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Pilot study to explore the accuracy of current prediction equations in assessing energy needs of patients with newly-diagnosed glioblastoma multiforme

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Abstract

Glioblastoma multiforme (GBM) is rare, yet is the most common brain malignancy and has a poor prognosis. In GBM, there is a dearth of research on resting energy expenditure (REE) and accuracy of extant prediction equations. The aim of this cross-sectional study was to compare measured REE (mREE) to commonly-used prediction equations in newly-diagnosed GBM patients. REE was collected by indirect calorimetry in 20 GBM patients. Calculated REE was derived from Harris-Benedict (again with weight adjusted for obesity), Mifflin-St Jeor, and 20 kcal/kg. Paired t-tests and Bland-Altman analyses were used to compare group means, evaluate the bias, and find the limits of agreement. Clinical accuracy was assessed by determining the percentage of patients with predicted REE within $\pm 10\%$ of mREE. Subjects were evenly distributed with regard to gender, primarily Caucasian, largely overweight or obese, and had a mean age of 57 years. All equations overestimated mREE. Mifflin-St Jeor and adjusted Harris-

Benedict had the narrowest limits of agreement and accurately predicted 60% and 65% of participants, respectively. Clinicians should be aware of the discrepancy between commonly used prediction equations and REE. More research is needed to verify these findings and decipher the cause and significance in the GBM population.

Keywords

clinical; glioblastoma multiforme; resting energy expenditure; prediction equations

Introduction

While brain cancers are rare, glioblastoma multiforme (GBM) is notable as the most common primary adulthood malignant brain tumor (1), with a 5-year survival rate of only 10%, despite treatment by surgical removal, radiation, and chemotherapy (2). New therapies are under investigation to increase life expectancy and maintain quality of life for GBM patients (3, 4). However, there remains limited documentation of the nutritional implications of this disease or the appropriate nutritional recommendations, including resting energy expenditure (REE) and caloric requirements of GBM patients. To date there exist no published reports of the quantification of REE in GBM patients or documentation of the optimal prediction equations for REE in GBM.

Prediction equations for REE are beneficial when indirect calorimetry or other measures of REE are not feasible. Numerous equations have been developed from variables easily attained in the clinical setting (i.e., height, weight, age). Over the last few decades, more attention has been paid to the metabolic rate of specific disease states, including cancer (5-11) and other neurological diseases, such as amyotrophic lateral sclerosis (12). Individualized nutrition approaches can improve dietary intake and quality of life of cancer patients (13) and calorie needs are often the foundation for these recommendations (14). Previous research in other cancer populations yields mixed results of whether the REE of cancer patients differs from individuals without malignancies (8, 9) and if prediction equations underestimate (6, 8, 10), overestimate (5), or accurately predict (5) actual needs. It is likely these conclusions will vary by type of cancer, phase of the disease, and the treatment strategy.

Given its poor prognosis, the maintenance of quality of life is critical during the treatment of GBM (3). Nutrition interventions in other cancer populations have proven beneficial (13) and potentially could offer a strategy for maintaining quality of life in GBM patients. However, a notable knowledge gap in the current treatment of GBM is the absence of information about calorie needs for these patients. Therefore, the aim of this study was to measure REE of newly diagnosed GBM patients and evaluate previously published prediction equations of REE to determine the most suitable equation.

Subjects and Methods

Subjects

Men and women with newly diagnosed GBM (histological confirmation of WHO grade IV astrocytoma) were recruited from the outpatient Neuro-oncology Clinic at University of Alabama at Birmingham (UAB) from April 2011 to Oct 2014. The full study was a longitudinal, feasibility study intended to collect nutrition and treatment-related information from GBM patients as they completed the first year of standard-of-care treatment (registered at clinicaltrials.gov as NCT01770626). Data from the first research visit, collected before or early into chemoradiation treatment, were used to address the current research question. Inclusion criteria included enrollment within six weeks of diagnosis, 19 years of age, and a negative pregnancy test for women of childbearing potential. Exclusion criteria included an implanted pacemaker, pregnancy, chronic edema, or an amputated extremity. Individuals with thyroid or metabolic disturbances were not excluded from the study. The UAB Institutional Review Board approved this study, and signed informed consent was obtained from all participants.

