Scaling of computed tomography body composition to height: relevance of height-normalized indices in patients with colorectal cancer

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Abstract

Background   Body weight scales to height with a power of ≈ 2 (weight/height^2), forming the basis of body mass index (BMI). The corresponding scaling of body composition measured by abdominal computed tomography (CT) to height has not been established. The objective of this analysis was to quantify the scaling of body composition measured by a single-slice axial abdominal CT image (skeletal muscle, and visceral, subcutaneous, and total adipose tissue) to height in patients with colorectal cancer (CRC).

Methods   This cross-sectional study included non-Hispanic white males and females, aged 18–80 years, who were diagnosed with stage I–III CRC at an integrated health care system in North America between January 2006 and December 2011. Body composition was measured by a single-slice axial CT image of the third lumbar vertebra and analysed with a semi-automated threshold segmentation procedure. Allometric regression models were used to quantify height scaling powers ($\beta \pm$ standard error) for each body composition measure, adjusted for age, for males and females. An interaction test was used to determine if height scaling powers were statistically significantly different between males and females.

Results   Among 2036 subjects, the mean (standard deviation) age was 64 ± 11 years, 1008 (49.5%) were female, and the mean (standard deviation) BMI was 27.9 ± 5.4 kg/m^2. Powers for skeletal muscle area were 1.06 ± 0.12 for males and 0.80 ± 0.12 for females ($P = 0.049$). Powers for visceral adipose tissue area were 1.81 ± 0.64 for males and 0.57 ± 0.79 for females ($P = 0.16$). Powers for subcutaneous adipose tissue area were 2.04 ± 0.42 for males and 0.81 ± 0.45 for females ($P = 0.056$). Powers for total abdominal adipose tissue area were 1.80 ± 0.46 for males and 0.76 ± 0.50 for females ($P = 0.20$).

Conclusions   Body composition measured by single-slice axial abdominal CT, particularly muscle area, scales to height with age-adjusted powers that are different than 2 and are distinct between males and females. These observations may have implications for the development of height-adjusted body composition indices in patients with cancer.

Keywords   Adiposity; Allometric analysis; Height; Scaling powers; Skeletal muscle; Obesity; Nutritional assessment

Introduction

For two centuries, it has been recognized that adult body weight increases proportionally to the square of height,[1] forming the basis of body mass index (BMI; weight/ height[2]).[2] Among all weight-to-height indices, BMI has the strongest correlation with measures of adiposity.[3] Given its relative ease of measure, BMI is ubiquitous in public health and medicine.[4] However, BMI has been subject to criticism within the field of oncology,[5,6] principally because of the unexpected observation that a higher BMI is associated with a lower risk of death among patients with various types and stages of cancer.[7] This observation may be explained, in part, by the inability of BMI to differentiate skeletal muscle from adipose tissue,[8] which exert opposing prognostic effects.[9,10]

Multi-slice whole-body computed tomography (CT) and magnetic resonance imaging (MRI) are gold-standard techniques to quantify skeletal muscle and adipose tissue.[11] Skeletal muscle and adipose tissue mass, measured using whole-body MRI, scale to height with powers of ≈ 2.[12] A single-slice axial image at the third lumbar vertebra is a surrogate for whole-body skeletal muscle and adipose tissue volume.[13–15] At the time of cancer diagnosis, CT or MRI is often used to characterize the primary tumour and identify distant metastatic foci.[16] Due to the abundance and accessibility of clinically acquired abdominal CT images in patients with cancer, use of surrogate single-slice approach is widespread.[17]

In a seminal analysis published more than a decade ago, skeletal muscle area, derived from a single-slice axial image, was scaled to height with a power of 2 in a cohort of 250 patients with cancer.[18] Since then, scaling of skeletal muscle and adipose tissue area to the square of height (e.g. cm^2/m^2) has become common in oncology cohort studies.[19,20] Despite widespread use, however, the optimal scaling of skeletal muscle and adipose tissue obtained from a single-slice axial CT image to height remains unspecified. A recent analysis conducted in adults under consideration for kidney donation reported that scaling skeletal muscle area to height with a power of ≈ 1 (e.g. cm^2/m^1), produced less biased estimates than a power of 2 (e.g. cm^2/m^2).[21] However, the degree to which these prior findings (reference[21]) generalize to other populations, such as patients with cancer, and other tissue compartments, such as visceral and subcutaneous adipose tissue, is unknown.

