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Body surface area in normal-weight, overweight, and obese adults. A comparison study

Johan Verbraecken[a,d,e,*], Paul Van de Heyning[b], Wilfried De Backer[a,d], Luc Van Gaal[c,d]

[a]*Department of Pulmonary Medicine, University Hospital Antwerp, 2650 Edegem, Belgium*
[b]*Department of ENT, University Hospital Antwerp, 2650 Edegem, Belgium*
[c]*Department of Diabetology and Metabolic Diseases, University Hospital Antwerp, 2650 Edegem, Belgium*
[d]*Antwerp Metabolic Research Unit (AMRU), University of Antwerp, 2610 Antwerp, Belgium*
[e]*Department of Respiratory Medicine, University Hospital Maastricht, 6202 AZ Maastricht, The Netherlands*

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Abstract

Values for body surface area (BSA) are commonly used in medicine, particularly to calculate doses of chemotherapeutic agents and index cardiac output. Various BSA formulas have been developed over the years. The DuBois and DuBois (*Arch Intern Med* 1916;17:863-71) BSA equation is the most widely used, although derived from only 9 subjects. More recently, Mosteller (*N Engl J Med* 1987;317:1098) produced a simple formula, [weight (kg) × height (cm)/3600]$^{1/2}$, which could be easily remembered and evaluated on a pocket calculator, but validation data in adults are rare. The purpose of the present study was to examine the BSA based on Mosteller's formula in normal-weight (body mass index [BMI], 20-24.9 kg/m^2), overweight (BMI, 25-29.9 kg/m^2), and obese (BMI, ≥30 kg/m^2) adults (>18 years old) in comparison with other empirically derived formulas (DuBois and DuBois, Boyd [*The growth of the surface area of the human body*. Minneapolis: University of Minnesota Press; 1935], Gehan and George [*Cancer Chemother Rep* 1970;54:225-35], US Environmental Protection Agency [*Development of statistical distributions or ranges of standard factors used in exposure assessments Washington, EPA/600/8-85-010*. Office of Health and Environmental Assessment; 1985), Haycock et al [*J Pediatr* 1978;93:62-6], Mattar [*Crit Care Med* 1989;17:846-7], Livingston and Scott [*Am J Physiol Endocrinol Metab* 2001;281:E586-91]) and with the new 3-dimensional–derived formula of Yu et al (*Appl Ergon*. 2003;34:273-8). One thousand eight hundred sixty-eight patients were evaluated (397 normal weight [BMI, 23 ± 1 kg/m^2; age, 50 ± 14 years; M/F, 289/108], 714 overweight [BMI, 27 ± 1 kg/m^2; age, 52 ± 11 years; M/F, 594/120], and 757 obese [BMI, 36 ± 6 kg/m^2; age, 53 ± 11 years; M/F, 543/215]). The overall BSA was 2.04 ± 0.24 m^2: 1.81 ± 0.19 m^2 in normal-weight, 1.99 ± 0.16 m^2 in overweight, and 2.21 ± 0.22 m^2 in obese subjects. These values were significantly higher in overweight and obese patients compared with the values using the DuBois-DuBois formula (overall, 2.00 ± 0.22 m^2, $P < .01$; normal weight, 1.81 ± 0.19 m^2, $P = .93$; overweight, 1.97 ± 0.16 m^2, $P < .01$; obese, 2.14 ± 0.21 m^2, $P < .001$). We could show an excellent correlation between the results obtained from each formula, with all correlations of 0.97 or higher (between 0.971 and 0.999). Body surface area prediction with the commonly used DuBois formula underestimated BSA in obese patients by as much as 3% (male) to 5% (female). Based on the formula of Yu et al, however, BSA is overestimated when these traditional formulas are used. Although Mosteller's formula is recommended based on its simplicity and suitability for laboratory and clinical work in adults, accuracy studies in whites with 3-dimensional one-pass whole-body scanning are needed.

1. Introduction

It is a frequent practice in medicine to estimate the human body surface area (BSA). The BSA is widely used as the biometric unit for normalizing physiologic parameters (cardiac output, left ventricular mass, renal clearance) and for the determination of appropriate drug dosages in cancer chemotherapy, in individuals of different body size [1-3]. It derives from the finding that such parameters correlate better with BSA than with any other index of body size and the fact that differences in the maximum tolerable dosages of anticancer drugs among men were normalized when doses were expressed in milligrams per square meter of BSA [4]. The commonly accepted 50th percentiles for BSA are 1.94 m^2 for adult men and 1.69 m^2 for adult women [5]. Physicians often depend upon elaborate formulas to

* Corresponding author. Department of Pulmonary Medicine, University Hospital Antwerp, 2650 Edegem, Belgium. Tel.: +32 3 821 35 37; fax: +32 3 821 44 47.
E-mail address: johan.verbraecken@uza.be (J. Verbraecken).

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establish BSA. However, these formulas are too complex to mentally calculate; even a 4-function calculator is insufficient because of the biexponential nature of the formulas [5-10]. Moreover, the most widely used formula (DuBois and DuBois) was derived from only 9 patients [7]. Mosteller [11] proposed a simplified calculation of BSA in 1987, which can be easily used on a pocket calculator with a square root function. This formula is a modification of the BSA equation by Gehan and George [8]. However, no supporting data were included. Validation studies were only published in children [12,13]. We wanted to compare Mosteller's formula in an extensive series of normal-weight, overweight, and obese adults to data obtained with 7 previously described and empirically derived formulas.

2. Subjects and methods

Three groups of patients were studied: normal-weight (body mass index [BMI], 20-24.9 kg/m^2), overweight (BMI, 25-29.9 kg/m^2), and obese adults (BMI, $\geq$30 kg/m^2), selected from a consecutive series of patients visiting our sleep disorders center. We evaluated 1868 patients (M/F, 1425/443; age, 52 $\pm$ 12 years; BMI, 30 $\pm$ 6 kg/m^2; weight, 88 $\pm$ 19 kg; height, 172 $\pm$ 9 cm). We found 397 normal-weight (M/F, 289/108; age, 50 $\pm$ 14 years; BMI, 23 $\pm$ 1 kg/m^2; weight, 69 $\pm$ 10 kg; height, 172 $\pm$ 10 cm), 714 overweight (M/F, 594/120; age, 52 $\pm$ 11 years; BMI, 27 $\pm$ 1 kg/m^2; weight, 83 $\pm$ 10 kg; height, 173 $\pm$ 9 cm), and 757 obese adults (M/F, 543/215; age, 53 $\pm$ 11 years; BMI, 36 $\pm$ 6 kg/m^2; weight, 104 $\pm$ 18 kg; height, 170 $\pm$ 10 cm). Body surface area was calculated from the height and the weight according to Mosteller's formula [11]:

$$\mathrm{BSA} = [(\mathrm{weight} \times \mathrm{height})/3600]^{1/2}$$

The calculated BSA values were correlated (Spearman) with BSA values obtained with 7 formulas from the literature (see footnote to Table 1). Statistica package (Statsoft, Tulsa, OK) was used for statistical analysis. Accuracy was assessed

Table 1
Separated data for anthropometry and BSA in normal-weight, overweight, and obese adults and according to sex

