Original article

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The appropriate whole body metric for calculating standardised uptake value and the influence of sex

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Aim **To compare weight, lean body mass and body surface area for calculation of standardised uptake value (SUV) in fluorine-18-fluorodeoxyglucose PET/computed tomography, taking sex into account.**

Patients and methods **This was a retrospective study of 161 (97 men) patients. Maximum standardised uptake value (SUV_{max}) and mean standardised uptake value (SUV_{mean}) were obtained from a 3-cm region of interest over the right lobe of the liver and scaled to weight, scaled to lean body mass (SUL) and scaled to body surface area (SUA). Mean hepatic computed tomography density was used to adjust SUV_{mean} for hepatic fat (SUV_{FA}). Hepatic SUV indices were divided by SUV from left ventricular cavity, thereby, eliminating whole body metric, to obtain a surrogate of blood fluorine-18-fluorodeoxyglucose clearance into liver, and multiplied by blood glucose to give a surrogate of hepatic glucose uptake rate (mSUV).**

Results **SUL_{max}, SUA_{max} and all scaled to weight indices correlated strongly with weight. SUL_{mean}, SUL_{FA}, SUA_{mean} and SUA_{FA}, however, correlated weakly or not at all with weight, nor with their corresponding whole body metric in men or women, but correlated strongly when the sexes were combined into one group. This was the result of sex differences in SUL (greater in men) and SUA (greater in women). There was, however, no sex difference in mSUV.**

Conclusion **Weight is unsuitable for calculating SUV. SUL and SUA are also inappropriate as maxima but appropriate as mean and fat-adjusted values. However, SUL is recommended for both sexes because SUA is influenced by both body fat and weight. Sex differences in SUL and SUA give rise to misleading correlations when sexes are combined into one group.** ***Nucl Med Commun*** **40:3–7**

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Introduction

Standardised uptake value (SUV) is the conventional parameter for quantifying accumulation of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) in tissue in routine PET/computed tomography (CT). It is the fraction of injected activity per ml of tissue multiplied by a metric of whole body size to account for the dilution of the tracer throughout the ^{18}F-FDG whole body distribution 'space'.

The whole body metric most widely used is weight, giving SUV scaled to weight (SUW). Apart from brown fat, which is variable and unrelated to BMI, accumulation of ^{18}F-FDG in adipose tissue is minimal [1] resulting in overestimation of SUV in obese persons [2–5]. Lean body mass (LBM), giving SUV scaled to lean body mass (SUL) [2,4–6], and body surface area (BSA), giving SUV scaled to body surface area (SUA) [3,7], have therefore been proposed as more appropriate metrics for calculating SUV. As Delanaye *et al.* [8] emphasised in the context of whole body metrics for normalising glomerular filtration rate, an appropriate normalisation variable should result in no significant correlation between the normalised variable and the metric used to make the normalisation. SUW should therefore be tested by correlation with weight, while SUL and SUA should be respectively tested by correlation with LBM and BSA.

SUV may be based on a single pixel of maximum standardised uptake value count rate (giving SUV_{max}) or as the mean standardised uptake value (SUV_{mean}) of all pixel values in an region of interest (ROI). Moreover, with respect to the liver, on which most previous studies focussing on this issue have been based, SUV is influenced by hepatic fat [9]. Thus, SUV_{mean} tends to be decreased in hepatic steatosis because ^{18}F-FDG does not enter hepatocyte fat droplets, which in effect physically dilute the ^{18}F-FDG signal. Hepatic fat is heterogeneously distributed [10] so SUV_{max} is less influenced by this dilution effect because it tends to be selectively located in a fat free region. On the other hand, SUV_{max} is more susceptible to statistical noise than SUV_{mean} [11,12] for the simple reason that peak and trough values are more widely separated when noise is increased. Noise is

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increased in larger persons [13], which would be expected to increase SUV_{max}. Sex is also an important consideration because, first, there is evidence to suggest that hepatic glucose metabolism differs between sexes [14, 15], second, men are larger than women, and thirdly, women have more body fat than men [16].

The purpose of the current study was to re-examine the issue of most appropriate whole body metric for calculating SUV using the liver as reference tissue in the context of sex.

Patients and methods

Patients

This was a retrospective study of 161 (97 men) adult patients, in whom height as well as weight was measured immediately prior to imaging, referred for routine ^{18}F-FDG PET/CT almost all for the management of cancer. The population comprised two groups of 101 and 60 patients that have been separately reported in studies elsewhere [6,9,13] and combined into one group for this study. The study received ethical approval from a National Research Ethics Committee of the UK.