Determining the optimal scaling of skeletal muscle and adipose tissue obtained from a single-slice axial abdominal CT image to height has the potential to inform the analysis of prognostic modelling studies of body composition in oncology. The Colorectal Cancer-Sarcopenia And Near-Term Survival (C-SCANS) cohort provided the opportunity to test the hypothesis that the scaling of skeletal muscle and adipose tissue obtained from a single-slice axial abdominal CT image to height would be different from a power of 2 and distinct between males and females.

Methods

Study cohort and design

The C-SCANS cohort was derived from the Kaiser Permanente Northern California (KPNC) cancer registry, with ascertainment of all males and females, aged 18–80 years, who were diagnosed with stage I–III invasive colorectal cancer (CRC) and underwent surgical resection with curative intent between January 2006 and December 2011 (n = 4465). We excluded subjects without abdominal or pelvic CT images (n = 693), subjects without valid measures of body mass (n = 411), and subjects whose CT images were unreadable because of poor image quality (n = 207). Recognizing that body composition varies among racial and ethnic groups,[22,23] this cross-sectional analysis was restricted to subjects who self-reported their race as non-Hispanic white (n = 2036). A waiver of written informed consent was obtained by the study investigators. This study was approved by the KPNC institutional review board.

Body composition

Height (cm) and weight (kg) were measured at the time of diagnosis. BMI was calculated as kilograms per square metre of height (kg/m^2). Body composition was measured with CT images originally collected for diagnostic purposes using standard clinical protocols. A single-slice axial CT image of the third lumbar vertebra (L_3) was identified and isolated for body composition analysis. Tissue cross-sectional areas at L_3 correlate with whole-body skeletal muscle (R^2 = 0.86) as well as visceral (R^2 = 0.94) and subcutaneous adipose tissue (R^2 = 0.91) volumes in males and females.[13–15] Tissues were quantified with a semi-automated procedure (sliceOmatic, V5.0, TomoVision, Montreal, Canada) using Hounsfield unit thresholds of -29 to 150 for skeletal muscle tissue, -150 to -50 for visceral adipose tissue, and -190 to -30 for subcutaneous adipose tissue.[24] Cross-sectional areas were calculated for each tissue compartment by summing tissue pixels and multiplying by the pixel surface area. Total abdominal adipose tissue area was calculated as the sum of the visceral and subcutaneous adipose tissue areas. For quality control and reproducibility, a randomly selected subsample of 50 CT images were analysed by two trained staff, and the remaining images were analysed by a single trained staff. The coefficients of variation for skeletal muscle area, visceral adipose tissue area, and subcutaneous adipose tissue area were 1.2%, 1.1%, and 2.7%, respectively.[25] Staff who analysed CT images were blinded to study objective.

Statistical methods

The age-adjusted relationship between body composition measures with height can be described by the allometric model $Y = \alpha X^{\beta} Z^{\gamma}$, where Y is the outcome, X is height, β is the scaling exponent (e.g. power), Z is the covariate for age with power γ, and α is the proportionality constant.[26] The allometric model can be expressed in logarithmic form as $\log_e Y = \log_e \alpha + \beta \log_e X + \gamma \log_e Z + \varepsilon$, where ε is the error term. Application and interpretation of allometric regression models have been described in detail.[2,27–30] Regression models were fit separately for males and females. An interaction term between subject sex and height was entered into a regression model that consolidated both sexes to determine if height scaling powers were statistically significantly different between males and females. Four coefficients were estimated for each multiple regression model: α (intercept), β (height), γ (age), and R^2 with corresponding P values. Regression coefficients are presented with corresponding standard errors. A t-test was used to compare baseline demographic and anthropometric differences in males and females; between-group differences are reported as the absolute means and standardized means (e.g. Cohen's d). A two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Among 2036 subjects, 1008 (49.5%) were female (*Table 1*). The mean (standard deviation) age was 64 ± 11 years, body weight was 82.1 ± 18.8 kg, height was 171.0 ± 0.23 cm, and BMI was 27.9 ± 5.4 kg/m². As compared with females, males were statistically significantly younger (Δ: −1.1 ± 0.49 years; $P = 0.024$) and taller (Δ: 15.2 ± 0.31 cm; $P < 0.001$), with a larger body weight (Δ: 17.0 ± 0.75 kg; $P < 0.001$), BMI (Δ: 0.77 ± 0.24 kg/m²; $P = 0.001$), skeletal muscle area (Δ: 57.0 ± 1.08 cm²; $P < 0.001$), visceral adipose tissue area (Δ: 106.6 ± 4.51 cm²; $P < 0.001$), smaller subcutaneous adipose

tissue area (Δ: −42.5 ± 4.59 cm²; $P < 0.001$), and larger total adipose tissue area (Δ: 64.2 ± 7.98 cm²; $P < 0.001$).

