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1   A single weekly Kt/Vurea target for peritoneal dialysis patients does not provide
2   an equal dialysis dose for all
3

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44   <u>Abstract</u>

45   Dialysis adequacy is traditionally based on urea clearance, adjusted for

46   total body volume (Kt/Vurea), and clinical guidelines recommend a Kt/Vurea

47   target for peritoneal dialysis (PD). We wished to determine whether adjusting

48   dialysis dose by resting (REE) and total energy expenditure (TEE), would alter

49   the delivered dialysis dose.

50   We determined REE and TEE by equations based on doubly labelled

51   isotopic water studies, and adjusted Kturea for REE and TEE.

52   We studied 148 PD patients, 97 male (65.5%), 54 diabetic (36.5%), mean

53   age 60.6±17.6 years. The mean REE was 1534±241 kcal/day and TEE 1974±414

54   kcal/day. Adjusting Kt for REE showed a reduced delivered dialysis dose (ml

55   /kcal/day) for women vs men (5.5±0.4 vs 6.2±0.6), age < 65 vs > 65 years

56   (5.6±0.56 vs 6.4±0.5), weight < 65 kg vs >80 kg (5.8±0.6 vs 6.1±0.5), low co-

57   morbidity vs high co-morbidity (6.2±0.6 vs 5.9±0.6), all p<0.01. Adjusting for TEE

58   showed reduced dosing for those employed vs no employment (4.3±0.7 vs

59   4.8±0.8), low frailty vs high frailty score (4.5±08 vs 5.0±0.7), both p<0.01.

60   Adjusting the dialysis target dose for REE shows that for the same Kt

61   urea, women, younger, smaller and less co-morbid patients would all receive less

62   dialysis, and adjusting for TEE additionally shows that those employed and

63   physically fitter would receive less dialysis. The current paradigm for a single

64   target Kt/Vurea for all PD patients does not take into account energy

65   expenditure and metabolic rate, and may lead to lowered dialysis delivery for

66   the younger more active female patient.

67

Introduction

69   More than 2 million patients with end stage kidney disease are currently

70   treated by dialysis worldwide, with around 300,000 treated by peritoneal

71   dialysis. As with for haemodialysis, there are clinical guidelines recommending

72   that patients receive a minimal amount of dialysis based on urea clearance [1].

73   These urea based clearance targets are derived from observational studies [2].

74   However prospective studies comparing different peritoneal dialysis regimes

75   designed to achieve different urea clearance targets consistently failed to

76   demonstrate any advantage for greater urea clearance, in terms of patient

77   morbidity or mortality [3-5]. Indeed peritoneal dialysis technique and patient

78   survival have been linked to preservation of residual renal function [6], rather

79   than peritoneal dialysis urea clearance [7].

80   The amount of urea clearance, Kt/Vurea, for dialysis patients are

81   currently based on volume of distribution of urea, total body water (TBW)

82   derived from anthropomorphic measurements [8]. However total body water

83   varies with body composition, as some tissues, such as muscle contain more

84   water than fat [9], and also varies between racial groups [10], and patients with

85   diabetes and other co-morbidities [11]. As such for the same Kt/Vurea, the

86   delivered urea clearance has been suggested to differ between patients [12].

87   Rather than dosing the amount of dialysis required on urea clearance

88   based on volume of distribution, an alternative approach based upon metabolic

89   activity has been proposed [13]. Urea is generated as a by-product of

90 intracellular nitrogen metabolism. Total body metabolic activity is a composite of

91 resting metabolic rate and that due to physical activity. Previous studies in

92 peritoneal dialysis patients have concentrated on measuring resting energy

93 expenditure (REE) [14,15], but this under estimates total energy expenditure

94 (TEE), by excluding that due to activity energy expenditure (AEE),

95 We recently validated an assessment of TEE, and REE in dialysis patients

96 using a patient self-reported questionnaire and double isotopic labelled water

97 [16]. To establish whether there is a difference in the amount of dialysis

98 delivered for a fixed Kt/Vurea target, we calculated urea clearance adjusted

99 for energy expenditure, to determine whether some groups of patients would be

100 disadvantaged under current clinical guideline recommendations.