Imaging

The PET/CT imaging protocol is described elsewhere [6,9,13]. In brief, PET/CT was performed with unenhanced CT-based attenuation correction using a Siemens Biograph, Siemens, Erlangen, Germany. 64-slice PET scanner with immediate nonenhanced CT scanning (120 kVp/50 mA-Care dose4D; slice 5 mm; pitch 0.8; rotational speed 0.5/s). Arms were up, as arms down may result in artificial elevation of the liver ^{18}F-FDG signal due to beam-hardening effects. Emission data were acquired at 3 min per bed position. Imaging was performed 60 min after injection of ~400 MBq, not scaled for body size, after 6 h of fasting.

Image analysis

SUV_{max}, SUV_{mean} and mean CT density were recorded in a 3 cm diameter ROI over the right lobe of the liver, avoiding any known or suspected regional pathology, as described previously [6,9,13]. Blood pool SUV was obtained from an ROI of 1.5 cm diameter over the left ventricular blood pool (SUV_{LV}). Reproducibility of SUV measurement was performed in the group of 60 patients.

Data analysis

SUV_{mean} was adjusted for hepatic fat using a recently described exponential equation [17] that relates CT density to the proportion of the liver that is fat (P_F).

$$P_F = \exp[-0.0238\,(CTD+50)].$$

The fat-adjustment procedure was to divide SUV_{mean} by $1-P_F$ to give SUV_{FA} [18]. SUV_{max} is not considered to require correction.

SUV_{max} was divided by maximum SUV_{LV}, and SUV_{mean} and SUV_{FA} were divided by mean SUV_{LV}. Expressing tissue SUV in relation to blood pool SUV has two desirable effects. Firstly, it eliminates whole body metric and secondly renders SUV a closer surrogate of blood ^{18}F-FDG clearance into tissue (i.e. blood clearance of ^{18}F-FDG that is phosphorylated) [19]. SUV/SUV_{LV} was then multiplied by blood glucose concentration to give mSUV as an estimate of hepatic glucose phosphorylation rate [20].

Estimation of lean body mass and body fat percentage

Sex-specific LBM was estimated from the formulae of Boer [21] to give ^{B}LBM and from the formulae of Janmahasatian *et al.* [22] to give ^{J}LBM. Body fat percentage was calculated as: $100 \times (\text{weight} - \text{LBM})/\text{weight}$.

Estimation of body surface area

Sex-non-specific BSA was estimated from the formula of Haycock *et al.* [23] to give ^{H}BSA and from the sex-specific formulae of Tikuisis *et al.* [24] to give ^{T}BSA.

Statistical analysis

Linear regression analysis was used to determine the Pearson correlation coefficients between variables. Student's unpaired *t*-test was used to determine the significance of the differences of variables between men and women. A P value of less than 0.05 was taken to indicate statistical significance.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Correlations with body weight

SUW indices correlated strongly with body weight in both men and women (Table 1). SUL_{max} and SUA_{max} also correlated strongly with body weight. SUL_{mean}, SUL_{FA}, SUA_{mean} and SUA_{FA} showed weak or no correlations with body weight in men or women analysed separately but showed some strong correlations when the sexes were combined into one group (Table 1).

Whole body metric-specific correlations

In contrast to maximum SUL and SUA, mean and fat-adjusted SUL and SUA showed no correlations with their whole body metric equivalents in men or women, except for $^{T}SUA_{mean}$ in men (Tables 2 and 3). However, several strong correlations were again noted when the sexes were combined (Fig. 1).

Table 1 Correlation coefficients and their significance levels (*P*) of the linear relationships between SUV indices and body weight in men, women and both combined

