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Hypermetabolism and symptom burden in advanced cancer patients evaluated in a cachexia clinic

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Abstract

Background Elevated resting energy expenditure (REE) may contribute to weight loss and symptom burden in cancer patients.

Aims The aim of this study was to compare the velocity of weight loss, symptom burden (fatigue, insomnia, anxiety, and anorexia—combined score as measured by the Edmonton Symptom Assessment Score), high-sensitivity C-reactive protein, and survival among cancer patients referred to a cachexia clinic with hypermetabolism, elevated REE > 110% of predicted, with normal REE.

Methods A retrospective analysis of 60 advanced cancer patients evaluated in a cachexia clinic for either >5% weight loss or anorexia who underwent indirect calorimetry to measure REE. Patients were dichotomized to either elevated or normal REE. Descriptive statistics were generated, and a two-sample Student's *t*-tests were used to compare the outcomes between the groups. Kaplan–Meier and Cox regression methodology were used to examine the survival times between groups.

Results Thirty-seven patients (62%) were men, 41 (68%) were White, 59 (98%) solid tumours, predominantly 23 gastrointestinal cancers (38%), with a median age of 60 (95% confidence interval 57.0–62.9). Thirty-five patients (58%) were hypermetabolic. Non-Caucasian patients were more likely to have high REE [odds ratio = 6.17 (1.56, 24.8), $P = 0.01$]. No statistical difference regarding age, cancer type, gender, active treatment with chemotherapy, and/or radiation between hypermetabolic and normal REE was noted. The velocity of weight loss over a 3 month period (−8.5 kg vs. −7.2 kg, $P = 0.68$), C-reactive protein (37.3 vs. 55.6 mg/L, $P = 0.70$), symptom burden (4.2 vs. 4.5, $P = 0.54$), and survival (288 vs. 276 days, $P = 0.68$) was not significantly different between high vs. normal REE, respectively.

Conclusion Hypermetabolism is common in cancer patients with weight loss and noted to be more frequent in non-Caucasian patients. No association among velocity of weight loss, symptom burden, C-reactive protein, and survival was noted in advanced cancer patients with elevated REE.

Keywords Hypermetabolism; Palliative care; Symptoms; Advanced cancer; Cachexia

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Introduction

Cachexia affects most patients with advanced cancer, being more common and severe in patients with gastrointestinal tract or lung malignancies. The devastating consequences of cancer cachexia impact survival, treatment planning, and quality of life.[1–4] Although the important characteristics of cachexia such as progressive weight loss, fat and muscle wasting, and metabolic and hormonal alterations are recognized, efforts to treat weight loss have met with limited success.

Hypermetabolism, elevated resting energy expenditure (REE) > 110% of predicted REE, is characterized by an increase in the body's basal metabolic rate and is noted in patients with burns, hyperthyroidism, and sepsis and who are receiving steroid therapy. It is associated with increased peripheral

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insulin resistance, elevated protein catabolism, and a negative nitrogen balance.[5] We have previously reviewed 151 consecutive cancer patients referred to a cancer cachexia clinic and reported a high frequency of secondary nutritional impact symptoms, hypogonadism in male patients, and elevated REE indicating hypermetabolism.[6] Hypermetabolism is most likely secondary to the underlying cancer and may contribute to an increased symptom burden or poor prognosis.

The primary objective of our study was to compare the velocity of weight loss over a 3 month period in hypermetabolic advanced cancer patients with patients with normal REE who were referred to a cachexia clinic. Secondary objectives included comparing C-reactive protein, a marker of systemic inflammation, symptom burden [fatigue, insomnia, anxiety, and anorexia combined score as measured by the Edmonton Symptom Assessment Scale (ESAS, scale 0–10)], and survival time between cachectic patients with hypermetabolism and patients with normal REE. In addition, the effect of treatment with chemotherapy and/or radiation treatment within the past 2 weeks on the measurement of REE in cachectic cancer patients was assessed.

