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Extracellular fluid volume and glomerular filtration rate in 1878 healthy potential renal transplant donors: effects of age, gender, obesity and scaling

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Abstract

Aim. The aim of this study was to investigate the influence of age, gender, obesity and scaling on glomerular filtration rate (GFR) and extracellular fluid volume (ECV) in healthy subjects.

Methods. This is a retrospective multi-centre study of 1878 healthy prospective kidney transplant donors (819 men) from 15 centres. Age and body mass index (BMI) were not significantly different between men and women. Slope-intercept GFR was measured (using Cr-51-EDTA in 14 centres; Tc-99m-DTPA in one) and scaled to body surface area (BSA) and lean body mass (LBM), both estimated from height and weight. GFR was also expressed as the slope rate constant, with one-compartment correction (GFR/ECV). ECV was measured as the ratio, GFR to GFR/ECV.

Results. ECV was age independent but GFR declined with age, at a significantly faster rate in women than men. GFR/BSA was higher in men but GFR/ECV and GFR/LBM were higher in women. Young women (<30 years) had higher GFR than young men but the reverse was recorded in the elderly (>65 years). There was no difference in GFR between obese (BMI > 30 kg/m^2) and non-obese men. Obese women, however, had lower GFR than non-obese women and negative correlations were observed between GFR and both BMI and %fat. The decline in GFR with age was no faster in obese versus non-obese subjects. ECV/BSA was higher in men but ECV/LBM was higher in women. ECV/weight was almost gender independent, suggesting that fat-free mass in women contains more extracellular water. BSA is therefore a misleading scaling variable.

Conclusion. There are several significant differences in GFR and ECV between healthy men and women.

Keywords: age; extracellular fluid volume; gender; glomerular filtration rate; obesity; scaling

Introduction

Several previous studies have examined the effect of ageing on glomerular filtration rate (GFR) in healthy subjects (usually healthy prospective renal transplant donors), finding GFR to decline with advancing age. Most showed no difference between men and women [1–3], but two suggested a faster decline in women [4, 5] and one a faster decline in men, although only in the age range of 20–50 [6].

There is extensive literature suggesting that obesity has an adverse effect on renal function [7–12], but it is difficult to separate the effects of comorbidity, such as hypertension and metabolic syndrome. Moreover, scaling GFR to body size may be misleading and is controversial in obese subjects [13–15] and indeed no attempt at scaling was made in some studies [9]. In one study, the age-related decline in GFR was no faster in obese compared with non-obese subjects, but insufficient numbers were present to separate men from women [16].

In order to study the effects of age and gender on GFR and ECV and of obesity on GFR, a very large database of healthy subjects is required. It would be difficult to assemble a database of normal volunteers of sufficient size to address these issues. Prospective kidney transplant donors

represent a normal population but even a single centre would be unlikely to assemble a database of sufficient size. In the current study, therefore, we assembled a population of transplant donors from 15 different centres performing GFR measurement for transplant 'workup'. The aim of this paper was to study men and women separately with respect to the effects of ageing on GFR and ECV and of obesity on GFR. The merits of whole body scaling variables [body surface area (BSA), estimated lean body mass (LBM) and ECV] are also examined.

Materials and methods

Participants

The subjects were potential live kidney transplant donors from 15 regional centres in the UK. All had serum creatinine levels sufficiently low for them to be considered as potential donors. A requirement of entry to the study for an individual centre was recruitment of at least 25 men and 25 women. Total numbers of patients recruited were 819 men and 1059 women (Table 1). In all centres, patients were not instructed to fast prior to their GFR measurement.

Measurement of GFR and ECV

GFR was measured using the slope-intercept technique from two to five blood samples obtained between 120 and 300 min post-injection. In one centre (using three samples), the filtration marker was ^{99m}Tc-diethyltriaminepentaacetic acid (DTPA) and in the remainder, it was ^{51}Cr-ethylenediaminetetraacetic acid. One-compartment clearance was scaled to 1.73 m^2 (using the equation of Haycock *et al.* [17] to estimate BSA) and one pool corrected using Brochner–Mortensen's equation [18] to give GFR/BSA. GFR/BSA was converted to GFR (i.e. 'descaled' but still one-compartment corrected) by multiplication with BSA/1.73 m^2.

Slope-only GFR, which is based exclusively on the half-time of the exponential between 120 and 300 min and gives GFR scaled to ECV [19], was measured as the rate constant (α_2) of the exponential and one pool-corrected using the following equation [20] to give GFR/ECV (mL/min/mL)

$$\mathrm{GFR/ECV} = \alpha_2 + \left[15.4 \times \left(\alpha_2^2\right)\right].$$

ECV/BSA was calculated as the quotient GFR/BSA:GFR/ECV, from which GFR cancels out. This technique has recently been validated by comparison with ECV measured simultaneously and independently using multi-sample plasma iohexol clearance [20]. ECV/BSA was descaled (but still one-compartment corrected) by multiplication with BSA/1.73 m^2.