Procedures

Participants presented to the UAB Center for Clinical and Translational Science (CCTS) Clinical Research Unit (CRU) in the morning after an overnight fast. Age was collected from the electronic medical chart and confirmed with the participant. Body weight was measured in kilograms to the nearest 0.1 kg using a digital scale (Scale-Tronix Model 6702, Wheaton, IL, USA) in light street clothing without shoes. Height was measured to the nearest 0.01 cm by a wall-mounted, digital stadiometer (Digi-Kit, Measurements Concepts & Quick Medical, North Bend, WA, USA). Body mass index (BMI) was calculated as kilograms of body weight divided by meters squared. Fat-free mass (FFM) was calculated by an equation developed by Kyle et al. (15) which uses variables collected by bioelectrical impedance analysis (BIA), along with height, weight, and gender. BIA was performed with a Biodynamics Body Composition Analyzer, Model 310e (Seattle, Washington, USA) according to the manufacturer's procedures and by the same individual to prevent inter-operator differences.

Performance Scale

As part of standard care, the participant's ability to perform at usual and full functional capacity was evaluated in the Neuro-oncology clinic by a medical doctor or nurse practitioner and reported as the Karnofsky Performance Scale (KPS), ranging from 100% (no limitations in activities of daily living) to 0% (death) (16, 17).

REE

Measured REE (mREE) was determined by canopy indirect calorimetry (Vmax Encore 29, Yorba Linda, CA, USA) in the supine position according to standard procedures (18). Gas and flow calibrations were completed before each measurement. After a 30 minute rest period, a minimum of 30 minutes of data was collected and the first five minutes deleted to account for the participant acclimating to breathing under the canopy. The steady state data

points were selected to determine REE. Steady state regions were determined by the computer software as a variation of VO_2 and VCO_2 less than 10% and RQ less than 5% for a 5-minute period. The IC software then determined the calories expended by the participant with the de Weir calculation (19).

Prediction Equations

Equations commonly used in clinical practice (11, 20, 21) were selected for inclusion in this study if they utilized variables easily attained in the clinical setting (i.e. weight, height, age, and sex). Since participants were free living at the time of measurement, equations developed in hospitalized patients or with factors for trauma, mechanical ventilation, and burns, such as Ireton-Jones (22), were excluded from the study. The previously described formulas by Harris-Benedict (23), Mifflin-St Jeor (24), and 20 kcal/kg body weight ratio method (11, 25) were selected and used to calculate REE (cREE) (Table 1). In obese individuals (BMI ≥ 30), adjusted weight was calculated using the Hamwi equation (26) for ideal body weight and then used in a second calculation of Harris-Benedict (27).

Statistical Analysis

Distributions of the differences between mREE and cREE for each of the four predictive equations was examined using box-and-whisker plots, normal probability plots, and the Kolmogorov-Smirnov test. Based on the results of these plots and test, we determined that the differences for each of the four predictive equations are normally distributed. Paired t-tests were used to compare the difference between mREE and cREE from each prediction equation. If the mean difference was close to zero and not statistically significant, we would conclude that cREE is a reasonably accurate representation of mREE. The Bland-Altman approach (5, 28) was used to assess the agreement between mREE and each cREE. This method calculates bias, which is defined as the mean of the differences between the predicted and measured REE, and the limits of agreement, which are defined as ± 2 standard deviations from the mean difference. A smaller bias and narrower limits of agreement would indicate which of the prediction methods was most accurate for our dataset. The accuracy of each equation was quantified by the percentage of patients with cREE within 10% of mREE, which is the level of accuracy commonly used to assess clinical significance (14), as well as the bias, which is defined as the average percent difference between cREE and mREE (29). A greater level of accuracy and a smaller amount of bias would indicate that the cREE is a better predictor of mREE. The root mean squared prediction error (RMSE) was also used to examine the ability of each equation to predict mREE. A smaller value for RMSE would indicate that the cREE is a better predictor of mREE. The strength of the relationship between mREE and each cREE was evaluated by Pearson correlation analysis. A statistically significant correlation of 0.80 or greater would indicate that there is a strong relationship between cREE and mREE. Simple (unadjusted) linear regression analyses were used to determine the strength of associations between mREE and each cREE. These analyses allowed us to quantify the percent of variance in mREE that was explained by each cREE and clinical variables of interest. Individuals with missing variables were excluded from the analysis. Statistical significance was achieved at $P < 0.05$, and all statistical tests were two-tailed. All analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Cary, NC).