101

102 <u>Patients and methods</u>

103 Adult patients with end stage kidney disease established on

104 peritoneal dialysis were recruited from University College London partner

105 hospitals when attending for outpatient assessments of peritoneal dialysis

106 adequacy. Corresponding spent dialysate effluent, 24 hour urine collections and

107 serum samples were analysed by standard methods, and weekly dialysis dose

108 calculated as Kt/Vurea. Protein Nitrogen Appearance rate was estimated using

109 the Bergström equation, and normalised for body weight (nPNA) g/kg/day [17].

110 Patient demographics were obtained from computerised hospital records and

111 comorbidity determined using a self-administered co-morbidity grading [18], and

112 a recognised frailty score [19].

113   Total body water was calculated using the Watson equation [20]. In

114   addition we measured total body water by bioimpedance (InBody 720, InBody,

115   Seoul, South Korea; Body Composition Monitor (BCM), Fresenius, Bad Homberg,

116   Germany) which was performed in a standardised manner in 118 patients [21,22].

117   Bioimpedance measurements made by the BCM and InBody were standardised

118   using previously derived equations [23].Body surface area was calculated using

119   the Gehan and George equation as recommended by the European Best Clinical

120   Practice guidelines [24]..

121   Physical activity data was obtained using the Recent Physical Activity

122   Questionnaire (RPAQ) [16], which collects information about both activity and

123   the time spent performing activities over the preceding four weeks;

124   encompassing activities performed at home, work and during leisure time. The

125   RPAQ has been validated against doubly labelled water technique in general

126   population [16], and has been shown to be a reliable tool for estimation of energy

127   expenditure in patients with chronic kidney disease [25]. Physical activity data

128   was determined by each reported activity being assigned a Metabolic Equivalent

129   of Task (MET) value according to the Compendium of Physical Activities [26].

130   The equations for calculating REE and TTE are detailed in the Appendix.

131   UK clinical guidelines recommend a minimum weekly Kt/V of 1.7 [1]. Hence,

132   in order to compare minimum dialysis targets using alternative scaling

133   parameters, weekly Kt was calculated as Kt = 1.7 * V. Corresponding target

134   values of Kt/BSA, Kt/REE and Kt/TEE were calculated by dividing daily Kt by

135   the respective parameters.

136   Ethical approval was granted by the UK National Research Ethics

137 Committee - Essex and the study was registered in UK Clinical Research

138 Network (CRN) Portfolio number 14018. All patients provided written informed

139 consent in keeping with the declaration of Helsinki.

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141 <u>Statistical analysis</u>

142   Statistical analysis was by students' t test, or Mann Whitney U test,

143 ANOVA and Kruskal Wallis , with appropriate post hoc correction, Pearson or

144 Spearman's test for univariate correlation (GraphPad Prism version 6.0, San

145 Diego, USA) and step backward linear regression, of variables on univariate

146 analysis of p<0.1, with log transformation of variables which were not normally

147 distributed, and removal of variables which were not statistically significant

148 unless they improved model fit, and models were checked for collinearity (SPSS

149 version 22, University of Chicago, Illinois, USA), and Bland Altman comparison

150 (Analyse-It version 3.0, Leeds, UK). Data are presented as mean ± standard

151 deviation, median (inter quartile range), or mean and 95% confidence limits (CL),

152 or as a percentage.

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154 <u>Results</u>

155   We studied 148 patients, 97 male (65.5%), 54 diabetic (36.5%), mean age

156 60.6±17.6 years, with a median duration of peritoneal dialysis 9.1 (3.5-25.2)

157 months. The median co-morbidity score was 2 (0-3.8), and frailty score 4 (2-5).

158 43.2% of patients were Caucasian, 27.1% African-Afro-Caribbean, 24.3% South

159 Asian, and 5.4% Far Asian. A minority, 20.3% of patients had some form of

160 employment.