	Men	Women	Both
SUW_{max}	0.62 (<0.0001)	0.76 (<0.0001)	0.65 (<0.0001)
SUW_{mean}	0.48 (<0.001)	0.61 (<0.0001)	0.45 (<0.0001)
SUW_{FA}	0.55 (<0.001)	0.67 (<0.0001)	0.53 (<0.0001)
$^{B}SUL_{max}$	0.29 (0.004)	0.26 (0.04)	0.38 (<0.0001)
$^{B}SUL_{mean}$	−0.02 (NS)	−0.15 (NS)	0.01 (NS)
$^{B}SUL_{FA}$	0.1 (NS)	−0.04 (NS)	0.13 (NS)
$^{J}SUL_{max}$	0.27 (0.007)	0.45 (0.0002)	0.46 (<0.0001)
$^{J}SUL_{mean}$	−0.06 (NS)	0.09 (NS)	0.18 (0.02)[a]
$^{J}SUL_{FA}$	0.07 (NS)	0.21 (NS)	0.28 (0.0003)[a]
$^{H}SUA_{max}$	0.25 (0.01)	0.40 (0.001)	0.27 (0.0005)
$^{H}SUA_{mean}$	−0.08 (NS)	0.02 (NS)	−0.15 (NS)
$^{H}SUA_{FA}$	0.0 (NS)	0.14 (NS)	−0.03 (NS)
$^{T}SUA_{max}$	0.14 (NS)	0.32 (0.01)	0.17 (0.03)
$^{T}SUA_{mean}$	−0.21 (0.04)	−0.08 (NS)	−0.26 (0.0009)[a]
$^{T}SUA_{FA}$	−0.09 (NS)	0.03 (NS)	−0.15 (NS)

^{B}SUL, Boer scaled to body surface area; ^{H}SUA, Haycock scaled to body surface area; ^{J}SUL, Janmahasatian scaled to lean body mass; ^{T}SUA, Tikuisis scaled to body surface area; SUV, standardised uptake value; SUW, scaled to weight.
[a]Note how sex differences in the two co-ordinates have generated a significant correlation not present in either sex.

Table 2 Correlation coefficients and their significance levels (*P*) of the linear relationships between scaled to lean body mass indices and the same lean body mass used to calculate them in men, women and both combined

	Men	Women	Both
$^{B}SUL_{max}$	0.28 (0.005)	0.42 (0.0006)	0.49 (<0.0001)
$^{B}SUL_{mean}$	0.02 (NS)	0.1 (NS)	0.20 (0.01)[a]
$^{B}SUL_{FA}$	0.13 (NS)	0.16 (NS)	0.29 (0.0002)[a]
$^{J}SUL_{max}$	0.23 (0.02)	0.49 (<0.0001)	0.63 (<0.0001)
$^{J}SUL_{mean}$	−0.09 (NS)	0.14 (NS)	0.44 (<0.0001)[a]
$^{J}SUL_{FA}$	0.10 (NS)	0.24 (NS)	0.50 (<0.0001)[a]

^{B}SUL, Boer scaled to body surface area; ^{J}SUL, Janmahasatian scaled to lean body mass.
[a]Note how sex differences in the two co-ordinates have generated a significant correlation not present in either sex.

Table 3 Correlation coefficients and their significance levels (*P*) of the linear relationships between scaled to body surface area indices and the same body surface area used to calculate them in men, women and both combined

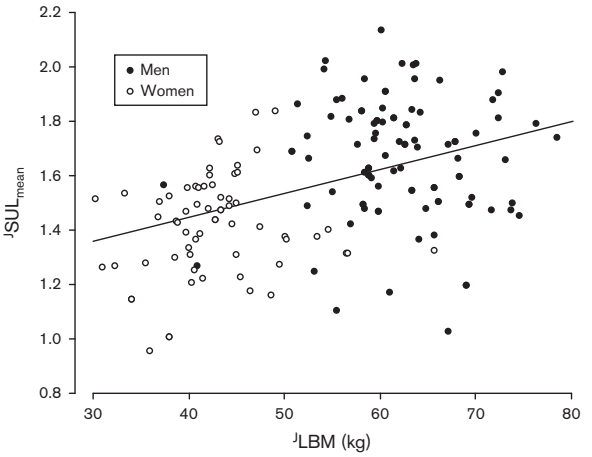
	Men	Women	Both
$^{H}SUA_{max}$	0.22 (0.03)	0.41 (0.0008)	0.24 (0.002)
$^{H}SUA_{mean}$	−0.09 (NS)	0.03 (NS)	−0.18 (0.02)[a]
$^{H}SUA_{FA}$	0.03 (NS)	0.14 (NS)	−0.07 (NS)
$^{T}SUA_{max}$	0.1 (NS)	0.34 (0.006)	0.13 (NS)
$^{T}SUA_{mean}$	−0.21 (0.04)	−0.07 (NS)	−0.29 (0.0002)[a]
$^{T}SUA_{FA}$	−0.09 (NS)	0.04 (NS)	−0.19 (0.02)[a]

^{H}SUA, Haycock scaled to body surface area; ^{T}SUA, Tikuisis scaled to body surface area.
[a]Note how sex differences in the two co-ordinates have generated a significant correlation not present or weak in either sex.