	Range	Overall	Normal weight	Overweight	Obese
n		1868	397	714	757
Weight (kg)	44-196	88 ± 19	69 ± 10	83 ± 10†	104 ± 18†,‡
Height (cm)	139-200	172 ± 9	172 ± 10	173 ± 9	170 ± 10†,‡
BMI (kg/m^2)	16-75	30 ± 6	23 ± 1	27 ± 1†	36 ± 6†,‡
Mosteller (m^2)	1.34-3.10	2.04 ± 0.24	1.81 ± 0.19	1.99 ± 0.16†	2.21± 0.22†,‡
DuBois-DuBois (m^2)	1.34-2.94	2.00 ± 0.22	1.81 ± 0.19	1.97 ± 0.16†	2.14 ± 0.21†,‡
Boyd (m^2)	1.35-3.05	2.03 ± 0.24	1.81 ± 0.18	1.98 ± 0.16†	2.19 ± 0.22†,‡
Gehan and George (m^2)	1.36-3.14	2.06 ± 0.25	1.83 ± 0.19	2.01 ± 0.16†	2.24 ± 0.23†,‡
EPA (m^2)	1.36-3.14	2.06 ± 0.25	1.82 ± 0.19	2.01 ± 0.16†	2.24 ± 0.23†,‡
Haycock et al (m^2)	1.35-3.19	2.07 ± 0.26	1.82 ± 0.19	2.01 ± 0.16†	2.25 ± 0.24†,‡
Mattar (m^2)	1.32-3.12	2.00 ± 0.24	1.81 ± 0.19	1.96 ± 0.18†	2.14 ± 0.24†,‡
Livingston and Scott (m^2)	1.36-3.56	2.11 ± 0.30	1.81 ± 0.18	2.04 ± 0.16†	2.35 ± 0.26†,‡
Mean (m^2)	1.35-3.14	2.05 ± 0.25	1.82 ± 0.17	2.00 ± 0.16†	2.22 ± 0.23†,‡
Yu et al (m^2)	1.28-2.96	1.95 ± 0.23	1.74 ± 0.16	1.90 ± 0.16†	2.11 ± 0.21†,‡

	Overall		Normal weight		Overweight		Obese	
	Male	Female	Male	Female	Male	Female	Male	Female
n	1425	443	289	108	594	120	542	215
Weight (kg)	90 ± 18	83 ± 23*	72 ± 8	61 ± 9*	85 ± 9	72 ± 8*	106 ± 17	99 ± 20*
Height (cm)	175 ± 7	162 ± 7*	176 ± 8	163 ± 7*	176 ± 7	162 ± 8*	174 ± 7	161 ± 6*
BMI (kg/m^2)	29 ± 6	31 ± 8*	23 ± 1	23 ± 2*	27 ± 1	28 ± 1	35 ± 5	38 ± 7*
Mosteller (m^2)	2.09 ± 0.22	1.91 ± 0.26*	1.88 ± 0.14	1.65 ± 0.20*	2.03 ± 0.14	1.80 ± 0.14*	2.25 ± 0.21	2.10 ± 0.23*
DuBois-DuBois (m^2)	2.05 ± 0.20	1.86 ± 0.23*	1.88 ± 0.14	1.64 ± 0.20*	2.01 ± 0.14	1.77 ± 0.14*	2.19 ± 0.19	2.01 ± 0.20*
Boyd (m^2)	2.07 ± 0.21	1.90 ± 0.26*	1.87 ± 0.13	1.64 ± 0.20*	2.02 ± 0.14	1.80 ± 0.14*	2.23 ± 0.20	2.08 ± 0.22*
Gehan and George (m^2)	2.10 ± 0.23	1.94 ± 0.27*	1.89 ± 0.14	1.66 ± 0.20*	2.05 ± 0.14	1.82 ± 0.14*	2.28 ± 0.21	2.13 ± 0.23*
EPA (m^2)	2.10 ± 0.23	1.94 ± 0.27*	1.88 ± 0.14	1.66 ± 0.20*	2.05 ± 0.14	1.82 ± 0.14*	2.28 ± 0.21	2.13 ± 0.23*
Haycock et al (m^2)	2.11 ± 0.24	1.94 ± 0.29*	1.88 ± 0.14	1.65 ± 0.20*	2.05 ± 0.14	1.82 ± 0.14*	2.29 ± 0.22	2.15 ± 0.24*
Mattar (m^2)	2.05 ± 0.22	1.84 ± 0.25*	1.88 ± 0.15	1.63 ± 0.15*	2.00 ± 0.15	1.74 ± 0.15*	2.20 ± 0.22	2.01 ± 0.24*
Livingston and Scott (m^2)	2.15 ± 0.27	2.02 ± 0.35*	1.86 ± 0.13	1.66 ± 0.20*	2.07 ± 0.14	1.87 ± 0.13*	2.38 ± 0.24	2.28 ± 0.29*
Mean (m^2)	2.09 ± 0.23	1.92 ± 0.27*	1.88 ± 0.14	1.66 ± 0.13*	2.04 ± 0.14	1.80 ± 0.14*	2.26 ± 0.21	2.11 ± 0.23*
Yu et al (m^2)	1.99 ± 0.21	1.83 ± 0.25*	1.79 ± 0.13	1.59 ± 0.12*	1.94 ± 0.13	1.72 ± 0.13*	2.15 ± 0.20	2.01 ± 0.22*

Data are expressed as mean ± SEM. Mosteller, $[(H \times W)/3600]^{0.50}$; DuBois and DuBois, $0.00718 \times H^{0.725} \times W^{0.425}$; Boyd, $0.0178 \times H^{0.5} \times W^{0.484}$; Gehan and George, $0.0235 \times H^{0.42246} \times W^{0.51456}$; EPA, $0.0239 \times H^{0.417} \times W^{0.517}$; Haycock et al, $W^{0.5378} \times H^{0.3964} \times 0.024265$; Mattar, $(H + W - 60)/100$; Livingston and Scott, $0.1173 \times W^{0.6466}$; mean, from the DuBois and DuBois formula to Livingston and Scott' formula; Yu et al, $0.015925 \times (H \times W)^{0.50}$. H indicates height (cm); W, weight (kg).

* $P < .05$ compared with male (Mann-Whitney U test).

† $P < .001$ compared with normal weight (Mann-Whitney U test).

‡ $P < .001$ compared with overweight (Mann-Whitney U test).