Lean body mass

LBM was estimated from height (H; m) and weight (W; kg) using the equations of Boer [21]:

$$\text{Men}: \mathrm{LBM} = (0.407 \times \mathrm{W} + 26.7 \times \mathrm{H}) - 19.2 \text{ kg}, \quad (1)$$

$$\text{Women}: \mathrm{LBM} = (0.252 \times \mathrm{W} + 47.3 \times \mathrm{H}) - 48.3 \text{ kg}. \quad (2)$$

Scaling the physiological variables

ECV was scaled to BSA, LBM and body weight and GFR to BSA, ECV and LBM.

Measures of obesity

Fat percentage (%fat) was estimated as 1 − [LBM/body weight]. Body mass index (BMI) was taken as weight/height^2. Obesity was defined as a BMI of >30 kg/m^2 and very obese subjects as having a BMI of >35 kg/m^2.

Statistical analysis

Data from men and women were analysed separately throughout. Variables were expressed as the mean and SD. Significance of differences in variables between men and women were calculated using Student's unpaired *t*-test. Relations between paired variables were assessed using Pearson's correlation analysis (coefficient = *r*), with the confidence intervals of the regression slope and intercept expressed as the standard errors (SEs). Significance of difference ($x_1 - x_2$) between regression slopes and intercepts were then calculated using the *t* distribution

$$t = (x_1 - x_2) \Big/ \left[\left(\mathrm{SE}_1^2 + \mathrm{SE}_2^2\right)\right]^{0.5} \quad (3)$$

Results

Demographics

Numbers of patients recruited from centre to centre, their mean ages and mean values of BSA and GFR/BSA are shown in Table 1. There was no correlation between the number of samples obtained and either GFR/BSA or its SD, indicating that variation in sample number will not have had any influence on the results. The single centre using Tc-99m-DTPA obtained mean values of GFR/BSA and

Table 1. Patient numbers, sample numbers, age ranges and mean values of BSA and GFR/BSA in the 15 participating centres[a]

		Men				Women			
Centre	*N*	*n*	Age (range)	BSA (m^2)	GFR/BSA (mL/min/1.73 m^2)	*n*	Age (range)	BSA (m^2)	GFR/BSA (mL/min/1.73 m^2)
1	3	56	50 (23–72)	2.07 [0.19]	84 [16]	97	50 (24–70)	1.82 [0.18]	82 [16]
2	4	50	44 (19–70)	2.01 [0.17]	99 [17]	51	48 (21–76)	1.77 [0.17]	88 [16]
3	3	115	45 (19–69)	2.04 [0.17]	97 [13]	146	46 (21–71)	1.76 [0.17]	94 [17]
4	3	93	47 (24–69)	2.08 [0.16]	94 [13]	102	48 (21–71)	1.79 [0.18]	87 [16]
5	4	76	44 (23–69)	2.04 [0.16]	95 [15]	105	45 (24–67)	1.79 [0.20]	94 [15]
6	4	43	46 (26–70)	2.03 [0.22]	90 [12]	42	48 (28–71)	1.74 [0.16]	87 [13]
7	3	47	47 (21–74)	2.02 [0.14]	90 [13]	75	47 (20–71)	1.82 [0.17]	88 [15]
8	2	43	44 (25–66)	2.03 [0.20]	90 [13]	53	47 (20–77)	1.82 [0.22]	83 [15]
9	4	29	46 (21–66)	1.99 [0.18]	76 [17]	28	47 (29–74)	1.87 [0.17]	79 [19]
10	4	28	47 (23–71)	2.05 [0.27]	94 [20]	29	44 (23–70)	1.82 [0.24]	93 [20]
11	5	44	40 (23–66)	2.04 [0.22]	93 [17]	50	42 (20–65)	1.85 [0.17]	91 [18]
12	2	68	44 (20–72)	2.04 [0.22]	88 [16]	81	48 (19–73)	1.75 [0.18]	83 [19]
13	3	33	47 (21–73)	2.03 [0.20]	95 [15]	48	49 (24–68)	1.80 [0.15]	90 [17]
14	3	44	45 (20–77)	2.07 [0.18]	91 [16]	91	46 (19–72)	1.79 [0.18]	88 [14]
15	3	50	43 (21–71)	2.12 [0.25]	94 [17]	61	49 (21–73)	1.78 [0.19]	85 [15]

[a]SD in square brackets; *N*, number of blood samples; *n*, number of patients. Tracer: Cr-51-EDTA, except centre 3 (Tc-99m-DTPA).