Allometric analyses

Body weight
Among males, body weight scaled to height with a power of 2.11 ± 0.12 (*Table 2*), which was not different from 2 ($P = 0.38$); age was a negative predictor of body weight (−0.002 ± 0.001; $P < 0.001$). Among females, body weight scaled to height with a power of 1.49 ± 0.16, which was different from 2 ($P = 0.002$); age was a negative predictor of body weight (−0.002 ± 0.001; $P < 0.001$). The difference in powers between males and females was statistically significant ($P = 0.003$).

Skeletal muscle area
Among males, skeletal muscle area scaled to height with a power of 1.06 ± 0.12, which was different from 2 ($P < 0.001$); age was a negative predictor of skeletal muscle area (−0.006 ± 0.001; $P < 0.001$). Among females, skeletal muscle area scaled to height with a power of 0.80 ± 0.12, which was different from 2 ($P < 0.001$); age was a negative predictor of skeletal muscle area (−0.005 ± 0.001; $P < 0.001$). The difference in powers between males and females was statistically significant ($P = 0.049$).

Visceral adipose tissue area
Among males, visceral adipose tissue area scaled to height with a power of 1.81 ± 0.64, which was not different from 2 ($P = 0.77$); age was a positive predictor of visceral adipose tissue (0.014 ± 0.002; $P < 0.001$). Among females, visceral adipose tissue area scaled to height with a power of 0.57 ± 0.79, which was not different from 2 ($P = 0.072$); age was a positive predictor of visceral adipose tissue area (0.018 ± 0.003; $P < 0.001$). The difference in powers between males and females was not statistically significant ($P = 0.16$).

Subcutaneous adipose tissue area
Among males, subcutaneous adipose tissue area scaled to height with a power of 2.04 ± 0.42, which was not different from 2 ($P = 0.93$); age was a negative predictor of subcutane-

Table 1 Participant characteristics

	Male ($n = 1028$)	Female ($n = 1008$)	Difference (Δ)	Standardized difference (d)
Age, years	63.3 ± 0.34	64.4 ± 0.35	−1.1 ± 0.49[a]	−0.10
Weight, kg	90.5 ± 0.52	73.6 ± 0.53	17.0 ± 0.75[a]	1.00
Height, cm	178.5 ± 0.22	163.3 ± 0.21	15.2 ± 0.31[a]	2.18
Body mass index, kg/m²	28.3 ± 0.14	27.5 ± 0.19	0.77 ± 0.24[a]	0.14
Muscle area, cm²	169.8 ± 0.90	112.8 ± 0.59	57.0 ± 1.08[a]	2.34
Visceral adipose area, cm²	215.8 ± 3.72	109.2 ± 2.53	106.6 ± 4.51[a]	1.05
Subcutaneous adipose area, cm²	186.3 ± 2.86	228.8 ± 3.60	−42.5 ± 4.59[a]	−0.41
Total abdominal adipose area, cm²	402.1 ± 5.6	337.9 ± 5.1	64.2 ± 7.98[a]	0.36

All values are means ± standard errors.
[a]$P < 0.05$.

Table 2 Results of allometric analyses

| | Male (n = 1028) | | | | Female (n = 1008) | | | |
| | Power | | | | Power | | | |
	Height	Age	Intercept	R^2	Height	Age	Intercept	R^2
Weight, kg	2.11 ± 0.12[b]	−0.002 ± 0.001	−6.34 ± 0.66	0.24	1.49 ± 0.16[a,b]	−0.002 ± 0.001	−3.19 ± 0.84	0.10
Muscle area, cm^2	1.06 ± 0.12[a,b]	−0.006 ± 0.001	0.03 ± 0.60	0.26	0.80 ± 0.12[a,b]	−0.005 ± 0.001	0.94 ± 0.59	0.19
Visceral adipose area, cm^2	1.81 ± 0.64	0.014 ± 0.002	−5.15 ± 3.17	0.04	0.57 ± 0.79	0.018 ± 0.003	0.22 ± 4.09	0.04
Subcutaneous adipose area, cm^2	2.04 ± 0.42	−0.004 ± 0.001	−5.21 ± 2.17	0.03	0.81 ± 0.45[a]	−0.006 ± 0.002	1.51 ± 2.33	0.02
Total abdominal adipose area, cm^2	1.80 ± 0.46	0.005 ± 0.002	−3.76 ± 2.38	0.02	0.76 ± 0.50[a]	0.001 ± 0.002	1.72 ± 2.58	0.01