Table 2
Correlation analysis between Mosteller's BSA and BSA values obtained with other formulas in normal-weight, overweight, and obese adults

	r	R^2	RMSE	r	R^2	RMSE	r	R^2	RMSE
	Overall			*Overall male*			*Overall female*		
Mosteller	–	–	–	–	–	–	–	–	–
DuBois-DuBois	0.991	0.984	0.0302	0.994	0.987	0.0250	0.995	0.990	0.0264
Boyd	0.999	0.999	0.0018	0.999	0.999	0.0014	0.999	0.999	0.0016
Gehan and George	0.999	0.998	0.0085	0.999	0.999	0.0069	0.999	0.999	0.0069
EPA	0.999	0.998	0.0093	0.999	0.998	0.0075	0.999	0.999	0.0075
Haycock et al	0.999	0.997	0.0129	0.998	0.997	0.0104	0.999	0.998	0.0105
Mattar	0.984	0.978	0.0356	0.990	0.980	0.0310	0.990	0.981	0.0362
Livingston and Scott	0.971	0.953	0.0529	0.981	0.963	0.0422	0.987	0.975	0.0413
Mean	0.999	0.999	0.0056	0.999	0.999	0.0042	0.999	0.999	0.0057
Yu et al	0.999	0.999	0.0110	1.0	1.0	0	1.0	1.0	0
	All normal weight			*Normal-weight male*			*Normal-weight female*		
Mosteller	–	–	–	–	–	–	–	–	–
DuBois-DuBois	0.997	0.996	0.0100	0.997	0.994	0.0099	0.996	0.993	0.0103
Boyd	0.999	0.999	0.0006	0.999	0.999	0.0005	0.999	0.999	0.0006
Gehan and George	0.999	0.999	0.0032	0.999	0.999	0.0031	0.999	0.999	0.0032
EPA	0.999	0.999	0.0030	0.999	0.999	0.0034	0.999	0.999	0.0035
Haycock et al	0.999	0.999	0.0049	0.999	0.998	0.0047	0.999	0.998	0.0048
Mattar	0.991	0.987	0.0187	0.991	0.982	0.0180	0.988	0.976	0.0197
Livingston and Scott	0.986	0.979	0.0239	0.986	0.973	0.0225	0.984	0.968	0.0226
Mean	0.999	0.999	0.0005	0.999	0.999	0.0005	0.999	0.999	0.0005
Yu et al	1.0	1.0	–	1.0	1.0	–	1.0	1.0	–
	All overweight			*Overweight male*			*Overweight female*		
Mosteller	–	–	–	–	–	–	–	–	–
DuBois-DuBois	0.997	0.995	0.0105	0.997	0.994	0.0106	0.998	0.996	0.0087
Boyd	0.999	0.999	0.0007	0.999	0.999	0.0006	0.999	0.999	0.0005
Gehan and George	0.999	0.999	0.0034	0.999	0.999	0.0034	0.999	0.999	0.0028
EPA	0.999	0.999	0.0037	0.999	0.999	0.0037	0.999	0.999	0.0031
Haycock et al	0.999	0.999	0.0052	0.999	0.998	0.0052	0.999	0.999	0.0043
Mattar	0.995	0.992	0.0145	0.994	0.989	0.0144	0.995	0.990	0.0135
Livingston and Scott	0.986	0.976	0.0254	0.984	0.968	0.0249	0.989	0.977	0.0211
Mean	0.999	0.999	0.0013	0.999	0.999	0.0013	0.999	0.999	0.0009
Yu et al	1.0	1.0	–	1.0	1.0	–	1.0	1.0	–
	All obese			*Obese male*			*Obese female*		
Mosteller	–	–	–	–	–	–	–	–	–
DuBois-DuBois	0.992	0.984	0.0200	0.994	0.989	0.0217	0.994	0.988	0.0240
Boyd	0.999	0.999	0.0017	0.999	0.999	0.0006	0.999	0.999	0.0014
Gehan and George	0.999	0.998	0.0082	0.999	0.999	0.0063	0.999	0.999	0.0065
EPA	0.999	0.998	0.0089	0.999	0.999	0.0068	0.999	0.999	0.0070
Haycock et al	0.998	0.997	0.0124	0.999	0.998	0.0095	0.999	0.998	0.0060
Mattar	0.995	0.991	0.0068	0.996	0.992	0.0178	0.996	0.992	0.0110
Livingston and Scott	0.971	0.943	0.0536	0.981	0.962	0.0406	0.984	0.969	0.0400
Mean	0.999	0.999	0.0067	0.999	0.999	0.0047	0.999	0.999	0.0061
Yu et al	1.0	1.0	–	1.0	1.0	–	1.0	1.0	–

r indicates correlation; R^2, correlation coefficient. For formulas, see footnote to Table 1.

using the root mean square error (RMSE) method of prediction. The RMSE measures concordance between "measured" and "predicted" data. In the absence of a "gold standard" for BSA against which one can determine the accuracy of any one formula, we also calculated the arithmetic mean of BSA of the 7 formulas and designated this as the mean BSA. Mosteller's BSA should then be proportional to the mean BSA. This mean is a more accurate physiologic measure of the actual BSA because the 7 formulas have all been derived in independent studies and the mean of any available independent estimates is the best measure [14].

Mosteller's BSA was also correlated with this mean BSA. To support accuracy, we applied the most recent formula for BSA derived by the completely new and independent method of 3-dimensional (3D) one-pass whole-body scanning [15].

The formula of Yu et al [15] was derived in Chinese adults and could be considered as the "most accurate" BSA.

Bland and Altman [14] plots were examined to determine relationships between the magnitude and degree of variation in the BSA measurements. Horizontal lines were drawn at the mean difference and at the mean difference $\pm$ 1.96 $\times$ the

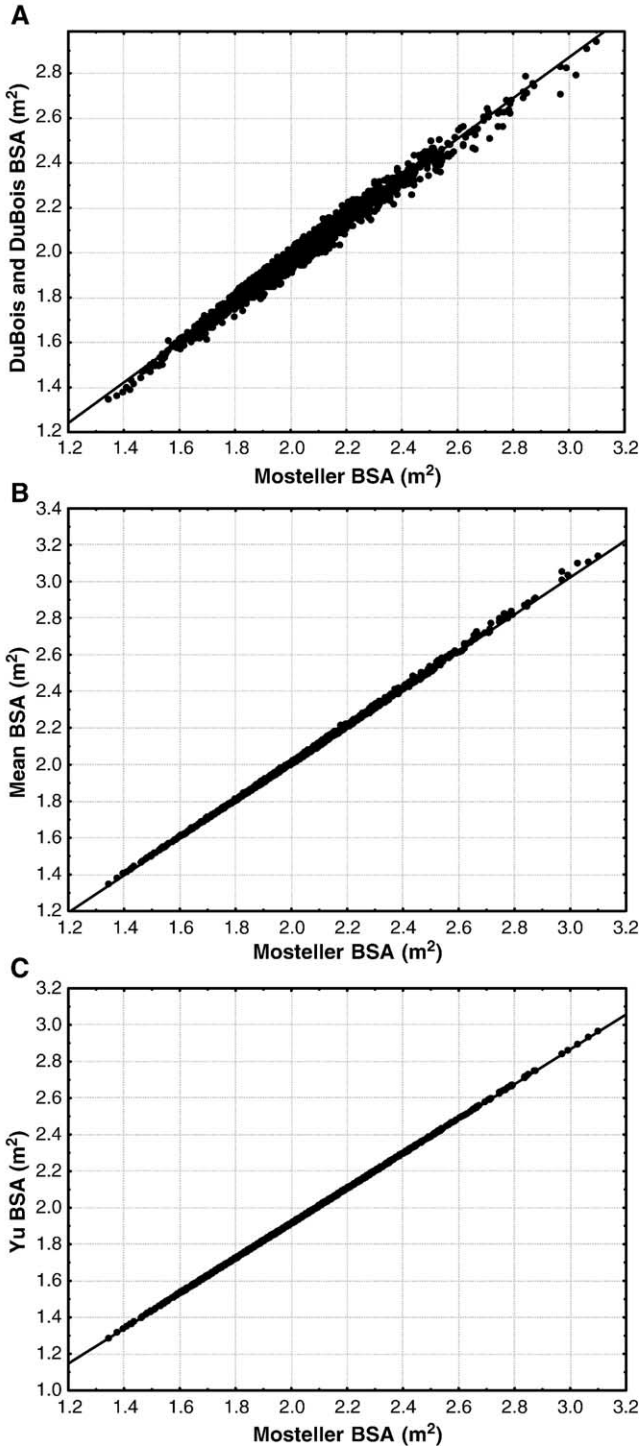

Fig. 1. Correlation analysis between Mosteller's BSA and BSA based on different BSA formulas: DuBois and DuBois BSA (A), mean BSA calculated from different formulas (B), BSA from Yu et al (C).