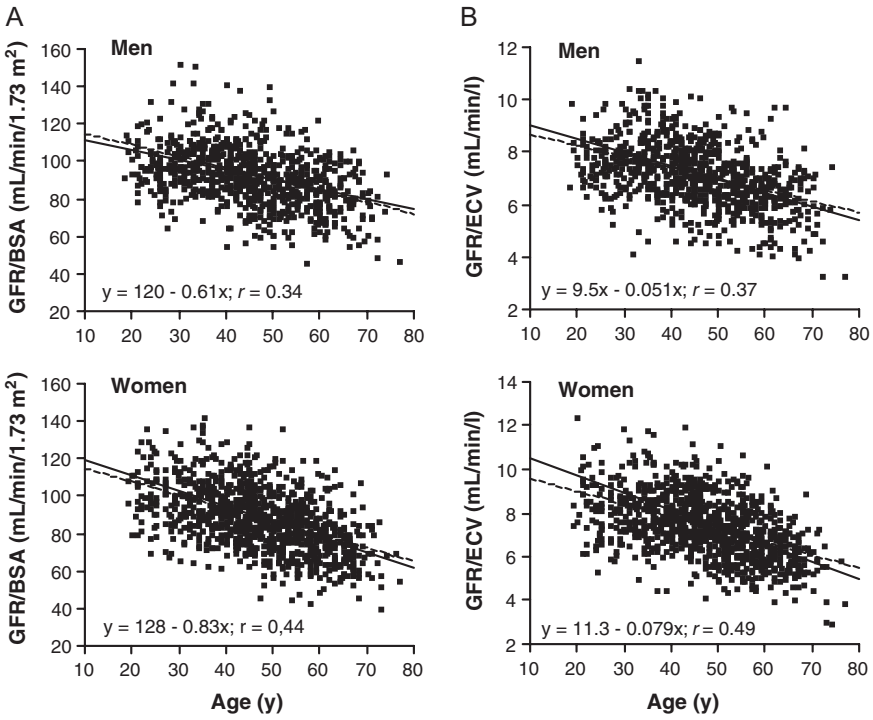

Fig. 1. Relations between GFR and age in all subjects (upper panels, men; lower panels, women). (**A**) GFR scaled to BSA; (**B**) GFR scaled to ECV. Broken and continuous lines are the least squares regressions fitted to data from age 30 to 40 years, respectively. The regression equations are from age 40 years. Note the more rapid age-dependent decline in GFR in women.

ECV/BSA and corresponding SDs that were within the inter-departmental ranges, justifying the inclusion of this centre in the analysis. The inter-centre coefficients of variation of GFR/BSA and ECV/BSA showed a normal distribution, so there was no reason to discard the data from any individual centre.

Effects of age

GFR showed an inverse correlation with age in both men and women, whether scaled to BSA or ECV (Figure 1). In contrast, there was no correlation between age and ECV, whether scaled to BSA (Figure 2), LBM or weight. The precise age at which GFR starts to decline or whether there is a specific age is difficult to determine. Nevertheless, the regression slopes for GFR/BSA and GFR/ECV for both men and women were slightly less when the fit included patients from age 30 compared with age 40 (Figure 1).

Effects of gender

GFR/BSA was slightly higher in men [92.3 (SD 15.7) mL/min/1.73 m^2] than women [88.0 (16.6) mL/min/1.73 m^2; $P < 0.001$] but GFR/ECV was higher in women [7.40 (1.39) versus 7.15 (1.23) mL/min/L; $P < 0.001$; Table 2]. GFR/LBM was also clearly higher in women [1.96 (0.38) versus 1.75 (0.30) mL/min/kg; $P < 0.001$; Table 2].

Mean values of ECV/BSA, ECV/LBM and ECV/weight in women were 12.0 (1.8) L/1.73 m^2, 0.268 (0.043) L/kg and 0.179 (0.030) L/kg, respectively, compared with 13.0 (1.9) L/1.73 m^2, 0.247 (0.036) L/kg and 0.184 (0.029) L/kg