The model for each outcome variable has the general form $\log_e Y = \log_e \alpha + \beta \log_e X + \gamma \log_e Z + \varepsilon$, where ε is the error term with age as an adjusting covariate. All values are means ± standard errors.
[a] $P < 0.05$, compared with scaling power of 2.
[b] $P < 0.05$, comparing male vs. female.

ous adipose tissue (−0.004 ± 0.001; P = 0.01). Among females, subcutaneous adipose tissue area scaled to height with a power of 0.81 ± 0.45, which was different from 2 (P = 0.009); age was a negative predictor of subcutaneous adipose tissue area (−0.006 ± 0.002; P = 0.001). The difference in powers between males and females was not statistically significant (P = 0.056).

Total abdominal adipose tissue area

Among males, total abdominal adipose tissue area scaled to height with a power of 1.80 ± 0.46, which was not different from 2 (P = 0.66); age was a positive predictor of total abdominal adipose tissue area (0.005 ± 0.002; P = 0.002). Among females, total abdominal adipose tissue area scaled to height with a power of 0.76 ± 0.50, which was different from 2 (P = 0.014); age was not a predictor of total abdominal adipose tissue area (0.001 ± 0.002; P = 0.73). The difference in powers between males and females was not statistically significant (P = 0.20).

Discussion

The major finding from this analysis is that body composition, derived from a single-slice axial CT image at the third lumbar vertebra, scales to height with age-adjusted powers that are different than 2 and are distinct between males and females. To facilitate unbiased comparisons across a range of statures, an important property of a body composition index measure is independence from height.[31] Measures of mass, such as body mass, skeletal muscle mass, and adipose tissue mass, scale to height with age-adjusted powers ≈2.[2,12] However, our analyses demonstrate that body composition area, as measured by a single slice abdominal CT image, particularly muscle area, may not possess similar scaling properties as the measure for which it serves as a surrogate (e.g. skeletal muscle mass). The findings from the current analysis are consistent with a recent report in healthy adults under consideration for kidney donation.[21] These findings may have important implications for the many prognostic modelling studies in oncology that calculate body composition index measures using a single-slice axial CT image.

To create a skeletal muscle index that is independent from height, our analyses indicate that skeletal muscle area should be scaled to height with a power of 1.08 for males (e.g. cm^2/m$^{1.08}$) and 0.80 for females (e.g. cm^2/m$^{0.80}$). When scaled in this manner (*Figure* 1), skeletal muscle is statistically independent from height in males (r = −0.006; P = 0.86) and females (r = −0.003; P = 0.92). When skeletal muscle area is scaled to a power of 2, as commonly performed in prognostic modelling studies in oncology,[18] the index remains statistically correlated with height in males (r = −0.25; $P < 0.001$) and females (r = −0.31; $P < 0.001$). Our data indicate that scaling
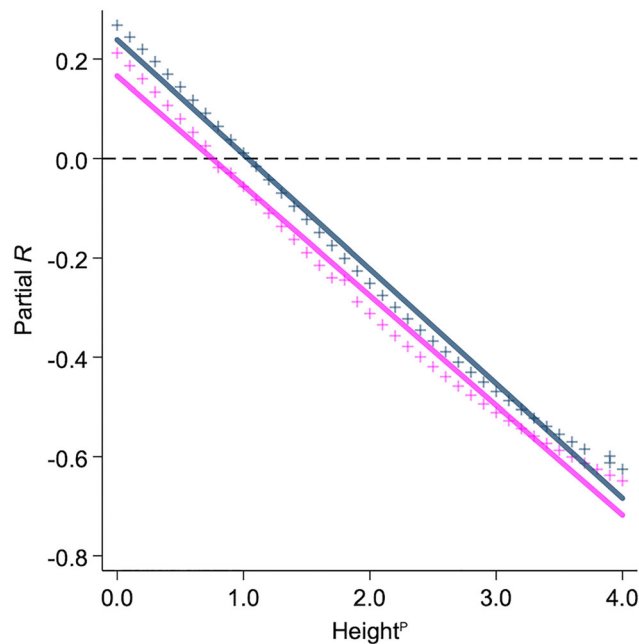
Figure 1 Age-adjusted partial correlation coefficients for the regression of muscle area/height^P compared with height for values of p, ranging from 0.0 to 4.0 in increments of 0.1. Simple linear regression analysis, the exponent of height, was used to generate the lines $y = -3.96 + 1.04$ ($R^2 = 0.99$, $P < 0.001$) for males (navy blue) and $y = -4.05 + 0.79$ ($R^2 = 0.99$, $P < 0.001$) for females (magenta). The regression line crosses the x axis at powers of 1.04 and 0.79 for males and females, respectively. Height^P values greater than or less than the values that cross the x axis will produce muscle area indexes that correlate positively or negatively with height, respectively.