161 Mean haemoglobin was 109.9±14.8 g/l, with a serum albumin 36.5±5.5 g/l

162 and serum C reactive protein (CRP) 6 (2-16) mg/l. Mean weight of the cohort was

163 73.6±16.7 kg, BMI 26.0±4.9 kg/m2, and BSA 1.86±0.24 m^2. The majority of

164 patients were treated by automated peritoneal dialysis cyclers (APD) 85.8% vs

165 14.2% by continuous ambulatory peritoneal dialysis (CAPD). The median total

166 weekly Kt/Vurea was 2.15 (1.8-2.71), with a median 24 hour urine volume of 946

167 (450-1249) ml/day. The mean REE was 1534±241 kcal/day and TEE 1974±414

168 kcal/day. Mean PNA was 64.5±19.7 g/day and nPNA 0.89±0.26 g/kg/day.

169 Male patients were heavier than female (77.0±15.6 vs 72.6±16.6 kg), and

170 had greater REE and TEE (table 1). Patients who were employed, those with

171 greater weight, and greater PNA had higher TEE (Table1), whereas those with

172 greater frailty and co-morbidity, and those who were diabetic and Asian

173 patients tended to have lower TEE.

174 We then adjusted a weekly Kturea of 1.7 for all patients for both BSA

175 and TBW. Bland Altman analysis showed that for both men and women the

176 adjusted Kturea was greater for smaller patients with a relatively greater BSA

177 to TBW, and lower for larger patients with a relatively lower BSA compared to

178 TBW (Figure 1).

179 In a subset of 118 (79.7%) of the study group; 75 male (63.6%), 33

180 diabetic (28.5%), mean age 59.3±18.2 years, with a median duration of peritoneal

181 dialysis 9.4 (3.8-25.5) months, we also measured TBW by bioimpedance. The

182 mean weight of this cohort was 73.1±16.6 kg with a body mass index of 26.0±4.9

183 kg/m², with a median co-morbidity grade of 2 (0-4) and frailty score of 4 (2-5),

184 and did not differ from the main study group. There was no significant

185 difference in TBW: Watson equation 40.3±6.1 vs bioimpedance 40.6±3.4 L, mean

186 difference on Bland Altman analysis 0.72 L (Figure 2). There were positive

187 correlations between BSA and both REE and TEE (r=0.92, p<0.001 and r =0.59,

188 p<0.001) and also between TBW and both REE and TEE (r=0.85, p<0.001 and

189 r=0.62, p<0.001) respectively.

190   We then calculated Kt values for a prescribed Kt/V of 1.7 using for

191 both Watson and bioimpedance estimates of TBW These values were then

192 patients from adjusted by BSA, REE and TEE. The results are shown in Table 2

193 and Figure 3 for different patient groups For the same prescribed dialysis dose,

194 women, younger patients, those employed and those weighing less (Figure 3)

195 received less dialysis than men, older patients, those not employed and heavier

196 patients (table 2). In addition generally patients with less co-morbidity and

197 frailty and non-Asian races also tended to receive less dialysis than those who

198 were more co-morbid, frail and of Asian ethnicity.

199   We used a step backward approach to develop multivariable models of

200 adjusted Kt, including all variables with p<0.1 on univariate analysis, and then

201 eliminating variables which were not significant or did not improve model fit to

202 determine associations with adjusted dialysis dose. Sex was a significant

203 predictor of Kt/BSA. Sex and age were significant predictors of Kt/REE. the

204 predominant variables (table 3). For Kt/TEE, sex, age and employment were

205   common predictive factors whether Kt was derived using TBW derived by

206   Watson and bioimpedance methods. Both high co-morbidity, and diabetes were

207   additional predictive factors for TEE adjusted using the Watson formula for

208   TBW (table 3).

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211   <u>Discussion</u>

212   Traditionally the target dialysis for patients with end stage kidney

213   failure has been based on urea clearance adjusted for total body water volume.