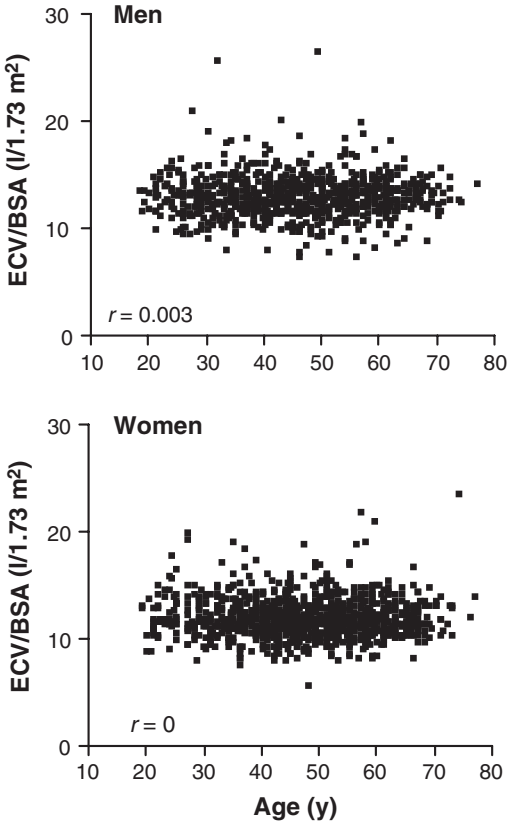

Fig. 2. Relations between ECV and age in all subjects (upper panel, men; lower panel, women). No correlation is seen with either gender.

in men (all P < 0.0001; Table 2). Fat (% of body weight) in men was 25.3 (4.9)% compared with 32.9 (7.0)% in women (P < 0.001). Thus, although there was only a 2.8% gender difference in ECV/weight, there was a 30% difference in %fat.

The age-related decline in GFR/ECV in 778 women aged ≥40 was 0.0786 (SE 0.00502) mL/min/L/year (r^2 = 0.240), significantly faster than in 543 men aged ≥40 [0.0507 (SE 0.00543) mL/min/L; r^2 = 0.139; P < 0.001; Table 3]. Corresponding values for GFR/BSA were 0.826 (SE 0.0606) mL/min/1.73 m^2/year (r^2 = 0.193) for women and 0.611 (SE 0.0721) mL/min/1.73 m^2/year (r^2 = 0.117) for men (P < 0.001). In line with this, young women (age < 30) had a significantly higher GFR than young men, whereas elderly men (age 65+) had a higher GFR than elderly women (Table 4).

Effects of obesity

GFR/ECV was not significantly different between obese [7.10 (1.25) mL/min/L) and non-obese men [7.17 (1.22) mL/min/L] but obese women [7.09 (1.30) mL/min/L; n = 219] had a significantly lower GFR/ECV than non-obese women [7.49 (1.40) mL/min/L; n = 837; P < 0.001; Table 5]. Similar results were seen with GFR/BSA. Accordingly, BMI did not correlate with either GFR/BSA or GFR/ECV in men; but in women, it showed a significant correlation with both (Table 6). Similarly, %fat did not correlate with either GFR/BSA or GFR/ECV in men, but in women, it correlated significantly with both (Table 6).

In 39 very obese women (BMI > 35 kg/m^2), GFR/BSA and GFR/ECV were significantly reduced compared with non-obese women but in 25 very obese men, they were not significantly different compared with non-obese men (Table 5).

Absolute (unscaled) GFR was significantly higher in obese and very obese subjects compared with non-obese subjects, especially in men (Table 5). None of the very obese subjects, however, had strikingly high values of scaled GFR (Figure 3). There was no evidence, therefore, to support the notion that filtration function is increased in obese subjects when allowance is made for ECV.

Table 2. GFR, ECV, BMI and %fat 100 × (1 − [LBM/weight]) compared between men and women

	Men (n = 819)		Women (n = 1059)			
	Mean	SD	Mean	SD	% Difference	P
GFR/BSA (mL/min/1.73 m^2)	92.3	15.7	88.0	16.6	4.9	<0.001
GFR/ECV (mL/min/L)	7.15	1.23	7.40	1.39	3.5	<0.001
GFR/LBM (mL/min/1.73 m^2)	1.75	0.30	1.96	0.38	12.0	<0.001
ECV/BSA 1/1.73 m^2)	13.0	1.9	12.0	1.8	8.3	<0.001
ECV/weight (1/10 kg)	1.84	0.29	1.79	0.30	2.8	<0.001
ECV/LBM (1/10 kg)	2.47	0.36	2.68	0.43	8.5	<0.001
BMI (kg/m^2)	26.8	3.8	26.5	4.4	1.1	NS
%fat	25.3	4.9	32.9	7.0	30.0	<0.001

Table 3. Rates of decline in GFR with advancing age from age 40 compared between men and women, determined by regressing GFR on age[a]

	Men (n = 543)			Women (n = 778)			
	Slope	SE	r^2	Slope	SE	r^2	P
GFR/BSA (mL/min/1.73 m^2/year)	0.611	0.072	0.117	0.826	0.061	0.193	<0.05
GFR/ECV (mL/min/L/year)	0.0507	0.0054	0.139	0.0786	0.0050	0.240	<0.001
GFR/LBM (mL/min/kg/year)	0.0114	0.0014	0.114	0.0170	0.0014	0.157	<0.005

[a]Women show a significantly faster rate of decline for all three forms of scaled GFR. SE, standard error of slope.