Power considerations

Power calculations to assess the mean overestimation of REE between the calculated values obtained from the prediction equations for REE and the measured REE were performed on a sample of 20 participants. Based on a two-sided paired t-test, a significance level of 5%, and standard deviations of the differences between the calculated values obtained from each prediction equation for REE and the measured REE (where all standard deviations were obtained from our data) of 142.10 kcal/day, 106.51 kcal/day, 132.06 kcal/day, and 223.02 kcal/day for the Harris-Benedict, adjusted Harris-Benedict, Mifflin-St Jeor, and ratio method equations, respectively, this study had 80% power to detect a mean overestimation (or underestimation) of 93.85 kcal/day, 70.35 kcal/day, 87.22 kcal/day, and 147.29 kcal/day for the Harris-Benedict, adjusted Harris-Benedict, Mifflin-St Jeor, and ratio method equations, respectively, as being statistically significant. Power calculations were performed using nQuery + nTerim, version 2.0 (Statistical Solutions, Ltd., Boston, MA).

Results

Demographics

One-hundred and forty-six neuro-oncology patients were assessed for eligibility. Between May 2011 and August 2013, 21 participants consented and one participant withdrew due to conflict with study schedule and standard-of-care treatment schedule. The current analysis includes 20 newly diagnosed GBM patients (9 male and 11 female; mean age 57 years). Figure 1 summarizes screening and enrollment in the study. Nineteen participants were Caucasian and one was African American. The analyses were run twice, once including the African American female and a second time excluding her from the analysis to check for racial differences others have observed in REE and FFM (30). Results obtained from both sets of analyses were nearly identical (data not shown), so the final data analyses include all 20 subjects.

Male participants were slightly older than female participants. The majority of participants were overweight or obese. FFM was available for 16 of the 20 participants, with four missing FFM due to unforeseen BIA malfunction. Table 2 presents participant characteristics.

Comparisons of mREE to cREE

All the prediction equations significantly overestimated measured kcal/day. The mean value predicted by Harris Benedict was 1548 (222) kcal/day ($t=5.21$; $P<0.001$), adjusted Harris Benedict was 1490 (187) kcal/day ($t=4.50$; $P<0.001$), Mifflin-St Jeor was 1478 (214) kcal/day ($t=3.24$; $P=0.004$), and the ratio method was 1584 (247) kcal/day ($t=4.04$; $P<0.001$). Results of the comparison of the prediction equations for mREE are presented in Table 3.

Bland-Altman plots

The Bland-Altman plots illustrate the mean overestimation (bias) of all the predictive equations (Figure 2). The limits of agreement for the Bland-Altman analysis (± 2 SD) are reported in Table 3 and are the solid lines in Figure 2. Adjusted Harris-Benedict has the

narrowest limits of agreement (-106, 320) and Mifflin-St Jeor achieved the lowest overestimation of mREE (96 kcal/day).

Assessment of clinical accuracy

The Harris-Benedict and Mifflin-St Jeor equations predicted REE in 60% of participants within clinical accuracy (Table 3). Harris-Benedict was further improved when weight was adjusted for obesity (accuracy in 65% of participants). Mifflin-St Jeor predicted two participants' REE under clinically acceptable levels, whereas both Harris-Benedict equations only overpredicted. When bias was considered as an average percent of the difference between cREE and mREE, the Mifflin-St Jeor and Adjusted Harris-Benedict equation displayed the least bias, 7.6% and 8.6% respectively. The ratio method had the fewest predictions within 10% of mREE (40%) and displayed the most bias (15.8%).