214   However multiple prospective trials have failed to show an association between

215   greater peritoneal dialysis urea clearance and survival [3,4,7]. Cellular

216   metabolism, in particular protein turnover generates waste products which

217   accumulate in patients with end stage kidney failure. As these azotaemic toxins

218   are generated by cellular metabolism, it has been suggested that the amount of

219   dialysis required for patients should be based on metabolic rate, rather than

220   urea clearance [2]. Studies to-date have concentrated on measuring resting

221   metabolic rate [3], but this ignores physical activity, and as such potentially

222   under estimates energy expenditure. We used equations based on patient self-

223   reported physical activity questionnaires, which have been validated using doubly

224   labelled isotopic water [4], to estimate REE and TEE. As expected energy

225   expenditure was associated with body weight, male sex and younger age group

226   [27]. Patients with higher REE and TEE had greater PNA rate due to increased

227   urinary and peritoneal urea losses However we also noted that although REE was

228 similar, TEE was lower with increasing frailty and co-morbidity, in particular

229 diabetes, and those without employment compared to those patients with lower

230 frailty and co-morbidity scores, who were not diabetic or those with

231 employment. We also found that patients from an Asian background had lower

232 TEE compared to Caucasoids and African-Afro-Caribbean patients. This is in

233 keeping with previous observations of lower energy expenditure, particularly

234 with South Asians, and this has been suggested to be due to differences in

235 terms of body composition, related to brown fat tissue stores [28].

236 We then compared the delivered dialysis dose for the minimum weekly

237 KtVurea target as recommended by clinical practice guidelines [1], using Kt

238 calculated by both the Watson formula [20], and also total body water measured

239 by bioimpedance [29]. We found no significant difference between total body

240 water by either method, although previous reports from haemodialysis patients

241 have reported differences [9]. However the major differences between total

242 body water derived by the Watson formula and bioimpedance were with obese

243 patients with a body mass index of > 35, and in our study group < 2% had a body

244 mass index of this level. We adjusted the delivered dialysis dose by both BSA,

245 which is relatively greater for patients with lower total body water, and

246 relatively lower for those with greater total body water and also for both REE

247 and TEE. Adjusting Kt for BSA, which has been advocated for haemodialysis

248 patients, we found that this resulted in a lower dose being delivered to women

249 and those with a high protein nitrogen appearance rate and lower body weight.

250 Whereas adjusting for REE, then female patients, and those who were younger,

251 weighed less, and who had lower protein nitrogen appearance along with those

252 with frailty and co-morbidity scores, and other ethnicities than Asian all

253 received relatively less delivered dialysis. When Kt was adjusted for TEE, then

254 women, younger patients and those weighing less, who were employed, and those

255 with less frailty, in particular those with diabetes, all would receive less

256 delivered dialysis dosing compared to men, heavier patients, those without

257 employment and the more frail, co-morbid patient and those with diabetes.

258   Previous studies targeting a dialysis dose defined by a weekly KtVurea

259 for peritoneal dialysis patients have not shown an advantage for one target

260 compared to another [3,4]. Our study shows that achieving the same urea

261 clearance does not equate to the same delivered dose of dialysis, and as such

262 potentially adds explanation as to why prospective studies have failed to show a

263 significant benefit for one KtVurea target for all patients. Although we

264 accepted that using Kt/Vurea for dialysis dosing has some limitations [31], more

265 recent observational studies have suggested an advantage for adjusting Kt for

266 BSA [30]. However we found that although adjusting for BSA detected a

267 difference between sexes and body weight, those who had higher nitrogen

268 appearance rates. Whereas in particular adjusting for TEE showed that in

269 addition, younger fitter patients received relatively less dialysis dose delivered

270 compared to older, more frail, co-morbid and diabetic patients. As such we

271 suggest that a single Kt/Vurea target dose us not applicable to all patients, and

272 the dose of dialysis should be increased for those who are more physically

273 active with greater TEE.