Methods

We conducted a retrospective review, approved by the MD Anderson Institutional Review Board, of the 151 consecutive advanced cancer patients seen in our supportive care clinic and were evaluated for cancer cachexia for either $>5\%$ weight loss or poor appetite between December 2005 and 31 July 2009. Assessments included measurement of REE, which was offered to all patients. Of the 151 patients identified, 60 patients received assessments of their REE by handheld indirect calorimetry, MedGem (HealthTech, Golden, CO, USA), a simple and non-invasive test. Patients with difficulties tolerating nasal clamping and/or breathing through the indirect calorimeter, time constraints, lack of interest, or non-compliant with instructions were unable to obtain measurements of REE and excluded. Patients were advised not to exercise or eat 4 h prior to assessment.

We also collected demographic factors including date of birth, age, sex, race, and primary tumour diagnosis and clinical relevant data including the ESAS, laboratory tests, and results of bioelectrical impedance assay, which were used to calculate the predicted REE using the Harris–Benedict equation. In addition, we have collected data of palliative care diagnosis and interventions, including medications changes and time of death or last follow-up visit to the institution. We also retrospectively documented whether or not patients received chemotherapy within 2 weeks of REE assessment.

Descriptive statistics were calculated for all 60 patients who received assessments of the REE. Those patients were dichotomized into hypermetabolic and elevated REE, and normal REE groups and descriptive statistics were generated for each group. Two-sample Student's *t*-tests, or Wilcoxon rank-sum tests when appropriate, were used to compare the velocity of weight loss over a 3 month period prior to assessment of REE between those with elevated REE and those with normal REE. Similar analyses were carried out addressing the secondary objectives including comparisons of C-reactive protein and symptom burden, measured by the ESAS composite scores, and between elevated REE and normal groups. Kaplan–Meier estimates and plots were generated to examine the survival times in the two REE groups, and logrank tests were computed.

Results

A total of 60 cancer patients completed a handheld indirect calorimetry measurement of REE on consultation for symptoms of anorexia–cachexia. Thirty-nine patients (65%) were men, 41 (68%) were White, 59 (98%) solid tumours, predominantly 23 gastrointestinal cancers (38%) and 19 thoracic malignancies (31.7%) (*Table 1*). Median age of the patient population was 60 years (95% confidence interval 57.0–62.9). The vast majority had advanced cancer, and 58 (97%) and 36 patients (60%) received chemotherapy and/or radiation therapy prior to assessment of their REE.

Of the 60 patients evaluated, 35 patients (58%) were hypermetabolic. No statistical difference regarding age, cancer type, gender, active treatment with chemotherapy, and/or radiation between hypermetabolic and normal REE was noted (*Table 1*). However, non-Caucasian patients were more likely to have high REE [odds ratio = 6.17 (1.56, 24.8), $P = 0.01$].

The velocity of weight loss over a 3 month period (-8.5 vs. -7.2 kg, $P = 0.68$), C-reactive protein (37.3 vs. 55.6 mg/L, $P = 0.70$), symptom burden as measured by the combined ESAS (4.2 vs. 4.5, $P = 0.54$), and survival (288 vs. 276 days, $P = 0.68$) were not significantly different between high vs. normal REE, respectively (*Table 1*).

Linear regression analysis did not show any association between REE and REE adjusted for lean body mass (REE/LBM) with velocity of weight loss and C-reactive protein; however, a statistically significant but weak association was noted with REE (R square = 0.07, $P = 0.045$) with symptom burden (ESAS combined score), while REE/LBM (R square = 0.06, $P = 0.053$) was not statistically associated with symptom burden.