Strength and associations with mREE

The Harris-Benedict, adjusted Harris-Benedict, and Mifflin-St Jeor equations were highly correlated with mREE ($r=0.80$, $P<0.001$; $r=0.88$, $P<0.001$; and $r=0.82$, $P<0.001$, respectively), while the ratio method was moderately correlated with mREE ($r=0.56$, $p=0.011$). In simple linear regression models, the percent of the variance in mREE explained by the Harris-Benedict, adjusted Harris-Benedict, Mifflin-St Jeor, and ratio method equations was 64% ($P<0.001$), 78% ($P<0.001$), 67% ($P<0.001$), and 31% ($P=0.011$), respectively. Among the clinical and demographic variables that were examined, gender, height, weight, and FFM were individually associated with mREE ($P<0.001$, $P<0.001$, $P=0.011$, and $P<0.001$, respectively), while age, BMI, KPS, and days after diagnosis were not. FFM was the best predictor of mREE, accounting for 64% of the variance in mREE.

Discussion

In this first study to assess the energy requirements of brain cancer patients, we found that the mean for each cREE overestimated the mean for actual mREE. The Mifflin-St Jeor equation had the lowest overestimation of mREE (96 kcal/day) and achieved a clinically accurate prediction of mREE in 60% of participants. Adjusting weight for obesity in the Harris-Benedict equation the narrower limits of agreement achieved clinical accuracy in 65% of participants (Table 3). With the exception of the ratio method, all predicted values correlated well with mREE, indicating the ability of the remaining prediction equations to partially explain at least 64% of the variance observed in mREE. Of the clinical variables tested, FFM was the best predictor of mREE.

Prediction equations offer an estimate of REE based on easily attained clinical measures (i.e. height and weight) and a few depend on less accessible measures (i.e. FFM). In the absence of mREE, as in many clinical settings where the measurement of REE may not be feasible, these methods of estimation offer valuable insight into the caloric needs of patients based on regression analyses from other populations. Unfortunately, these sample populations can look vastly different from a population seen in clinic. For instance, the Harris-Benedict equation remains prevalent in the clinical setting (20, 31) despite its development in a sample of healthy, normal weight, mostly young adults almost a century ago (20, 23). In the

current sample, the performance of Harris-Benedict was slightly improved when weight was adjusted in the presence of obesity. Unfortunately, adjusting weight has the potential to introduce error. An estimated 69% of the 2011-2012 adult U.S. population is overweight or obese (32). Therefore, it is imperative to not only know or develop the best prediction equations for healthy overweight and obese individuals who make up the majority of our population, but also for the overweight and obese across a broad spectrum of health conditions.

In this sample, we saw wide limits of agreement ($\text{mean} \pm 2 \text{ SD}$) and limited clinical accuracy (i.e., within $\pm 10\%$ of mREE). It is well established that prediction equations better estimate at the group level and often lose their accuracy for individuals (14). A systematic review of validation studies (14) found the Harris-Benedict equation overestimated REE and was within clinical accuracy of 45%-81% for normal weight subjects, but only up to 64% of obese subjects. The Mifflin equation was clinically accurate in the majority of normal weight and obese individuals, but tended to underestimate REE. Body weight should be monitored when using equations, and clinical judgment should be used to regulate weight loss or gain (14).

Similar to others (33, 34) we found FFM to be the largest contributor to REE. FFM is more metabolically active than fat mass (33, 34). REE increases with increasing body weight, but as adiposity increases, the proportions of FFM and fat mass changes, thus the rate of REE per body weight differs in the lean and the obese (33). The assumption that all components contributing to body weight have the same metabolic rate is a deficiency in the ratio method.

Seventy-five percent of the current sample was overweight or obese. Mifflin-St Jeor is recommended for predicting REE, especially in obese healthy, non-hospitalized individuals due to its accuracy in predicting REE in large groups (14, 29, 35). It is also the most accurate in older individuals (> 70 years old) (36). In a pilot study similar to our own, Bauer et al. (5) found in pancreatic cancer patients Mifflin-St Jeor had the greatest underestimation, but was still accurate at the group level. The differences in our conclusions and those of Bauer et al. (5) could be related to the narrower age range (55-70 years), the current weight status of their patients (currently normal weight or overweight with a weight loss of $\geq 5\%$ in the last six months), or the repeated observations on four participants. Our analysis had a wider age range (35-73 years), six obese individuals, and no repeat measures. In addition, the different results could also be due to differences in the two cancer sites.