Table 4. GFR at extremes of age range in men and women[a]

	<30					65+				
	Men (n = 105)		Women (n = 91)			Men (n = 53)		Women (n = 81)		
Age (years)	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
GFR/BSA	98.5	13.2	100.8	15.4	NS	78.5	14.3	70.9	11.6	<0.001
GFR/ECV	7.63	0.91	8.26	1.41	<0.001	5.98	1.13	5.91	1.00	NS
GFR/LBM	1.86	0.26	2.21	0.36	<0.001	1.49	0.28	1.60	0.27	<0.05

[a]Subject numbers are in brackets. Units as in Table 5. Young women have a higher GFR than young men but this difference is attenuated or reversed in the elderly.

Table 5. Scaled and unscaled GFR in obese and non-obese subjects[a]

	Non-obese (<30 kg/m^2)			Obese (>30 kg/m^2)				Very obese (>30 kg/m^2)			
	Mean	SD	*n*	Mean	SD	*n*	[b]P	Mean	SD	*n*	[b]P
Men			656			160				25	
GFR/BSA (mL/min/1.73 m^2)	92.3	15.7		92.6	15.4		NS	96.6	18.4		NS
GFR/ECV (mL/min/L)	7.17	1.22		7.10	1.25		NS	7.26	0.97		NS
GFR/LBM (mL/min/kg)	1.75	0.297		1.75	0.291		NS	1.81	0.348		NS
GFR (mL/min)	106.5	20.7		121.3	22.1		<0.001	134.9	26.1		<0.001
Women			837			219				39	
GFR/BSA (mL/min/1.73 m^2)	88.5	17.0		85.9	15.3		<0.05	82.5	18.0		<0.001
GFR/ECV (mL/min/L)	7.49	1.40		7.09	1.30		<0.001	6.62	1.26		<0.001
GFR/LBM (mL/min/kg)	1.95	0.381		1.99	0.357		NS	1.94	0.427		NS
GFR (mL/min)	89.0	18.3		99.6	19.9		<0.001	102.7	25.2		<0.001

[a]GFR is significantly lower in obese compared with non-obese women but in men there is no difference.
[b]versus non-obese subjects.

Table 6. Correlations between measures of obesity (BMI and %fat) and GFR in men ($n = 819$) and women ($n = 1059$), where, in the fitted regression equations, x is the measure of obesity and y is the corresponding value of GFR[a]

	GFR/BSA (mL/min/1.73 m^2)			GFR/ECV (mL/min/L)		
x	*y*	r^2	P	*y*	r^2	P
Men						
BMI (kg/m^2)		0.001	NS		0.001	NS
%fat		0.001	NS		0.002	NS
Women						
BMI (kg/m^2)	$100 - 0.457x$	0.014	<0.001	$8.66 - 0.0477x$	0.022	<0.001
%fat	$98 - 0.312x$	0.017	<0.001	$8.26 - 0.0260x$	0.017	<0.001

[a]NS, not significant.

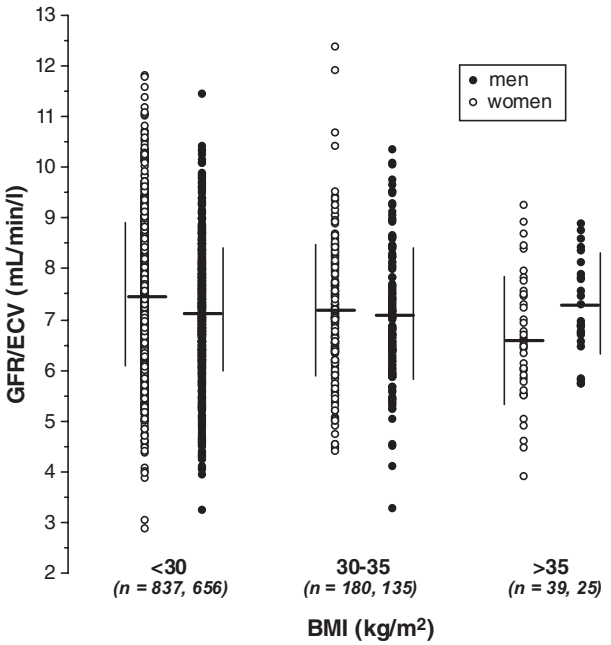

Fig. 3. Relations between BMI and GFR/ECV in men (closed circles) and women (open circles). Horizontal bars = mean values; vertical lines = ± SD. (Numbers in italics = subject numbers.)