skeletal muscle area to a power of 2 does not achieve the intended purpose of statistical independence from height.

There are several potential consequences of scaling body composition to powers that do not achieve statistical independence from height. Using skeletal muscle as an example, an index that is statistically significantly negatively correlated with height will be more likely to classify subjects with taller statures with low muscle (e.g. sarcopenia) using a fixed threshold value.[21] If height is associated with death,[32,33] using such indices becomes difficult to interpret and may result in effect size estimates that are incorrect or misleading. If the misclassification is nondifferential, the result would be effect size estimates that are biased towards the null. Conversely, if the misclassification is differential, the effect size estimates may be biased towards or away from the null.

In contrast to skeletal muscle area, adipose tissue area (e. g. visceral, subcutaneous, and total) scaled less consistently to height. Similar patterns have been described when fat mass is measured with MRI or dual-energy X-ray absorptiometry.[12] The reasons are not certain, but adipose tissue is characterized by its sensitivity to expand in response to surplus energy through adipocyte hypertrophy.[34] Sex differences in adipose tissue distribution and metabolic plasticity may obscure correlations of adipose tissue area and height in males and females.[12,35]

There are several important limitations of this study. The principal limitation is the focus on patients with CRC, and it

is unknown if our results generalize to other cancer sites. Our study quantified body composition at the L_3 anatomical landmark from clinically acquired CT; therefore, these findings may not apply to studies that quantify body composition at other anatomical landmarks or use other imaging modalities, such as MRI. Age and BMI are positively associated with incident CRC.[36] All of our regression analyses were age adjusted; however, due to the limited age range (e.g. $n = 47$ under age 40 years), we were unable to determine if height powers meaningfully varied by age. Cohorts with large sample sizes across the age spectrum may be able to address this limitation. Our study included a limited number of subjects with low BMI (e.g. $n = 34$ with BMI < 18.5 kg/m^2), and consideration should be given regarding how our findings may apply to subjects who are underweight. Our analysis of scaling powers for body mass in females was statistically significantly smaller than 2 (1.49 ± 0.16; $P = 0.002$), suggesting a possible bias that may be the result of taller females in our sample having a larger body weight than in the general population. This is not surprising, as taller height and heavier body weight are both risk factors for incident CRC[37]; future studies that measure total body fat percentage may offer additional insight on this issue. Our analysis was restricted to subjects who self-reported as non-Hispanic white race, and the generalizability of our findings to the broader diverse population warrant additional study.

There are several important strengths of this study. The principal strength is the large population-based sample size.

The large sample size offered sufficient statistical power to identify associations by male and female subgroups. Our analysis included multiple measures of body composition, including skeletal muscle area, and visceral, subcutaneous, and total abdominal adipose tissue area.

In summary, body composition measured by single-slice axial abdominal CT, particularly muscle area, scales to height with age-adjusted powers that are different than 2 and are distinct between males and females. These observations have implications for the development of height-adjusted body composition indices in patients with cancer. Scaling skeletal muscle area to height with a power of 2, the most common index (e.g. cm^2/m^2), to identify patients with sarcopenia may result in misclassification and biased estimates in prognostic modelling studies. Considering the integration of these new findings into prognostic modelling studies offers the potential to strengthen the rigour of statistical analyses and further substantiate the importance of body composition in oncology.[17]

Acknowledgements

Conflict of interest

Funding

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