SD of the differences. If the differences within mean ± 1.96 SD are not clinically important, the 2 methods may be used interchangeably.

Percentage of similarity between data pairs was also used [16]. The percentage of similarity value between Mosteller's formula and the more traditional formulas (the gold standard is calculated as the average between Mosteller's BSA and the gold standard BSA divided by the gold standard BSA and multiplied by 100). Data pairs with the same value are 100% similar. Data pairs in which Mosteller's BSA is greater than the gold standard BSA will be greater than 100%; conversely, data pairs in which Mosteller's BSA is less than the gold standard BSA will be less than 100%. The mean percentage of similarity and the SD can also be used to calculate a coefficient of variation (CV) between the 2 methods (formulas). The CV is calculated by dividing the SD by the mean percentage of similarity.

To evaluate the effect of weight reduction on BMI and BSA, we also studied a selected group of 21 predominantly obese patients in which a weight reduction program was successful (at least −6 kg). This group consisted of 7 male and 14 female patients (overall: 102 ± 15 kg, 173 ± 10 cm, BMI, 34 ± 5 kg/m^2).

3. Results

The records of 1868 patients were assessed. Eight hundred twenty-five (44%) had a BSA of 2 m^2 or less; of these, 120 patients (6%) were obese (BMI, > 30 kg/m^2), whereas 705 (38%) were not obese (BMI, <30 kg/m^2). One thousand forty-three patients (56%) had a BSA of more than 2 m^2 and more than 22% (n = 409) of these were not obese, whereas 34% (n = 634) were obese. There were 754 patients (40%) defined as obese, and 16% (n = 120) of these had a BSA of 2 m^2 or less.

Using Mosteller's formula, the median BSA value was 2.06 m^2 in male and 1.89 m^2 in female (overall); 1.88 m^2 in normal-weight male and 1.66 m^2 in normal-weight female; 2.03 m^2 in overweight male and 1.79 m^2 in overweight female; and 2.24 m^2 in obese male and 2.05 m^2 in obese female. The distribution curve (not included) showed some skewness to the right in male obese (0.87), in female overweight (0.42), and in female obese (1.20) subjects.

Body surface area data obtained with different formulas in normal-weight, overweight, and obese subjects are shown in Table 1, also including the mean BSA and the BSA from Yu et al. The overall mean range was between 1.34 and 3.13 m^2 (lowest value, 1.28 m^2 [Yu et al]; highest value, 3.56 m^2 [Livingston and Scott [10]]). Overweight and obese persons had a significantly higher BSA than normal-weight persons, whereas obese subjects had also higher BSA than the overweight subjects ($P < .001$). Subanalysis for sex showed significantly higher BSA values in male. Men were also taller ($P < .01$) and heavier than women ($P < .01$). Body mass index was however slightly higher in female subjects (predominantly in obese subjects). Only small differences among the BSA values from the different formulas could be observed. Livingston and Scott's formula produced consistently higher BSA values. Mosteller's BSA was 2% higher than the DuBois and DuBois BSA (overall, $P < .01$), which was most pronounced in obese subjects

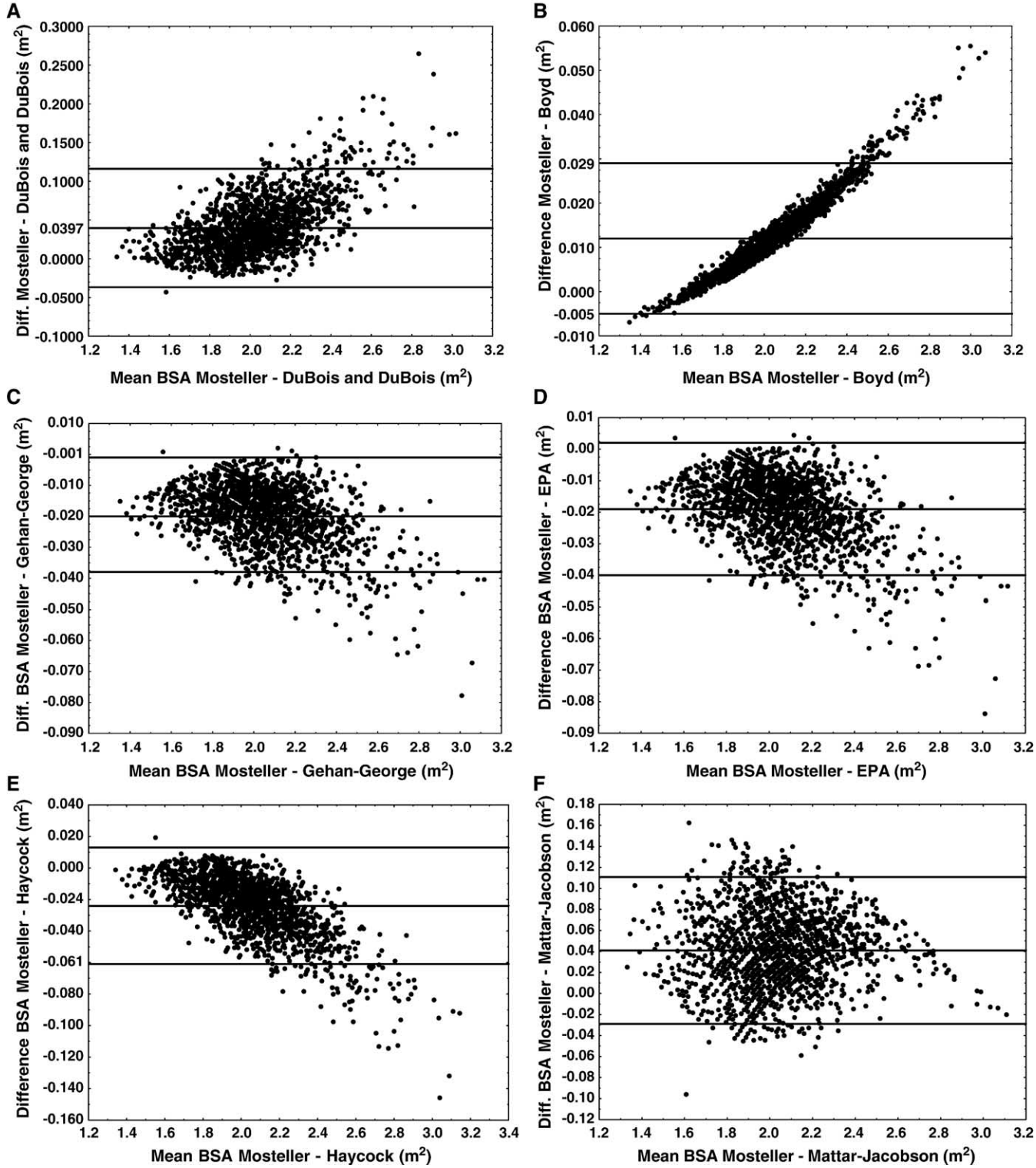

Fig. 2. Bland and Altman plots of the difference in BSA as a function of the mean BSA based on Mosteller's formula and on the DuBois and DuBois formula (A), Boyd's formula (B), Gehan and George's formula (C), EPA's formula (D), the formula of Haycock et al (E), Mattar's formula (F), Livingston and Scott's formula (G), the mean BSA of the previous formulas (H), the formula of Yu et al (I). Plots show the mean bias ± 1.96 SD.