The decline with age in GFR/ECV from age 40 years in 608 non-obese women was 0.0802 (SE 0.00562) mL/min/L/year ($r^2 = 0.251$), similar to that in 168 obese women aged ≥40 years in whom it was 0.0746 (SE 0.011) mL/min/L/year ($r^2 = 0.218$; Figure 4; Table 7). The decline in GFR/ECV in 108 obese men was 0.0607 mL/min/L/year (SE 0.0131; $r^2 = 0.169$), higher, but not significantly, than the decline in 432 non-obese men (0.0498 mL/min/L/year; SE 0.0060; $r^2 = 0.138$). Similarly, the age-dependent decline GFR/BSA was not significantly different between obese and non-obese subjects (Table 7).

Effects of scaling

When small men were compared with large women, such that all the men had lower values of BSA than the women, ECV/BSA and GFR/BSA were still significantly higher in men (on average by 0.5 L/1.73 m^2 ($P < 0.005$) and 3.3 mL/min/1.73 m^2 ($P < 0.01$), respectively; Table 8).

When ECV was regressed on LBM, the intercepts for both genders were not significantly different from zero (Table 9); i.e. the regression slopes passed close to the origin. In contrast, when ECV was regressed on BSA, intercepts were significantly lower than zero for both genders. When ECV was regressed on weight, large significant positive intercepts were recorded for both genders.

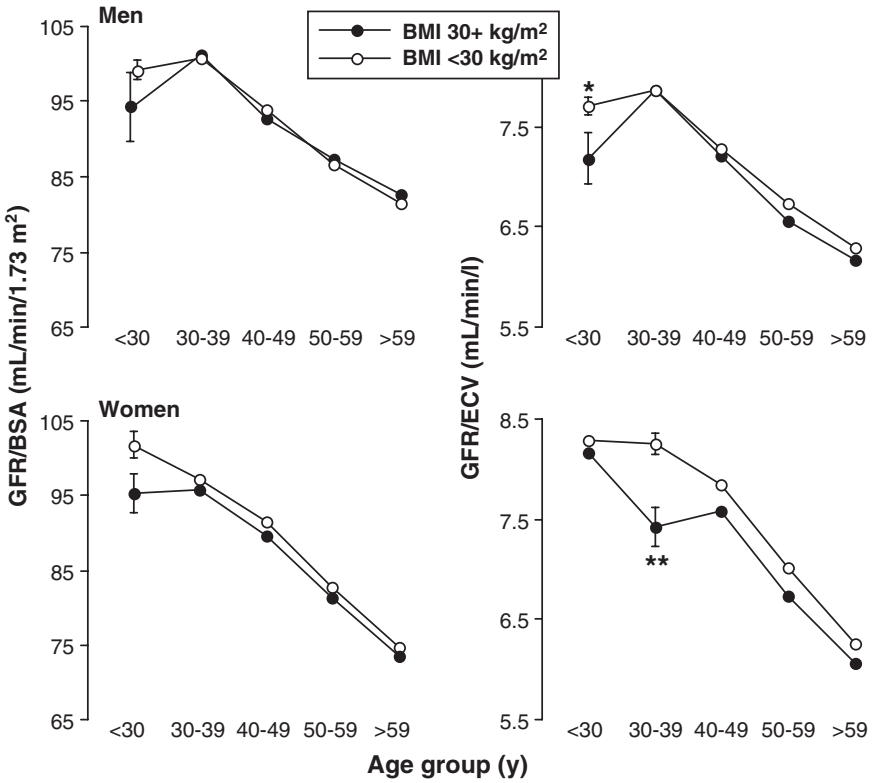

Fig. 4. Relations between age and GFR, scaled to BSA (left panels) or ECV (right panels) in men (upper panels) and women (lower panels); obese subjects: closed circles; non-obese subjects: open circles. Points correspond to mean values in patients aged <30, 30–39, 40–49, 50–59 and >59. *P < 0.05; **P < 0.001. No significant differences are seen between obese and non-obese subjects above the age of 39 years.

Table 7. Rates of decline of GFR as a function of age from age 40 in non-obese and obese subjects[a]

	Non-obese				Obese				
	Slope	SE	r^2	*n*	Slope	SE	r^2	*n*	P
Men				434				109	
GFR/BSA (mL/min/1.73 m^2/year)	0.620	0.080	0.122		0.626	0.168	0.116		NS
GFR/ECV (mL/min/L/year)	0.0498	0.0060	0.138		0.0607	0.0131	0.169		NS
Women				609				169	
GFR/BSA (mL/min/1.73 m^2/year)	0.842	0.068	0.200		0.781	0.131	0.176		NS
GFR/ECV (mL/min/L/year)	0.0802	0.0056	0.138		0.0746	0.0110	0.218		NS

[a]No significant differences were recorded between obese and non-obese men or women.