In inpatient nutrition assessment, while indirect calorimetry is the preferred method to obtain REE, it is often reserved for the more complex cases (14, 21). Previously, Boullata and colleagues (21) found that both Harris Benedict and Mifflin-St Jeor underestimated REE for non-specific hospitalized patients; this hypermetabolic state reported by Boullata et al. (21) likely reflects the acute metabolic stress induced by disease and surgery, which may not be present in cancer patients recovered from surgical resection.

Our findings of overestimation are congruent to the findings in healthy individuals, and in part suggest the initial phase of GBM management does not increase metabolic rate. Post curative tumor resection, metabolic rate returns to expected REE values (7), and we could be

observing the same phenomena. Unfortunately, this theory could not be tested in the current sample of GBM patients as REE was not collected prior to surgery. A pre-surgery measure poses a further problem as surgical resection of an unknown brain mass often precipitates the diagnosis of GBM by histological confirmation, resulting in the immediate need for treatment. REE during and post chemoradiation in GBM is also unknown.

Strengths and Limitations

The primary strength of this study is that it provides data in an area where currently none exist, i.e., predicting the energy requirements for patients with brain cancer. This is important since although this malignancy is relatively rare, there are roughly 144,463 Americans who are currently living with this diagnosis (37). Despite the need for such data, our study had some limitations. First is the small sample size; however, given the rarity of this disease and the anxiety related to diagnosis, it is difficult to assemble numbers that are larger than this without involving multiple sites. Moreover, a sample of 20 should provide reasonable parameter estimates to evaluate prediction equations for REE in this unstudied cancer population. Second, the interpretation and application of this study is limited by the absence of ethnic and minority groups. However, the clinical impact of this is minimal because the majority of GBM diagnoses in the U.S. are in Caucasians (1). Thirdly, some participants were measured after initiation of standard-of-care chemoradiation. Whereas others have found predictive equations underestimate REE in cancer patients undergoing treatment (6), we found predictive equations overestimated REE. Therefore, we postulate in the early phase of standard-of-care chemoradiation for GBM, REE is not affected as greatly as in other cancers. Finally, although BIA does not offer the most robust estimation of FFM and four participants were missing BIA measurements, our results were similar to other studies that evaluated FFM (10, 11) and the use of BIA allowed for more flexible research visits for the participants.

Importance and future directions

Accurate caloric recommendations are necessary to prevent under- and overfeeding. Obesity and positive energy balance is increasingly associated with less favorable outcomes in cancer patients (38, 39). Additionally, hyperglycemia is associated with a poorer prognosis in low-grade gliomas (40) and malignant gliomas, including GBM (41), suggesting the importance of glycemic control (which often tracks with body weight status). Conversely, a potential risk of underfeeding is the patient not meeting his or her caloric and micronutrient needs. While brain tumor patients are typically not considered at high risk for malnutrition (13), weight loss as a result of underfeeding is a worrisome scenario as it potentially predicts the inability to endure the upcoming standard-of-care chemoradiation. Likewise, adequate nutrition intake maintains quality of life in cancers at high risk for malnutrition (13), and may be beneficial in understudied cancer populations not traditionally considered at high-risk for nutritional deficiencies.

Conclusions

All prediction equations have limitations in their ability to accurately estimate REE. Thus, other outcomes (i.e. anthropometric changes) and professional judgment should be

considered when making nutritional plans and recommendations. Results from this sample suggest the Mifflin-St Jeor equation or Harris-Benedict equation when weight is adjusted for obesity are most appropriate for predicting REE of newly diagnosed GBM patients. These results are the first steps to a better understanding of the nutritional needs of an understudied population, and set the foundation for the development of dietary interventions and recommendations for brain tumor patients.

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Figure 1.
Participants screened, enrolled, measured, and analyzed.

Figure 2. Bland-Altman plots comparing measured resting energy expenditure (mREE) to calculated resting energy expenditure (cREE). The dashed line is the mean difference and the solid lines are the limits of agreement (± 2 SD of the mean difference).