(+3.27%, $P < .001$; male, +2.74%, $P < .001$; female, +4.74%, $P < .001$). Mosteller's BSA was ±1% lower than Gehan and George's BSA (most pronounced in obese: −1.33%, $P = .01$; −1.31% in male, $P = .04$; −1.41%, $P = .12$ in female). Compared with the mean BSA, Mosteller's BSA was 0.50% lower (comparable in all groups [$P = .46$]: in male, $P = .54$; in female, $P = .63$). Mosteller's BSA was +4.6% higher than the most accurate BSA from Yu et al

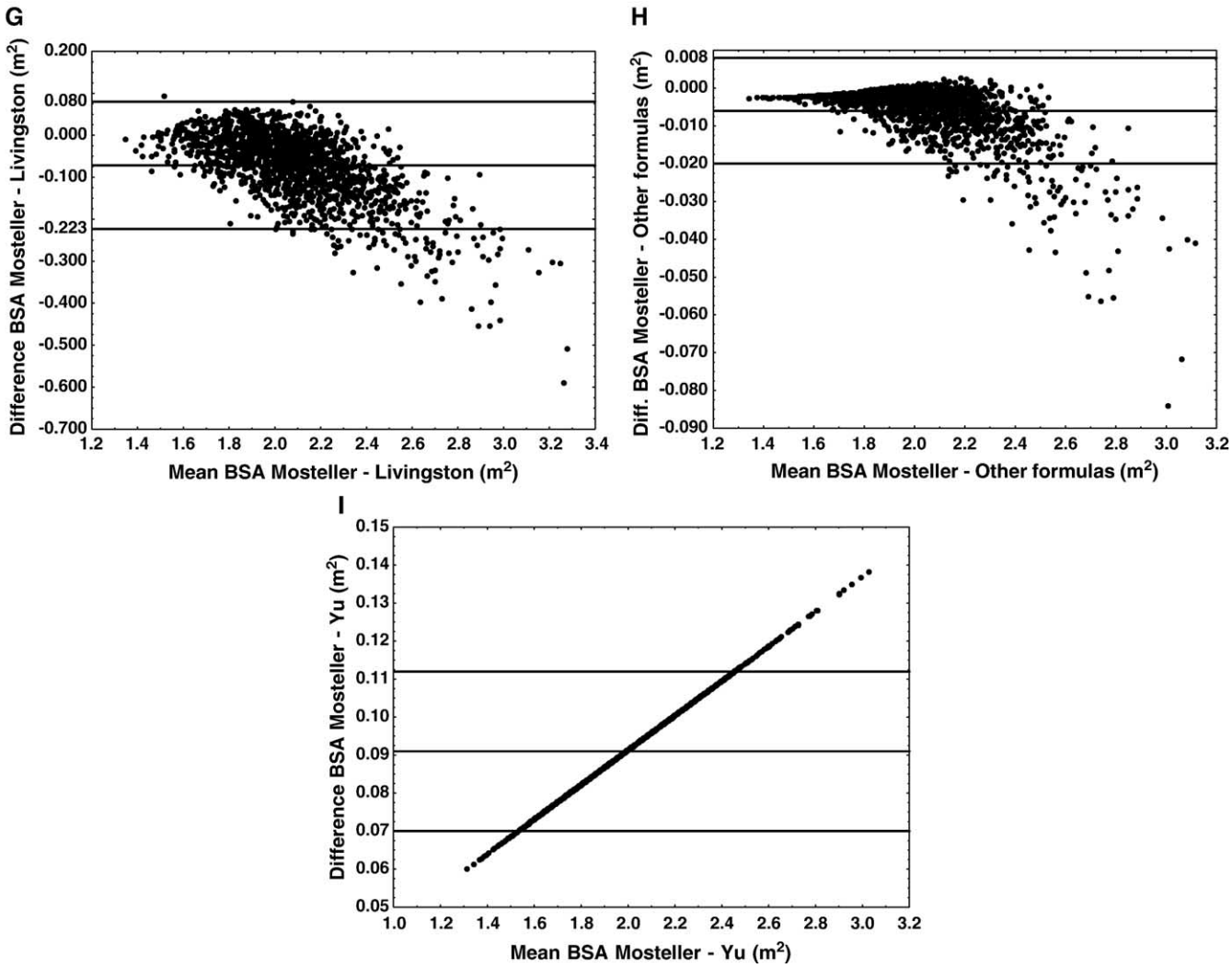

Fig. 2. (*continued*)

(comparable in all groups [$P < .001$], + 5.02% in male [$P < .001$], 4.37% in female [$P < .01$]).

Correlation analysis between Mosteller's BSA values and data obtained with the 7 more complex formulas is shown in Table 2, as well as its correlation with the mean BSA and the BSA from Yu et al. Subanalysis for sex was also included. Remarkably high correlations were found with Mosteller's BSA (Fig. 1A-C). The most consistent correlations were found with the formulas of Boyd, Gehan and George, US Environmental Protection Agency (EPA), and Haycock et al [9], as well as with the mean BSA (Fig. 1B) and the BSA from Yu et al (Fig. 1C). The equations of Mattar [17] and Livingston and Scott showed somewhat lower correlations and higher RMSE. The DuBois formula ranked only fifth for the lowest RMSE overall, in normal-weight subjects, and in overweight subjects, and sixth in

Table 3
Summary of the percentage of similarity and normal curve statistics

Formula pair with Mosteller	Mean similarity (%)	SD similarity (%)	MPD ± SD (%)	CV, (SD/mean) (%)
DuBois and DuBois	100.95	0.80	0.95 ± 0.80	0.79
Boyd	100.28	0.17	0.28 ± 0.17	0.17
Gehan and George	99.53	0.20	0.47 ± 0.20	0.20
EPA	99.54	0.22	0.45 ± 0.22	0.22
Haycock et al	99.45	0.38	0.55 ± 0.38	0.38
Mattar	101.05	0.94	1.05 ± 0.94	0.93
Livingston and Scott	98.44	1.54	1.56 ± 1.54	1.56
Mean	99.86	0.14	0.14 ± 0.14	0.14
Yu et al	102.33	0.0	2.33 ± 0.0	0

MPD indicates mean percentage of difference. For formulas, see footnote to Table 1.