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393 Figure 1: Relationship between body surface area (BSA) and Watson total body
394 water for man and women.
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396 Figure 2: Bland Altman analysis of total body water (TBW) measured by
397 bioimpedance or calculated by Watson equation. Mean difference 0.72 L (95%
398 limits of agreement -9.2 to +10.7 L).
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400 Figure 3: Adjusted daily urea clearance according to body weight. Fixed weekly
401 Kt of 1.7urea adjusted for body surface area (BSA) and resting energy (REE)
402 and total energy (TEE) expenditure using Watson total body water (W) or
403 bioimpedance measured total body water (BIA).* p <0.05, and **p<0.01 vs weight
404 < 64 kg after Bonferroni correction.
405
406

407 Table 1. Estimates of daily resting energy expenditure (REE) and total energy
408 expenditure (TEE) in patients according to age, co-morbidity, frailty and
409 ethnicity groupings. Daily protein nitrogen appearance (PNA) g/day. Results
410 expressed as mean ±standard deviation, or median (interquartile range). *p<0.05,
411 ** p<0.01 comparing groups, adjusted for multiple comparisons (Bonferroni
412 method).
413

variable	REE kcal/day	TEE kcal/day
male	1597±217	2029±423
female	1412±240**	1868±377*
Age < 65 years	1646±209	2173±392
Age > 65 years	1408±211**	1750±314**
Non-diabetic	1522±233	2021±435
diabetic	1556±254	1893±366*
employed	1577±237	2305±511
not employed	1523±242	1890±340**
Low comorbidity	1532±245	2012±441
High comorbidity	1539±231	1862±300
Low frailty score	1533±227	2049±453
High frailty score	1535±256	1894±353*
Weight < 64 kg	1305±151	1706±306
Weight 64-80 kg	1514±142**	1973±414**
Weight > 80 kg	1775±159**	2233±339**
PNA < 60 g/day	1450±214	1826±317
PNA > 60 g/day	1622±229**	2133±438**
Non Asian	1561±225	2060±462
Asian	1522±243	1866±359*

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431   Table 2. Comparison for a fixed total weekly Kt/V of 1.7 (urea clearance
432   L/m^2/day, or ml urea clearance/kcal/day) adjusted for body surface area (BSA),
433   resting energy expenditure (REE), total energy expenditure (TEE) for peritoneal
434   dialysis patients comparing sexes, age (years), diabetic, employment status, and
435   co-morbidity, weight and ethnicity. Diabetic (DM), High (H) and Low (L) frailty,
436   co-morbidity (Comorb), protein nitrogen appearance (PNA) employed (employ +),
437   not employed (employ -), ethnicity (Asian vs other races). *p<0.05 **p<0.01 after
438   Bonferroni post hoc correction for multiple testing.
439

variable	Kt/BSA	Kt/REE$_W$	Kt/TEE$_W$	Kt/REE$_{BIA}$	Kt/TEE$_{BIA}$
Male	5.13±.0.36	6.15±9.61	4.96±0.71	6.23±0.62	4.93±0.70
Female	4.42±0.40**	5.50±0.41**	4.23±0.65**	5.64±0.64**	4.27±0.71**
Age < 65	4.83±0.46	5.58±0.55	4.29±0.53	5.93±0.73	4.52±0.81
Age > 65	4.95±0.42	6.38±0.49**	5.18±0.61**	6.12±0.62	4.93±0.65**
DM yes	4.96±0.45	6.03±0.58	5.00±0.69**	5.92±0.65	4.93±0.69*
DM no	4.84±0.46	5.90±0.66	4.53±0.82	6.06±0.71	4.57±0.78
H frailty	4.91±0.47	6.06±0.66	4.96±0.75	6.01±0.61	4.90±0.71
L frailty	4.86±0.43	5.85±0.60*	4.46±0.78**	6.01±0.75	4.54±0.78**
HComorb	4.99±0.43	6.19±0.63	5.14±0.66	5.91±0.63	4.90±0.63
LComorb	4.85±0.45	5.87±0.62**	4.55±0.80**	6.05±0.71	4.62±0.81
Employ -	4.89±0.43	5.99±0.61	4.87±0.72	5.96±0.73	4.81±0.75
Employ +	4.89±0.54	5.82±0.71	4.07±0.82**	6.19±0.51	4.31±0.72**
H PNA	4.79±0.40	5.91±0.62	4.75±0.78	5.77±0.70	4.56±0.70
L PNA	4.95±0.48*	5.98±0.68	4.62±0.87	6.23±0.59*	4.81±0.81
Asian	4.87±0.46	5.97±0.65	4.67±0.85	6.10±0.65	4.71±0.76
Other	4.87±0.42	5.90±0.60	4.79±0.69	5.79±0.76*	4.64±0.80