Table 1
Selected prediction equations for resting energy expenditure (kcal/day) compared in 20 GBM patients

Equation	Formula
Harris-Benedict (23)	Men: BEE (kcal/day) = $66.47 + 13.75 \times \text{wt} + 5.0 \times \text{ht} - 6.75 \times \text{A}$ Women: BEE (kcal/day) = $655.09 + 9.56 \times \text{wt} + 1.84 \times \text{ht} - 4.67 \times \text{A}$
Adjusted ^a Harris-Benedict (27)	Men: BEE (kcal/day) = $66.47 + 13.75 \times \text{ABW}^b + 5.0 \times \text{ht} - 6.75 \times \text{A}$ Women: BEE (kcal/day) = $655.09 + 9.56 \times \text{ABW}^b + 1.84 \times \text{ht} - 4.67 \times \text{A}$
Mifflin-St Jeor (24)	Men: REE (kcal/day) = $10 \times \text{wt} + 6.25 \times \text{ht} - 5 \times \text{A} - 161$ Women REE (kcal/day) = $10 \times \text{wt} + 6.25 \times \text{ht} - 5 \times \text{A} + 5$
Ratio Method (11, 25)	Both sexes: REE (kcal/day) = $\text{wt} \times 20$

^a with weight adjusted in obese participants (described below)

^b ABW: adjusted body weight (calculated in lbs and converted to kg) = $0.5(\text{actual lbs} - \text{ideal lbs}^c) + \text{ideal lbs}^c$

^c ideal lbs calculated by the Hamwi equation (26)

women: 100 lbs for first 5ft and 5 lbs for each additional inch

men: 106 lbs for first 5ft and 6 lbs for each additional inch

A: age in years; ht: height in cm; lbs: body weight in pounds; wt: body weight in kg

Table 2
Descriptive statistics for n=20 newly diagnosed GBM patients

Characteristic	Mean (SD)	n (%)
Age (years)	57.4 (10.2)	
Sex		
Male		9 (45.0%)
Female		11 (55.0%)
Ethnicity		
Caucasian		19 (95.0%)
African American		1 (5.0%)
Post diagnosis (days)	29 (11)	
Height (cm)	169.5 (9.0)	
Weight (kg)	79.2 (12.4)	
BMI	27.6 (4.3)	
Normal		5 (25.0%)
Overweight		9 (45.0%)
Obese		6 (30.0%)
Fat-free mass^a (kg)	53.3 (12.1)	
KPS^b	85 (9)	
Measured REE (kcal/24 hr)	1383 (225)	
Respiratory quotient	0.83 (0.09)	
REE/FFM^a (kcal/kg)	26.6 (3.4)	

^aFat-free mass: FFM from bioelectrical impedance and Kyle equation; n=16

^bKPS: Karnofsky Performance Scale; n=19

Table 3
Comparison of predictive equations for resting energy expenditure in 20 newly diagnosed glioblastoma multiforme patients

Equation	REE (kcal/d $\pm$ SD)	Mean overestimation (kcal/d $\pm$ SD)	Limits of Agreement for Bland- Altman Analysis ($\pm$ 2 SD)	Within $\pm$ 10% of mREE (%)	<90% of mREE (%)	> 110% of mREE (%)	Bias ^d (%)	Maximum Negative Error ^b (%)	Maximum Positive Error ^c (%)	RMSE ^d (kcal/d)
Measured REE	1383 $\pm$ 225	-	-	-	-	-	-	-	-	-
Harris-Benedict	1548 $\pm$ 222	165 $\pm$ 142	-119, 450	60	0	40	12.7	-7.3	33.5	139
Adjusted Harris-Benedict	1490 $\pm$ 187	107 $\pm$ 107	-106, 320	65	0	35	8.6	-7.3	33.5	109
Mifflin-St Jeor	1478 $\pm$ 214	96 $\pm$ 132	-169, 360	60	10	30	7.6	-11.4	28.9	132
Ratio Method	1584 $\pm$ 247	202 $\pm$ 223	-245, 648	40	5	55	15.8	-14.2	47.0	192

^a Mean percentage error between calculated REE from each equation and measured REE.

^b The largest underprediction that was found with this predictive equation as a percentage of the measured value.

^c The largest overprediction that was found with this predictive equation as a percentage of the measured value.

^d RMSE: root mean squared prediction error.