Table 4
Intervention study: effect of weight reduction on BSA and BMI

	Before	After	Δ (%)
Weight (kg)	102 ± 15	86 ± 13	−16 (−15.7)
Length (cm)	173 ± 10	173 ± 10	
BMI (kg/m^2)	34 ± 5	29 ± 5	−5 (−14.70)
Mosteller BSA (m^2)	2.21 ± 0.20	2.02 ± 0.18	−0.19 (−9.40)
DuBois and DuBois BSA (m^2)	2.14 ± 0.20	1.99 ± 0.17	−0.15 (−7.50)
Boyd BSA (m^2)	2.19 ± 0.20	2.01 ± 0.17	−0.18 (−8.95)
Gehan and George BSA (m^2)	2.23 ± 0.20	2.04 ± 0.18	−0.19 (−9.31)
EPA BSA (m^2)	2.23 ± 0.20	2.04 ± 0.18	−0.19 (−9.31)
Haycock et al BSA (m^2)	2.24 ± 0.21	2.04 ± 0.18	−0.20 (−9.80)
Mattar BSA (m^2)	2.15 ± 0.22	1.98 ± 0.18	−0.17 (−8.59)
Livingston and Scott BSA (m^2)	2.32 ± 0.23	2.08 ± 0.20	−0.24 (−11.54)
Mean BSA (m^2)	2.22 ± 0.21	2.02 ± 0.18	−0.20 (−9.90)
Yu et al BSA (m^2)	2.11 ± 0.19	1.93 ± 0.17	−0.18 (−9.33)

For formulas, see footnote to Table 1.

obese subjects. Although the BSA from Yu et al was systematically lower than Mosteller's BSA, we found a very strong correlation with Mosteller's BSA and a low RMSE. Only 3 formulas showed a lower RMSE (Boyd, Gehan and George, EPA).

The Bland and Altman plots for all comparisons are shown in Fig. 2A to I. Mosteller's formula produced higher bias at high BSA (overestimation) compared with the DuBois and DuBois formula (Fig. 2A) and Boyd's formula (Fig. 2B). Mosteller's formula also showed higher bias at high BSA (underestimation) compared with EPA's formula (Fig. 2D), the formula of Haycock et al (Fig. 2E), and the mean of the formulas (Fig. 2H). Mosteller's formula showed high bias in the reference range (overestimation as well as underestimation) compared with Mattar's formula (Fig. 2F). Compared with the formula of Yu et al (Fig. 2I), Mosteller's formula showed high bias in the higher BSA values (overestimation). Of the 1868 patients, we observed that 73 (3.9%) compared with the DuBois formula, 84 (4.5%) compared with Boyd's formula, 89 (4.8%) compared with Gehan and George's formula, 119 (6.4%) compared with EPA's formula, 85 (4.6%) compared with the formula of Haycock et al, 107 (5.7%) compared with Mattar's formula, 88 (4.7%) compared with Livingston and Scott's formula, 83 (4.4%) compared with the mean of the formulas, and 101 (5.4%) compared with the formula of Yu et al were beyond the ±1.96 SD lines. Taking into account the small bias and the limits of agreement, Mosteller's formula best fits with the formulas of Boyd and Yu et al.

Table 3 summarizes the percentage of similarity and normal curve statistics. These data confirm the close agreement between Mosteller's and Boyd's BSA. According to this approach, Mosteller's BSA fitted best with Boyd's BSA and with mean BSA, although least well with the BSA from Yu et al, although these data were most consistent (CV = 0%). Table 4 summarizes the effect of weight reduction on BMI and BSA in a random series of 7 male and 14 female (predominantly obese) patients based on the different formulas. The decrease of BSA differed between 0.15 m^2 (7.5%) (DuBois) and 0.24 m^2 (11.5%) (Livingston and Scott) for a weight reduction of 16 kg (−15.7%) and a decrease in BMI of 5 kg/m^2 (−14.7%). This change in BSA is almost 2% higher with Mosteller's formula (0.19 m^2) compared with the DuBois formula.

4. Discussion

The present study provides the first large sample of BSA in normal-weight, overweight, and obese males and females, obtained with Mosteller's formula. We found close agreement between Mosteller's BSA values and BSA values obtained with the traditional complex methods, with all correlations of 0.97 or higher, as well as with the mean BSA and with the most accurate BSA from Yu et al [15]. The weakest correlation was found with the formula of Mattar [17] and with Livingston and Scott's [10] formula. Observed differences were very small, except for Mattar's BSA and Livingston's BSA. The difference with Gehan and George's formula [8] (from which Mosteller's formula was derived) was only 1%; thus, only a slight degree of accuracy has been lost in making the equation easy to remember. The difference with the most accurate BSA from Yu et al was however almost 5%, independent of body weight, but that formula was derived in Chinese adults and is therefore maybe not applicable in a white population.

We calculated that BSA values in obese subjects were 2.74% (male) to 4.47% (female) higher with Mosteller's formula compared with the DuBois and DuBois formula. This indicates an underestimation of BSA in obese when using the DuBois and DuBois formula. This was already suggested by Livingston and Scott [10], who reported that the "DuBois-type" equations (based on weight and height) underestimate BSA in obese people. To put this in perspective, a change in BSA from 2.21 (Mosteller) to 2.14 (DuBois and DuBois) is equivalent to a weight loss of 6 kg in a man who weigh 100 kg and is 176 cm tall. On the other hand, if one does not mind a 0.11 m^2 difference (1.96 SD on mean difference in the Bland and Altman plot), then they are agreeable. Comparison with the formula of Yu et al [15] (if applicable in whites) however indicates an

overestimation of BSA with all traditional formulas. These formulas were all developed from data gathered on subjects with dominantly European origins. Although frequently applied to other racial groups, there are little data to validate their use in those of Asian or African origin. In fact, at least one study of BSA in black Nigerians suggests that they overestimate the BSA by 6% to 22% in this population [18]. The BSA formula of Yu et al, derived from 3D anthropometric scanner technology, is unfortunately only validated in Chinese adults and, therefore, this formula should be used with caution for other racial groups.

The criticism on the DuBois and DuBois formula is that it is not only based on just 9 observations, but it is also recognized as producing underestimates of BSA of up to 8% in infants [9], whereas we found up to 5% in obese adults. The nutritional status of today's population differs from that up to 1916 when the measurements were made, and a repetition of the exercise today, combined with modern statistics, resulted in a different formula [19].

The rationale for indexing physiologic parameters was that BSA proved to correlate more closely to physiologic parameters than body weight [4,20]. Krovets [20] reviewed correlations of BSA and measurements such as cardiac index (CI), renal function, and metabolic rate and concluded that only CI resulted in a consistent correlation across age groups and sex. Nowadays, CI is used widely in many hemodynamic monitoring devices as an important marker of cardiac function. Differences in BSA across the formulas would be considered of little consequence in practice. However, application of an underestimated BSA in the calculation of the CI (cardiac output/BSA) can potentially result in inadequate treatment of shock. For example, if a 150-kg, 194-cm patient were to have a cardiac output of 6 L/min, the calculated CI would be 2.2 (L · min)/m^2 if the DuBois BSA prediction were used and 2.1 (L · min)/m^2 for Mosteller's formula. Vasopressor therapy is required for a CI of 2.1 (L · min)/m^2, but not for 2.2 (L · min)/m^2. Therefore, users of BSA-predicting equations must know the conditions for which the equation is valid.