Table 8. ECV/BSA and GFR/BSA in men compared with women when all the men have a lower BSA than all the women

	Men (n = 223)		Women (n = 230)		
	<1.936		>1.935		
BSA (m^2)[a]	Mean	SD	Mean	SD	P
ECV/BSA (L/1.73 m^2)	12.8	1.9	12.3	1.8	<0.005
GFR/BSA (mL/min/1.73 m^2)	90.5	14.8	87.2	16.0	<0.02

[a]BSA 'cut-off' values chosen so as to produce populations of men and women of similar numbers.

Differences in mean values between men and women were generally more significant, and correlation coefficients were generally higher when GFR was scaled to ECV instead of BSA (see Tables 3, 5, 6, 7 and 8).

Discussion

The main findings in this study are clear differences between the genders with respect to the influence of age and obesity on GFR. It was also found that in women, fat-free tissue contains more extracellular water than in men. While the use of different parameters to scale GFR and ECV

Table 9. Correlations between ECV (y) and scaling variables (x)[a]

	Men ($n = 819$)		Women ($n = 1059$)	
x	y	r^2	y	r^2
LBM (kg)	$-0.501\ (0.756) + 0.255x$	0.357	$0.786\ (0.528) + 0.251x$	0.321
BSA (m^2)	$-2.47\ (0.842) + 8.76x^b$	0.359	$-1.96\ (0.572) + 8.05x^b$	0.376
Weight (kg)	$5.01\ (0.591) + 0.124x^b$	0.350	$4.28\ (0.340) + 0.116x^b$	0.363

[a]Note high positive intercept values for weight, negative intercept values for BSA and intercept values for LBM closest to unity. SE of the intercept (litres) is shown in brackets.
[b]Intercept significantly different from zero. There were no significant differences between men and women for any intercept or regression slope.

affected the results, the differential effects of age and obesity were still seen.

Although the population in this study was not randomly selected, such as in a normal control population, but instead a population that came forward to offer a kidney for transplantation, they nevertheless represent a normal control population as there was no selection bias involved. So, given the size of the population, it is not surprising that several subjects had measured GFR that was outside what would be regarded as the normal range.

The specific effects of age, obesity and scaling are now discussed in turn below.

Age

GFR appears to decline with age from at least age 30 years (Figure 1). The decline then accelerates from age 40 years. At least two previous studies have reported a decline from 40 years [1, 3] and two from 30 years [2, 6]. In the current study, it is shown clearly that there is no relation between age and ECV in healthy subjects either men or women.

Gender

Previous, but not all [3], studies have shown a higher GFR/BSA in men compared with women [1, 22]. The current study shows it to be marginally, but significantly, higher in men. GFR/ECV has generally been found to be equal between the genders [22] but in the current study, it was significantly higher in women.

The scaling parameters appear to be influencing these differences. Thus, when scaled to BSA, men had a clearly higher value of ECV, but this difference was markedly attenuated when ECV was scaled to weight and reversed when scaled to LBM. BSA is two dimensional and depends on size and shape of the individual (e.g. the so-called 'BSA effect' [23]) but this does not fully explain the difference between men and women because men still had significantly higher GFR/BSA and ECV/BSA when populations were selected so that all the men had a lower BSA than the women (Table 8). While the higher ECV/LBM in women could possibly be the result of problems with Boer's equations, there is no technical challenge to weight measurement and, because women have more fat per unit weight than men [24], the gender independence of ECV/weight seems to confirm that they really do have a higher ECV/LBM. So the tendency for BSA to distort as a scaling variable is even greater than apparent from the higher ECV/BSA in men. It remains unexplained why ECV should be higher in women. It does not appear to be hormonal as there was no correlation between age and ECV (Figure 2).

It has previously been noted that GFR [5] and eGFR [4] decline more rapidly with age in women compared with men. The current study confirms this and moreover shows that the decline is more obvious when GFR is scaled to ECV than to BSA.

Obesity

There is a large body of literature showing an adverse effect of obesity on renal function [7–12]. The effects are complex because obesity is associated with comorbidities, such as hypertension and diabetes, directly related to renal disease [25–27]. Obese individuals without these comorbidities have an increased GFR, although it is difficult to judge by how much, as scaling to body size is problematic or not attempted [9]. In studies in which GFR was scaled to LBM, obese individuals did not have a higher GFR than non-obese individuals [13, 15]. The implication in most studies, nevertheless, is that in obesity, as in diabetes mellitus, an abnormally high GFR eventually leads to chronic kidney disease.