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458 Table 3. Multivariable step backward models for weekly Kt adjusted for Body
459 surface area (BSA), resting energy expenditure (REE), and total energy
460 expenditure (TEE), using both total body water calculated by Watson equation
461 (W) and measured by bioimpedance (BIA). Unstandardised β (β), standard error
462 (StE), standardised β (Standard β), 95% Confidence limits (95% CL). Protein
463 nitrogen accumulation rate (PNA).
464 Adjusted for BSA model $r^2$0.60, adjusted 0.59, model adjusted for REE$_W$ $r^2$0.60,
465 adjusted 0.59, model adjusted for REE$_{BIA}$ $r^2$0.42, adjusted 0.37, model adjusted
466 for TEE$_W$ $r^2$0.42, adjusted 0.3, and adjusted for TEE$_{BIA}$ $r^2$0.35, adjusted 0.33
467 Sex (female vs male), age years, high co-morbidity (H).
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	β	StE β	Standard β	t	95% CL	p
Kt$_{urea}$/BSA						
sex (M)	0.70	0.05	0.77	13.5	0.6-0.87	<0.001
Kt$_{urea}$/REE$_W$						
sex (M)	0.58	0.08	0.44	7.5	0.43-0.74	<0.001
age	0.02	0.01	0.54	9.3	0.2-0.25	<0.001
Kt$_{urea}$/REE$_{BIA}$						
PNA	0.01	0.01	0.37	4.4	0.01-0.02	<0.001
sex (M)	0.39	0.12	0.28	3.2	0.15-0.63	0.002
age	0.01	0.01	0.19	2.3	0.01-0.01	0.025
Kt$_{urea}$/TEE$_W$						
sex (M)	0.59	0.10	0.35	6.1	0.40-0.79	<0.001
age	0.02	0.01	0.44	7.5	0.02-0.013	<0.001
no employment	0.52	0.11	0.26	4.5	0.29-0.74	<0.001
comorbidity H	0.30	0.11	0.16	2.7	0.01-0.52	0.009
diabetic	0.21	0.10	0.12	2.0	0.01-0.41	0.045
Kt$_{urea}$/TEE$_{BIA}$						
sex (M)	0.51	0.13	0.33	3.8	0.25-0.77	<0.001
age	0.01	0.01	0.32	7.5	0.01-0.02	<0.001
no employment	0.44	0.15	0.24	3.0	0.15-0.74	0.004

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482   Appendix

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484   Resting Energy Expenditure (REE) was estimated from a newer novel predictive
485   equation which was derived and validated in a cohort of HD patients [18].

486

487   REE = -2.497 * Age(years) * $Factor_{age}$ + 0.011 * $Height^{2.023}$(cm) + 83.573 *
488    $Weight^{0.6291}$(kg) + 68.171 * $Factor_{sex}$

489

490   where Factor age is 0 if age <65 and 1 if $\geq$65 and Factor sex is 0 if female and 1
491   if male

492

493   Physical activity data - Each reported activity was assigned a Metabolic
494   Equivalent of Task (MET) value as per the Compendium of Physical Activities
495   [19]. Sleep time per day was assumed to be 8 hours and any unreported time
496   during the day was assumed as the time performing light activities at home. A
497   Mean daily MET value was calculated.

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499   Total Energy Expenditure (TEE) was estimated from the following equation.
500   TEE = REE * Mean Daily MET
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