Body size is clearly associated with left ventricular dimensions and mass [21,22] Indexing of a left ventricular mass (LVM) of 181 g (magnetic resonance imaging, steady-state free precession imaging sequences) [21] in a male (104 kg, 170 cm) results in a left ventricular mass index (left ventricular mass/BSA) of 81.9 g/m^2 (Mosteller) or 84.57 g/m^2 (DuBois) and a different classification concerning the presence of left ventricular hypertrophy (left ventricular mass index >83 g/m^2), with prognostic and therapeutic implications. Increases in left ventricular mass and left ventricular hypertrophy are independent and strong predictors of cardiovascular morbidity and mortality, and BSA indexing incorporates some of the risk associated with obesity [22].

In clinical studies, BSA is used in calculating the dose in cancer chemotherapy and other drugs [23]. Its use originates from an empirical interspecies toxic dose equivalence, noted in the early experience with chemotherapy [24] and on the intuitive belief that patients with a larger BSA require more drugs to induce the same drug effects. Moreover, it is established that a correlation exists between BSA and some particular characteristics of each patient (glomerular filtration rate, blood volume, and basal metabolic rate), and certainly this provides a condition to individualize doses. However, Felici et al [25] reported that, although BSA has been routinely used as the only independent variable, BSA failed to individualize the effect of most of the agents explored. They could, however, also identify an established relationship between BSA and pharmacokinetics of a number of modern anticancer drugs, like busulfan PO, eniluracil/5-fluorouracil, gemcitabine (Gemzar, Eli Lilly, Indianapolis, IN), and paclitaxel (Taxol, Bristol-Myers Squibb, New York, NY), which are widely used to treat a variety of solid tumors [26-30]. It was found that their clearance and distribution volume were sensitive to BSA. Using Mosteller's formula in our obese patients leads to a +3.27% higher dose (70 mg) of gemcitabine (1000 mg/m^2) and a 3.27% higher dose (12.25 mg) of paclitaxel (175 mg/m^2) compared with the DuBois and DuBois BSA method. This beneficial effect is however small when taking into account the practice of dose rounding of chemotherapy to the nearest vial size, without any negative clinical effect and given the significant interpatient pharmacokinetic and pharmacodynamic variability for most cytotoxics [31]. This could be explained by the fact that the dose-toxicity curve for most common chemotherapies is not steep enough to make a biologic difference in dosing [32]. Although body size dosing is intended to prevent overdosing, unrecognized underdosing is more common and may occur in 30% or more of patients receiving standard regimen [33]. Those patients who are underdosed are at risk for a significantly reduced anticancer effect. Therefore, a more accurate BSA calculation could be beneficial.

As said, individualization of drug doses that use measures of body size might reduce variability in drug exposure if drug disposition is related to physiologic processes that do vary with body size, such as cardiac output or glomerular filtration rate [34]. Recently, these basic principles have been, in part, questioned by a study where a poor relation between BSA and glomerular filtration rate was found [35]. Some authors point out that drug pharmacokinetics appears largely unexplained by variability in BSA [25,36]. Because individuals have a variable ability to metabolize and eliminate drugs, the same dose of drug will have a different effect among individuals. Factors involved are variation in drug absorption, drug metabolism, and variability between patients in body composition. Age-induced subclinical renal, hepatic, and cardiac dysfunction may alter drug disposition. Tumor cell infiltration, metastases, or paraneoplastic mechanisms may also alter basal metabolism or organ function. In addition to the size-independent factors that may limit use of BSA to calculate chemotherapeutic drug dose, drug-dependent

factors such as spontaneous degradation may limit its usefulness [37]. Body surface area fails to take into account this interpatient variation in pharmacokinetics for most cytotoxic drugs. However, disposition of some selected drugs has the unique feature in that the interindividual variability in exposure is greatly reduced by adjusting the dose to BSA. Therefore, arguments to abandon the current way of dose calculation on BSA are lacking for these specific molecules [26-28,38]. Moreover, until there is a better method, BSA will serve as a guide to the dosage initially administered because there has been more than 40 years of experience with this method and "old habits die hard" [33].

Accurate calculation is also very important in research experiments. Pinkel [4] showed that there was a similarity in dosage per unit of surface area of methotrexate, mechlorethamine, actinomycin D, and thio-N, N', N-triethylenephosphamide (TEPA) for 3 species of laboratory animals and man. In addition, it was demonstrated that the maximum tolerated dose of 18 chemotherapeutic agents was nearly equivalent in man and 5 animal species when dose was calculated on a BSA basis [24]. Thus, relating dose in man to dose in animal species is simplified if dosages are reported per unit of BSA. This point was however countered by Felici et al [25] who found that in animals, doses are usually tested until the 10% of the lethal dose (LD_{10}) is reached, and in human phase I studies, the first dose used is one tenth of the LD_{10}.

Body surface area is also more and more recognized as an outcome predictor: a very small BSA was found an independent predictor of worse 0- to 12-year mortality after coronary artery bypass surgery [39], whereas BSA can predict the effect of lamivudine therapy for chronic hepatitis B. The authors reported that even small differences in BSA could significantly influence the effect of the lamivudine treatment [40].

The present study shows consistently and significantly higher BSA values in males than in females (in normal-weight subjects as well as in overweight and obese subjects), although males demonstrated lower BMI. We also demonstrated that weight reduction (−16 kg or −15.7%) leads to a more pronounced change in BMI (−14.7%) than in BSA (−9.4%). This could also be understood from the point that obese subjects concentrate their (extra) weight disproportionately in the trunk, and the BSA decreases less as a result [41]. Because males are statistically taller than females, an obese man of 105 kg and 195 cm will have a BSA (Mosteller) of 2.38 m^2, whereas an obese woman of the same weight, but 168 cm, will have a BSA of 2.21 m^2. With the DuBois formula, this would be 2.37 m^2 in male and 2.13 m^2 in female. In this case of an obese female, the use of the DuBois formula should lead to a 3.6% lower drug dosage compared with Mosteller's formula. The female will receive a 10% (DuBois) or a 7% (Mosteller) lower drug dosage than the male with an equal weight. These facts demonstrate that BSA expresses another dimension than BMI and is not just a weight index. It could be speculated that BSA is linked to differences in body fat distribution. No attempts to prove this have been made in this study, as no data were obtained for the distribution in body fat. Systematically lower BSA in female patients can also be caused by a group effect because of their smaller stature. This does not mean however that a long-term underdosing of anticancer drugs takes place in an individual female: a female of 105 kg and 168 cm will have the same BSA than a male with the same weight and height. Because the differences in BSA between Mosteller's formula and DuBois formula are limited to 5% in obese females, taken into account the use of dose rounding and interpatient pharmacokinetics, its clinical influence is probably negligible.

Although this study included calculations on a large group of subjects, there were no actual BSA measurements using a criterion method such as 3D whole-body scanner and is therefore not a validation study. We tried however to overrule this by implementing the mean BSA based on the traditional formulas as well the BSA calculated from the 3D-derived formula of Yu et al. Moreover, we do not really know which is the exact BSA. There is a presumption that the formulas used are accurate or, at the very least, constant in error. With obesity, weight increases without a proportional increase in height. Consequently, it is possible that the DuBois-type predicting formulas, including height coefficients, could systematically miscalculate BSA for obese patients. Because many clinically important measurements are indexed to BSA, systematic errors in BSA estimation can adversely affect the clinical care of obese patients. Therefore, because BSA values differ more in the obese population, these formulas have to be used with caution.