Differences between men and women

CT density, P_F and blood glucose were all similar between men and women (Table 4). Body fat percentage, however, was higher in women compared with men. LBM and BSA were, as expected, higher in men than women but the ratio of BSA/LBM was higher in women.

Fig. 1



There is no significant correlation between lean body mass (^{J}LBM) estimated from the sex-specific formulae of Janmahasatian *et al.* [25] and mean SUV ($^{J}SUL_{mean}$) calculated using ^{J}LBM as whole body metric in women (open circles; $r=0.14$) or in men (closed circles; $r=-0.09$), but there is a strong correlation when the sexes are combined into a single group ($r=0.44$; $P<0.0001$). ^{J}LBM, Janmahasatian lean body mass; ^{J}SUL, Janmahasatian scaled to lean body mass; SUV, standardised uptake value.

SUW indices were not significantly different between men and women (Table 4). SUL indices, however, were greater in men than women, while in contrast SUA indices were higher in women. mSUV, however, was not significantly different between men and women (Table 4).

Discussion

The main finding in this study is that mean and fat-adjusted hepatic SUL showed no significant correlation with LBM in either sex, in spite of the presence of LBM in both co-ordinates, suggesting that LBM is an appropriate whole body metric for the calculation of SUV. SUA behaved similarly, although $^{T}SUA_{mean}$ did correlate significantly with ^{T}BSA in men. SUW, in contrast, correlated strongly with body weight, which can be explained by the relatively low penetration of ^{18}F-FDG into adipose tissue [1]. These findings are in line with Sugawara *et al.* [4] and Tahari *et al.* [5], who favoured LBM, and with Kim *et al.* [3] and Schomburg *et al.* [7], who favoured BSA, and are therefore not new. Nevertheless, we believe our study is important as it clarifies the role of sex and shows that ignoring sex results in misleading correlations.

LBM has the potential disadvantage of underestimating SUV because ^{18}F-FDG, at least to a limited extent, accumulates in adipose tissue [1], which SUL ignores. Because women have more adipose tissue than men, this may explain why SUL indices were higher in men. Conversely, BSA has the potential disadvantage of

Table 4 Mean (SD) values of computed tomography density (HU), blood glucose (mmol/l), liver fat (%), body fat (%), whole body metrics, SUV indices and mSUV in men and women

	Men	Women	*P*
Blood glucose	5.7 (0.8)	5.6 (0.9)	NS
CT density	46 (10)	50 (12)	NS
%Liver fat	10.5 (2.9)	9.7 (3.0)	NS
%Body fat (Boer)	26 (6)	32 (10)	< 0.0001
%Body fat (Janmahasatian)	25 (7)	39 (6)	< 0.0001
Body weight	84 (16)	71 (18)	< 0.0001
^{B}LBM	62 (7)	47 (6)	< 0.0001
^{J}LBM	62 (7)	43 (6)	< 0.0001
^{H}BSA	2.03 (0.22)	1.79 (0.24)	< 0.0001
^{T}BSA	2.00 (0.18)	1.78 (0.21)	< 0.0001
^{H}BSA/^{B}LBM	0.328 (0.0012)	0.0383 (0.0025)	< 0.0001
SUW_{max}	3.02 (0.62)	2.94 (0.65)	NS
SUW_{mean}	2.23 (0.34)	2.33 (0.39)	NS
SUW_{FA}	2.50 (0.41)	2.59 (0.46)	NS
$^{B}SUL_{max}$	2.25 (0.35)	1.96 (0.29)	< 0.0001
$^{B}SUL_{mean}$	1.67 (0.22)	1.57 (0.21)	0.005
$^{B}SUL_{FA}$	1.87 (0.25)	1.74 (0.23)	0.001
$^{J}SUL_{max}$	2.24 (0.34)	1.77 (0.28)	< 0.0001
$^{J}SUL_{mean}$	1.66 (0.22)	1.42 (0.18)	< 0.0001
$^{J}SUL_{FA}$	1.86 (0.25)	1.57 (0.20)	< 0.0001
$^{H}SUA_{max}$	0.074 (0.011)	0.075 (0.011)	NS
$^{H}SUA_{mean}$	0.055 (0.007)	0.060 (0.008)	< 0.0001
$^{H}SUA_{FA}$	0.061 (0.008)	0.066 (0.008)	0.0001
$^{T}SUA_{max}$	0.072 (0.011)	0.075 (0.011)	NS
$^{T}SUA_{mean}$	0.054 (0.007)	0.060 (0.008)	< 0.0001
$^{T}SUA_{FA}$	0.060 (0.008)	0.066 (0.008)	< 0.0001
$mSUV_{max}$	9.35 (2.17)	9.12 (2.71)	NS
$mSUV_{mean}$	7.96 (1.64)	8.22 (2.21)	NS
$mSUV_{FA}$	8.90 (1.82)	9.13 (2.54)	NS

