure*.[5] It's worth pointing out that this effect of gender was not seen in the ADEMEX study;[2] this might be because the creatinine clearance target was normalized to BSA, but could equally reflect the very different kinetics of urea removal by these dialysis modalities.

For the first time, in this issue of Kidney International, *El-Kateb et al.* have sought to understand the impact of normalising the dialysis dose to estimated total energy expenditure rather than volume of distribution.[6] To do this they employed a validated questionnaire to determine total and resting energy expenditure that was developed from double isotopic labelled water experiments. They compared the differential effect of normalising by first determining the theoretical (not measured) value for Kt, assuming a Kt/V of 1.7 for all patients (the minimum advised target) by substituting the estimates of V made by either the Watson formula or bioimpedance analysis, and then dividing this value

of Kt by the total or resting energy expenditure. In this way they were able to show that individuals who are smaller, especially women, more active or employed would receive less clearance per unit of energy expenditure.

Although of definite interest, interpreting the meaning of these results if fraught with complexity. First, it is important to be clear whether smaller size is a consequence of otherwise healthy gender/size differences or due to being under-nourished. Although the authors did not include formal measures of dietary protein intake, they did measure comorbidity, frailty and inflammation. Broadly speaking the predictions made by this study indicate that this is a gender/size issue rather than an issue of malnutrition, and thus largely explained by scaling, again *see figure*.[5] For example, the effect of different approaches to normalising the Kt were not worse in patients with lower protein catabolic rate or more frailty – if anything the opposite was seen. Care has to be taken, however, as it is known that protein nitrogen appearance underestimates dietary protein intake in PD patients as the comorbidity increases leading to under-recognition of malnutrition.[7] This is one of the flaws in urea kinetic modelling, which assumes steady state, whereas in fact sicker patients are likely to be in negative nitrogen balance. Second, maintaining stable nitrogen balance, which is surely one of the main goals of adequate dialysis dosing which the urea kinetic model is aiming to facilitate, is complex in PD patients. When PD was first introduced there was considerable concern that a higher protein intake would be required to compensate for peritoneal protein losses. This has not turned out to be the case however, and detailed nitrogen balance studies have shown that this can be maintained in prevalent patients provided there is sufficient total calorie intake – a significant proportion of which being derived from absorption of dialysate glucose.[8] The suggestion from El-Kateb's study that more active, employed PD patients might be at risk from under-dialysis is perhaps best rectified by simply ensuring they have adequate calorie intake rather than increasing the dialysis dose. Third, the majority of these patients, >85%, had significant residual kidney function and we know from previous studies that residual versus peritoneal Kt/V brings very different benefits which cannot be accounted for in the methodology used in this study.[9] If the actual, rather than theoretical Kt as determined here was disproportionately derived from residual kidney function in the more active and employed patients, as was likely to have been the case, then increasing their dialysis dose would not necessarily be required.

Indeed, given the cross sectional nature of the study it is impossible to determine the direction of cause and effect. It would have been more informative if the study had been undertaken in patients actually receiving a Kt/V of 1.7, preferably anuric, but this is not a practical proposition and likely would have excluded many of the more active, employed patients.

So how does this study affect clinical practice? Given the many problems associated with normalising the dialysis dose (and this study also confirms the problem of error in estimating volume, showing big differences, ±15%, in the use of the Watson formula versus bioimpedance for some patients) the use of a Kt/V can only be used as a rough guide, possibly a minimum standard, in patient management. The clinician needs to interpret the result with extreme care, perhaps substituting the ideal weight in the calculation for those at the extremes of size, cross referencing to the creatinine clearance normalized to BSA (so addressing the scaling concern) and working very closely with the dietician to establish if either protein or calorie intake is adequate. Should we be especially worried about women being under-dialysed? No studies have ever shown that survival of women on PD is worse than men, although there is some evidence that elderly diabetic women do less well on PD than HD, the explanations for which are far from clear. Active, working patients may struggle when anuric, so titrating the dialysis dose upwards may be worth considering while they are waiting for a successful transplant.

References:

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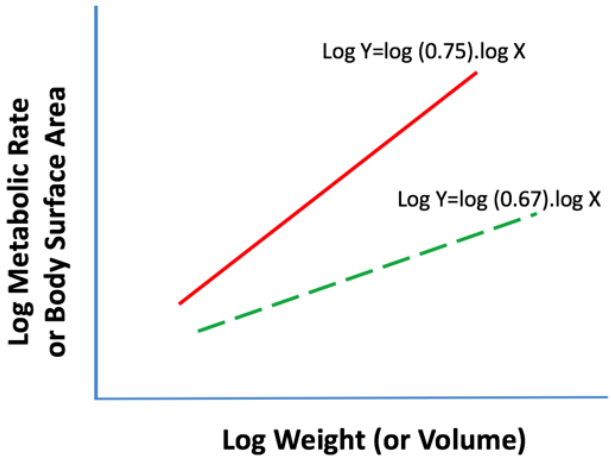
Caption for Figure:

Allometry is the study of biological scaling;[5] allometric data can be expressed as linear functions log Y = log a + b log X, where b (the gradient), indicates the type of scaling relationship. Two well established examples are shown here, the surface area to volume relationship, m^2/m^3, where b=0.67 (green dashed line) and Kleiber's law, which relates metabolic rate to mass across species, where b=0.75 is the typically quoted value (solid red line). In both cases the prediction is that smaller bodies will require more energy for a given weight upon which the argument rests that smaller people may need relatively more solute clearance.

Figure:


Log Y=log (0.75).log X
Log Y=log (0.67).log X
Log Metabolic Rate
or Body Surface Area
Log Weight (or Volume)