Mosteller's formula was already validated for use in children. Lam and Leung [12] calculated the BSA of 168 children between 1 month and 14 years of age using Mosteller's formula and confirmed Mosteller's formula is equally applicable to children. Therefore, taking into account the present data, with limited and clinically acceptable differences between the evaluated formulas, Mosteller's formula can be applied in the range from children to adults and can be preferred because of its simplicity.

5. Conclusions

Our recommendation is that the formula of Mosteller deserves to be used as the first choice in clinical research and practice. It combines an accurate BSA calculation with ease of use and is applicable in normal-weight, overweight, and obese adults. Accuracy studies in whites with 3D one-pass whole-body scanning are needed.

References

[1] Cosolo WC. Lean body mass, body surface area and epirubicin kinetics. Anticancer Drugs 1994;5:293-7.

[2] Daniels SR. Indexing left ventricular mass to account for differences in body size in children and adolescents without cardiovascular disease. Am J Cardiol 1995;76:699-701.
[3] Hallynck EC, Soepp HH, Thomis JA, Boelaept JA, Daneels R, Dettli L. Should clearance be normalized to body surface area or to lean body mass? Br J Clin Pharmacol 1981;11:523-6.
[4] Pinkel D. The use of body surface area as a criterion of drug dosage in cancer chemotherapy. Cancer Res 1958;18:853-6.
[5] US Environmental Protection Agency (EPA). Development of statistical distributions or ranges of standard factors used in exposure assessments. EPA/600/8-85-010. Washington (DC): Office of Health and Environmental Assessment; 1985.
[6] Boyd E. The growth of the surface area of the human body. Minneapolis: University of Minnesota Press; 1935.
[7] DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863-71.
[8] Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemother Rep 1970;54:225-35.
[9] Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. J Pediatr 1978;93:62-6.
[10] Livingston EH, Scott L. Body surface area prediction in normal-weight and obese patients. Am J Physiol Endocrinol Metab 2001; 281:E586-91.
[11] Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987;317:1098.
[12] Lam TKK, Leung DTY. More on simplified calculation of body-surface area. N Engl J Med 1988;318:1130.
[13] Briars GL, Bailey BJR. Surface area estimation: pocket calculator versus nomogram. Arch Dis Child 1994;70:246-7.
[14] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307-10.
[15] Yu CY, Lo YH, Chiou WK. The 3D scanner for measuring body surface area: a simplified calculation in the Chinese adult. Appl Ergon 2003;34:273-8.
[16] Scott LE, Galpin JS, Glencross DK. Multiple method comparison: statistical model using percentage similarity. Cytometry B Clin Cytom 2003;54B:46-53.
[17] Mattar JA. A simple calculation to estimate body surface area in adults and its correction with the Dubois formula. Crit Care Med 1989;17: 846-7.
[18] Nwaye LO. Body surface area of Africans: a study based on direct measurements of Nigerian males. Hum Biol 1989;61:439-57.
[19] Shuter B, Aslani A. Body surface area: Du Bois and Du Bois revisited. Eur J Appl Physiol 2000;82:250-4.
[20] Krovetz LJ. The physiologic significance of body surface area. Med Prog 1965;67:841-62.
[21] Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Res 2003;17:323-9.
[22] Foppa M, Duncan BB, Rohde LEP. Echocardiography-based left ventricular mass estimation. How should we define hypertrophy? Cardiovasc Ultrasound 2005;3:17 (http://www.cardiovascularultrasound.com/content/3/1/17).
[23] Siber GR, Smith AL, Levin MJ. Predictability of peak serum gentamicin concentration with dosage based on body surface area. J Pediatr 1979;94:135-8.
[24] Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE. Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey, and man. Cancer Chemother Rep 1966;50: 219-44.
[25] Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. Eur J Cancer 2002;38:1677-84.
[26] Baker SD, Diasio RB, O'Reilly S, Lucas VS, Khor SP, Sartorius SE, et al. Phase I and pharmacologic study on oral fluorouracil on a chronic daily schedule in combination with the dihydropyrimidine dehydrogenase inactivator eniluracil. J Clin Oncol 2005;18: 915-26.
[27] Gibbs JP, Gooley T, Corneau B, Murray G, Stewart P, Appelbaum FR, et al. The impact of obesity and disease on busulfan oral clearance in adults. Blood 1999;93:4436-40.
[28] Smorenburg CH, Sparreboom A, Bontenbal M, Stoter G, Nooter K, Verweij J. Randomized cross-over evaluation of body surface area-based dosing versus flat-fixed dosing of paclitaxel. J Clin Oncol 2005;21:197-202.
[29] Allerheiligen S, Johnson R, Hatcher B. Gemcitabine pharmacokinetics are influenced by gender, body surface area (BSA), and duration of infusion. Proc Am Soc Clin Oncol 1994;339 [abstract].
[30] Storniolo AM, Allerheiligen SR, Pearce HL. Preclinical, pharmacologic, and phase I studies on gemcitabine. Semin Oncol 1997; 2(Suppl 7):S7-S2.
[31] Dooley MJ, Singh S, Michael M. Implications of dose rounding of chemotherapy to the nearest vial size. Support Care Cancer 2004;12: 653-6.
[32] Gelman RS. Actual vs ideal weight in the calculation of surface area: effects on dose of 11 chemotherapy agents. Cancer Treat Rep 1987; 71:907-11.
[33] Gurney H. How to calculate the dose of chemotherapy. Br J Cancer 2002;86:1297-302.
[34] Grochow LB, Baraldi C, Noe D. Is dose normalization to weight or body surface area useful in adults? J Natl Cancer Inst 1990;21:323-5.
[35] Dooley MJ, Poole SG. Poor correlation between body surface area and glomerular filtration rate. Cancer Chemother Pharmacol 2000;46: 523-6.
[36] Vu Th. Standardization of body surface area calculations. http://www.halls.md/bsa/bsaVuReport.htm [UnPub].
[37] Alberts DS, Chang SY, Chen HSG, Moon TE, Evans TL, Furner RL, et al. Kinetics of intravenous melphalan. Clin Pharmacol Ther 1979;26:73-80.
[38] Baker SD, Wirth M, Statkevich P, Reidenberg P, Alton K, Sartorius SE, et al. Absorption, metabolism, and excretion of 14C-temozolomide following oral administration to patients with advanced cancer. Clin Cancer Res 1999;5:309-17.
[39] Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Effects of obesity and small body size on operative and long-term outcomes of coronary artery bypass surgery: a propensity-matched analysis. Ann Thorac Surg 2005;79:1976-86.
[40] Nakamuta M, Kotoh K, Tanabe Y, Kajiwara E, Shimono J, Masumoto A, et al. Body surface area is an independent factor contributing to the effects of lamivudine treatment. Hepatol Res 2005;31:13-7.
[41] Bailey BJR, Briars GL. Estimating the surface area of the human body. Stat Med 2005;15:1325-32.