^{B}LBM, Boer lean body mass; ^{B}SUL, Boer scaled to body surface area; CT, computed tomography; ^{H}BSA, Haycock body surface area; ^{H}SUA, Haycock scaled to body surface area; ^{J}LBM, Janmahasatian lean body mass; ^{J}SUL, Janmahasatian scaled to lean body mass; LBM, lean body mass; NS, not significantly different between men and women; SUV, standardised uptake value; ^{T}BSA, Tikuisis body surface area; ^{T}SUA, Tikuisis scaled to body surface area; SUW, scaled to weight.

overestimating SUV because, like body weight, it increases, with no change in LBM, when body fat increases, explaining why SUA indices were higher in women. Moreover, as a two-dimensional variable, BSA is relatively higher in small individuals compared with large. It is notable that the sex-specific equations of Tikuisis gave almost identical estimates of BSA as the sex-non-specific formula of Haycock (Table 4). There were no sex differences in SUW. However, because they have more fat, women might have been expected to have higher SUW indices.

The generally stronger correlations between SUV_{max} indices and corresponding whole body metrics compared with their mean and fat-adjusted equivalents are in keeping with the notion that SUV_{max} is influenced by statistical noise and increased in large persons. This tendency, however, is opposed by BSA as a whole body metric because large persons have low BSA relative to their size, explaining why SUA_{max} did not correlate so strongly with BSA compared with the correlations between SUL_{max} and LBM (Tables 2 and 3).

The finding of significant correlations between SUV indices and whole body metrics when men and women were combined when there was no correlation in either sex analysed separately (Tables 1–3 and Fig. 1) is the result of anthropometric differences and consequent differences in SUV indices between the two sexes. Batallés *et al.* [26] found higher SUV in men than women, while Demir *et al.* [25], like us, found SUL, but not SUW, to be higher in men. This sex difference indicates that correlations when the sexes are combined may be misleading. Some of the previous studies either included only women [2,4] or did not distinguish between men and women [3,7].

Division by blood pool SUV renders tissue SUV a closer reflection of ^{18}F-FDG clearance [19] (referred to as uptake constant in dynamic ^{18}F-FDG studies), and bypasses whole body metric normalisation, which cancels out. Multiplication of this ratio by blood glucose concentration makes it a closer surrogate of hepatic glucose phosphorylation [20], which in dynamic studies is uptake constant multiplied by blood glucose [27,28]. We found no difference in mSUV between men and women, in keeping with an artefactually lower SUL and artefactually higher SUA in women, as suggested above. However, although division by blood pool SUV bypasses the choice of whole body metric, partial volume effects in relation to blood pool ROI become an issue and may explain why no sex differences in mSUV were seen, because several previous studies have shown differences in glucose metabolism between men and women [14,15], including a higher glucose uptake rate [29].

SUV is sensitive to statistical noise and to hepatic fat content. Thus, in general, SUV_{max} indices, but not SUV_{mean} or SUV_{FA} indices, correlated strongly with all body size metrics, consistent with SUV_{max} being more susceptible to noise, and therefore reaching higher values in large persons in whom there is greater signal attenuation. Adjusting SUV for hepatic fat (to give SUV_{FA}) turned out to have no relevance to choice of whole body metric in our study probably because there was no significant difference in liver fat percentage between men and women, and correspondingly no difference in hepatic CT density.

Conclusion

We believe in common with others that in general LBM, as a 3-dimensional variable, is the preferred whole body metric for normalising SUV for the purpose of quantifying ^{18}F-FDG accumulation in pathological tissues, such as tumours, in both men and women. Although LBM tends to underestimate SUV in persons with high body fat percentage, we believe it is preferable to BSA because BSA is artefactually influenced not only by body fat percentage, which is greater in women, but also by body size, which is greater in men.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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