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FULL PAPER

New exponential functions based on CT density to estimate the percentage of liver that is fat

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Objective: In fluorine-18 fludeoxyglucose positron emission tomography/CT, hepatic standardized uptake value (SUV) is reduced through “signal dilution” by hepatic fat. The maximum SUV (SUV_{max}) is less affected than the mean SUV (SUV_{mean}), therefore SUV_{max}/SUV_{mean} correlates with hepatic fat. The SUV can be corrected for signal dilution using an equation relating CT density (CTD) to % fat. The objective was to exploit the relationship between SUV indices and CTD to assess the validity of two previously published equations (one linear and one sigmoid) for estimating %fat from CTD and two new exponential equations.

Methods: Study population comprised 465 patients having routine fluorine-18 fludeoxyglucose positron emission tomography/CT. The SUV_{max} , SUV_{mean} and CTD were measured from a 3-cm-diameter region of interest over the liver. The exponential equations assumed that 100% fat corresponds to CTD of -50 or -100 HU. The proportion of

liver occupied by fat (P_F) was estimated from all four equations. Then fat-corrected SUV_{mean} is $SUV_{mean}/(1 - P_F)$. The ideal equation should give SUV_{mean} approaching but not exceeding SUV_{max} and give fat-corrected SUV_{mean}/SUV_{max} that shows no correlation with CTD.

Results: The linear equation failed at CTD values exceeding 55.8 HU because it gave negative P_F values. Moreover, fat-corrected SUV_{mean}/SUV_{max} still correlated with CTD. The sigmoid equation grossly overcorrected SUV_{mean} at low CTD. The exponential equations abolished the correlation between fat-corrected SUV_{mean}/SUV_{max} and CTD.

Conclusion: The sigmoid equation is unsuitable for estimating %fat from CTD. The linear equation performed well, but the exponential equation assuming that 100% fat corresponds to -50 HU performed best.

Advances in knowledge: Improved (exponential) equations to estimate hepatic fat from hepatic CTD.

INTRODUCTION

CT density (CTD) is a marker of hepatic fat.^{1,2} At least two previous studies have described equations that relate CTD to hepatic fat content, expressed as the proportion of the liver that is fat (P_F). The first of these was developed by Ricci et al³ and is as follows

$$P_F = (55.8 - CTD)/170 \quad (1)$$

This is a linear equation and therefore fails when CTD exceeds 55.8 HU because P_F becomes negative, even though such values of CTD are not uncommon. Any linear equation will potentially run into the same problem of negative values, therefore the appropriate equation for fat estimation will be non-linear.

Accordingly, the second published equation is a sigmoid equation, which was developed by Kodama et al⁴ and is as follows

$$P_F = \exp\{-\exp[(0.051 \cdot CTD) - 0.915]\} \quad (2)$$

These two equations give strikingly different estimates for hepatic fat (Figure 1). The sigmoid equation [Equation (2)] generates a wider range of P_F values and appears questionable at low and high values of CTD. Thus, it gives values of %fat that appear too high for modestly reduced CTD (e.g. 33% fat when CTD is 20 HU) and %fat values too low when CTD is high (e.g. 0% fat when CTD is 60 HU). On the other hand, the linear equation [Equation (1)] may underestimate hepatic fat when CT density is very low (Figure 1) and gives non-sensical negative values when CTD is high. These considerations of P_F at extreme CT densities suggest that the equation that best describes the relationship between hepatic fat and CTD may be exponential.

In positron emission tomography (PET)/CT studies of hepatic steatosis aiming to determine the influence of steatosis on hepatic metabolic function, measured as the standardised uptake value (SUV), Keramida et al⁵ used Equation (1) to

correct the hepatic fluorine-18 fludeoxyglucose (^{18}F -FDG) signal from lean tissue for the “dilutional” effect of hepatic fat, into which they assumed ^{18}F -FDG did not significantly penetrate. They proposed that the mean SUV based on a 3-cm region of interest (ROI) over the right lobe (SUV_{mean}) is more influenced by this dilution than maximum voxel SUV (SUV_{max}) because liver fat is heterogeneously distributed.⁶ Thus, SUV_{max} is preferentially based on a voxel in a relatively fat-free area. Accordingly, they found a significant inverse relationship between CTD and the ratio, $\text{SUV}_{\text{max}}/\text{SUV}_{\text{mean}}$,⁷ which they suggested is a marker of hepatic fat. The correction for fat was achieved by dividing SUV_{mean} by the proportion of liver that is lean, which is $1 - P_F$.