Because BSA, LBM, BMI and %fat are all based on height and weight, they may potentially display a spurious inter-dependence with GFR/BSA and GFR/LBM. Therefore, GFR/ECV would appear to be the most reliable expression of filtration function in obesity because it is based exclusively on the rate constant of the slow exponential. It is therefore noteworthy that of 64 morbidly obese individuals (BMI > 35 kg/m^2), none had a GFR/ECV >10 mL/min/L (equivalent to 130 mL/min/13 L) compared to 39 of 837 women of BMI <30 kg/m^2. Likewise, the proportion of morbidly obese individuals with GFR/ECV <5 mL/min/L was not increased compared with subjects with normal BMI. GFR/ECV did, however, display a clear inverse relation with measures of obesity in women but not in men. There was no clear difference in the effects of age on GFR between obese and non-obese subjects as has been previously shown in a smaller clinical population of patients [16].

Scaling

As discussed above, differences between men and women with respect to GFR and ECV partly depended on the

scaling parameter used. Ideally, when a physiological variable is regressed on a potential scaling parameter, the regression line should pass through the origin [21]. When ECV was the variable to be scaled, LBM came closest to satisfying this requirement and weight the furthest (Table 9), giving large positive intercepts that indicate that as weight rises, ECV does not remain in proportion. When ECV was regressed on BSA, intercepts were significantly lower than zero for both men and women, confirming the previously demonstrated non-proportionate and non-linear relation between ECV (and GFR) and BSA [28, 29]. When GFR was the variable instead of ECV, the correlation coefficients with the scaling parameters were lower (results not shown), probably reflecting wider biological variation in GFR.

Several studies have focussed on the attraction of ECV as a scaling parameter for GFR [19, 22]. Firstly, GFR/ECV is easy to measure because it depends only on the half-time of the slow exponential and is not affected by errors in standard preparation, injection faults, errors in measurement of height and weight (especially in bed-bound patients) and missing limbs etc. In the current study, differences in GFR and correlations with age and measures of obesity were in general associated with higher degrees of statistical significance when GFR was scaled to ECV. Obesity presents a particular problem with respect to scaling and while there has been much discussion on the respective merits of BSA and LBM in particular, scaling to ECV, as presented in the current paper, seems the most attractive because it requires no measurements of height and weight.

Given the numerous differences between men and women that have been identified in the current study, BSA as a scaling variable may fail partly because, unlike LBM, it is based on a single common formula relating it to height and weight. This would explain why even when small men are compared with large women, as in Table 8, they still have larger values of GFR/BSA and ECV/BSA than women. If BSA is to continue as a scaling variable, the equations for its estimation should be revised. In the meantime, LBM or ECV are to be preferred; especially ECV in obesity. Indeed ECV should be increasingly used in anticipation of the forthcoming epidemic of obesity. A potential disadvantage of ECV as a scaling factor, however, arises in patients with an abnormal ECV, such as in cancer [30]. Moreover, an expanded ECV may also be encountered in patients with chronic kidney disease [31] although a recent study suggested that this may not be such a major limitation [32].

Our data suggest that young women, after adjustment for body size, have a higher filtration rate than young men and that this is obscured by the use of BSA as a scaling variable. We speculate that this higher filtration rate is the result of a higher ECV. It is not clear why GFR declines with age faster in women than in men, but perhaps, as in diabetes mellitus and obesity, a high rate of filtration leads to a faster rate of decline in GFR.

The main strength of this study is the large number of subjects, who because they are potential transplant donors closely represent a normal population. These large numbers have revealed differences between men and women not previously seen in single centre studies with smaller subject numbers. Thus, it has been previously shown that GFR/BSA is higher in men, but the higher value of GFR/ECV in women is a new finding as is the higher value of ECV in women. The main limitation of the study is inextricably linked to its main strength: thus, in order to achieve these high numbers, a multi-centre strategy had to be adopted. However, the customary undesirable technical variations of multi-centre studies were minimized by one person making all the corrections on the basis of the various algorithms (e.g. one-compartment correction and estimations of BSA and LBM) and performing all the analysis. Other technical variations, such as the single centre using Tc-99m-DTPA and the number of blood samples, were shown in another report not to have any statistically detectable effects [33].

In conclusion, this study has demonstrated clear differences between men and women with respect to GFR and ECV. Men and women should not therefore be combined into single groups in studies involving GFR and ECV.

Conflict of interest statement. None declared.

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