Exploiting the effect of hepatic fat on SUV_{mean} , the purpose of our study was to compare the validity of Equations (1) and (2) by examining the values of corrected SUV_{mean} that they respectively generate. Thus, assuming that hepatic SUV_{mean} is less than SUV_{max} in fatty liver because of signal dilution by fat, the ideal equation should give fat-corrected SUV_{mean} close to, but not exceeding, SUV_{max} and, at the same time, abolish the relationship that exists between the ratio $\text{SUV}_{\text{max}}/\text{SUV}_{\text{mean}}$ and CTD. Bearing in mind that a linear equation is intuitively unsuitable, we used the relationships between SUV_{mean} , SUV_{max} and CTD as tools to explore the utility of non-linear equations, including new exponential equations, from which to estimate P_F from CTD and compare with Equation (1).

METHODS AND MATERIALS

Patients

The population studied, comprising 465 patients, was a combination of 3 separate populations, which formed the cohorts for previously published studies.^{5,7–9} They were all referred for clinically indicated ^{18}F -FDG PET/CT mainly for cancer management. All patients attending our PET/CT unit are asked to give permission for use of their studies to be used anonymously for research purposes (a practice approved by our institutional review board), and all did so.

Imaging

The PET/CT imaging protocol is described in full elsewhere.^{5,7–9} In brief, PET/CT was performed with unenhanced CT-based attenuation correction using a Siemens Biograph 64-slice PET scanner with immediate non-enhanced CT scanning (120 kVp/50 mA-Care Dose4D; slice 5 mm; pitch 0.8; rotational speed 0.5 s^{-1}). 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 approximately 400 MBq, not scaled for body size.

Image analysis

The CTD, SUV_{max} and SUV_{mean} 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.^{5,7–9}

New exponential equations to estimate P_F

The CTD of pure fat is reported to lie between -50 and -100 HU.^{10,11} The Kodama and modified Ricci equations cross

when CTD is 31 HU (14.3% and 14.6% fat, respectively) and when CTD is 55.8 HU and P_F is zero (Figure 1). Ignoring the crossing point when P_F is zero and assuming firstly that the CTD of pure fat (100% fat) is either -50 or -100 HU and secondly that 31 HU corresponds to 14.5% fat, the exponential constants whereby P_F falls as CTD increases are 0.0238 and 0.0147 HU^{-1} for CTDs of 100% fat of -50 and -100 HU, respectively. This gives

$$P_F = \exp[-0.0238 * (\text{CTD} + 50)] \quad (3)$$

or

$$P_F = \exp[-0.0147 * (\text{CTD} + 100)] \quad (4)$$

Note that the terms in the index in Equations (3) and (4) are $(\text{CTD} + 50)$ and $(\text{CTD} + 100)$ because 100% fat is assumed to correspond to CTDs of -50 or -100 HU.

The SUV_{mean} was then corrected for fat by dividing it by $1 - P_F$.

RESULTS

The theoretical relationships of CTD with P_F are compared for linear [Equation (1)], sigmoid [Equation (2)] and exponential [Equations (3) and (4)] equations in Figure 1. It can be seen that the linear and exponential equations show good agreement over a range of CTD values from -20 to 45 HU. Above 55.8 HU, the linear equation fails because P_F becomes negative.

The relationships of fat-corrected SUV_{mean} with SUV_{max} are shown for each correction equation in Figure 2. There were similar and strong correlations between SUV_{max} and fat-corrected SUV_{mean} for linear and exponential equations with points generally lying below or occasionally marginally above the line of identity. By contrast, the sigmoid equation gave many

Figure 1. Theoretical relationships between P_F and CT density for Equations (1)–(4). The vertical continuous line is the mean CT density of the population ($n = 465$) and the vertical dashed lines are ± 2 standard deviations.

Figure 2. Relationships of fat-corrected mean standardized uptake value (SUV_{mean}) corrected using Equations (1)–(4) for calculation of P_F with maximum standardized uptake value (SUV_{max}). Fine lines are regression lines; bold lines are lines of identity. No regression equation is appropriate for Equation (2). Note that following fat correction using Equations (1), (3) and (4), The SUV_{mean} generally remains less than the SUV_{max} . Also, note multiple instances of gross overcorrection of SUV_{mean} using Equation (2).

values that were substantially higher than identity, consistent with gross overcorrection of SUV_{mean} at low values of SUV_{max} .

As previously shown elsewhere, the ratio of SUV_{mean}/SUV_{max} correlates with CTD; i.e. it is a marker of hepatic fat.⁷ In the current enlarged series of 465 patients, SUV_{mean}/SUV_{max} (y) also correlated significantly with CTD (x): $y = 0.65 + 0.0027x$ ($r = 0.34$; $p < 0.0001$). As can be seen in Figure 3, this correlation disappeared when the SUV_{mean} was fat corrected using either of the exponential equations. Using the linear equation [Equation (1)], however, the correlation between CTD and SUV_{mean}/SUV_{max} , albeit weak, was nevertheless significant ($r = -0.31$; $p < 0.0001$), consistent with undercorrection of

SUV_{mean} at high values of CTD as a result of negative values of P_F . When the SUV_{mean} was corrected using the sigmoid equation [Equation (2)], the SUV_{mean} was grossly overcorrected for hepatic fat at low values of CTD.

The linear and exponential equations showed good agreement in their correction of the SUV_{mean} for fat (Figure 4). Thus the correlation coefficients of the relationships of the SUV_{mean} corrected using the exponential equations with the SUV_{mean} corrected using the linear equation were 0.985 for Equation (3) and 0.961 for Equation (4). By contrast, the sigmoid equation gave multiple outliers in comparison with SUV_{mean} corrected using Equation (1).

Figure 3. Relationships of the ratio fat-corrected mean standardized uptake value (SUV_{mean})/maximum standardized uptake value (SUV_{max}), using Equations (1)–(4) for calculation of P_F , with CT density. No regression equation is appropriate for Equation (2). horizontal lines are unity. Note that Equation (1), but not Equations (3) and (4), gives a significant inverse correlation (regression line shown). Also note gross over-correction of the SUV_{mean} using Equation (2) at low CT density.

DISCUSSION

There are several reasons why the SUV_{max} exceeds the SUV_{mean} . In this study, we have focused on the differential effects of hepatic fat, which is heterogeneously distributed throughout the liver,⁶ on the two SUV indices. The SUV_{mean} , however, may also be reduced by the inclusion of non-hepatic tissue, whereas the SUV_{max} may be increased as a result of statistical noise, to which it is more susceptible than the SUV_{mean} ¹² and tends towards higher values in the presence of increased noise simply because, within an ROI, single-voxel SUV has a larger coefficient of variation. Nevertheless, when the SUV_{mean} is appropriately corrected for fat, it should approach the SUV_{max} but clearly not exceed it. Equation (2) failed to meet this requirement (Figure 2). Also, the optimal equation for correcting the SUV_{mean} for fat should abolish the significant association between SUV_{mean}/SUV_{max} and CTD. The exponential equations, but not linear and sigmoid equations, met this requirement (Figure 3). Nevertheless, although generating negative values at high CTD and thereby undercorrecting for fat, the linear equation [Equation (1)] gave values of fat-corrected SUV_{mean} that were in close

Figure 4. Relationships of mean standardized uptake value (SUV_{mean}) corrected for fat using Equations (2)–(4) with SUV_{mean} corrected for fat using Equation (1). The closest agreement is given by Equation (3). No regression equation is appropriate for Equation (2).

agreement with the values given by the exponential equations [Equations (3) and (4)] (Figure 4).

Uncertainties in this study include the assumption that the CTD of 100% fat lies between -100 and -50 HU. The linear equation gives a CTD of -114 (i.e. 55.8 – 170) HU for 100% fat [Equation (1)]. This tallies with CTD in subcutaneous and visceral fat (routine clinical observation), although the concept of the liver consisting of 100% fat is obviously virtual. Moreover, we have no evidence to support that CTD of 31 HU corresponds to 14.5% fat, therefore this assumption is a further uncertainty. Nevertheless, even if these assumptions are questionable, we still find that the exponential equations generate fat-corrected SUV_{mean} that appears to avoid the fairly obvious disadvantages of the sigmoid equation (especially at low values of CTD) and the negative values of P_F given by linear equation at high values of CTD.

CONCLUSION

In this study, we have exploited the relative values of SUV_{mean} and SUV_{max} , and their respective relationships with CTD, to examine the validity of previously published equations for estimating hepatic fat in comparison with new exponential equations described here. The equation of Kodama et al⁴ is not valid. The equation of Ricci et al³ appears to perform adequately but fails at high values of CTD. The new exponential equations described here are recommended, especially Equation (3).

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