Discussion

In our study, 58% (35/60) of advanced cancer patients referred to a cachexia clinic were noted to be hypermetabolic. The proportion of cancer patients with elevated REE was similar to a study of unselected patients with early stage solid

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Table 1 Characteristics of advanced cancer patients seen in a cancer cachexia clinic with elevated and normal resting energy expenditure

Patient characteristics and outcomes			Resting energy expenditure (REE)				*P*-value
			Hypermetabolic		Normal		
	N	%	N	%	N	%	
Age, mean (SD)	60	60.0 (57.0, 62.9)	35	60.7 (56.5, 64.9)	25	58.8 (54.4, 63.3)	0.43[a]
Cancer type							
Dermatological	2	(3.3)	2	(5.7)	0	(0.0)	0.20[b]
Gastrointestinal	23	(38.3)	15	(42.9)	8	(32.0)	
Genitourinary	2	(3.3)	2	(5.7)	0	(0.0)	
Gynaecological	3	(5.0)	1	(2.9)	2	(8.0)	
Head and neck	8	(13.3)	2	(5.7)	6	(24.0)	
Haematological	1	(1.7)	1	(2.9)	0	(0.0)	
Sarcoma	1	(1.7)	1	(2.9)	0	(0.0)	
Unknown primary	1	(1.7)	0	(0.0)	1	(4.0)	
Thoracic	19	(31.7)	11	(31.4)	8	(32.0)	
Race							
Caucasian	41	(68.3)	19	(54.3)	22	(88.0)	0.01[b]
Non-Caucasian	19	(31.7)	16	(45.7)	3	(12.0)	
Gender (male)	39	(65.0)	23	(65.7)	16	(64.0)	>0.99[b]
Advanced cancer stage	58	(96.7)	34	(97.1)	24	(96.0)	>0.99[b]
Chemotherapy and/or radiation treatment within 2 weeks of REE measurement	36	(60.0)	18	(51.4)	18	(72.0)	0.18[b]
Weight loss (kg)/3 months, mean (SD)	60	−7.9 (−10.0,−5.9)	35	−8.5 (−11.7, −5.3)	25	−7.2 (−9.3, −5.1)	0.68[c]
C-reactive protein (mg/L), mean (SD)	49	44.4 (26.9, 61.9)	30	37.3 (20.1, 54.5)	19	55.6 (17.3, 93.8)	0.70[c]
Combined ESAS, mean (SD)	60	4.4 (3.9, 4.9)	35	4.2 (3.6, 4.9)	25	4.5 (3.6, 5.4)	0.55[c]

ESAS, Edmonton Symptom Assessment Scale; SD, standard deviation
[a]χ^2 test.
[b]Fisher's exact test.
[c]Kruskal–Wallis test.

tumours and a prognosis of greater than 6 months.[7] Cancer patients evaluated in our cachexia clinic often have advanced disease and referred late in the disease trajectory. In a study of genitourinary malignancies, patients with advanced disease, Stage IV, had higher REE corrected for LBM.[8] In addition, the velocity of weight loss did not differ between cachectic cancer patients with hypermetabolism compared with patients with normal REE. The velocity of weight loss may vary across the disease trajectory; however, it is reassuring that both groups had a similar prognosis. Our patient population, being referred late, may have already depleted most of their fat and muscle reserves and could be in the 'refractory' stage of cancer cachexia affecting the velocity of weight loss.[9] A study of cancer patients using computed tomography (CT) to measure LBM loss found that few patients were able to maintain or gain weight in the 90 days preceding death.[10] Future studies should consider assessments of weight loss velocity and REE at multiple points during the disease trajectory.

In addition, non-Caucasian patients were noted to have a higher frequency of hypermetabolism, which may be attributed to differences in body composition. One study of patients with esophageal cancer found Black patients to have lower REE, but when corrected for FFM, no significant differences were noted in REE.[11] We have also reported that non-Caucasian patients with cancer cachexia have significantly lower vitamin D levels than Caucasian patients with weight loss.[12] Vitamin D is involved in regulation of the estrogen-to-androgen ratio,[13] which may contribute to altered body composition and REE among minorities. Future studies on REE in cancer patients need to account for variations in body composition among races.

Malnourished cancer patients with hypermetabolism may benefit from interventions, which decrease REE. In cachectic cancer patients, small pilot studies evaluating non-steroidal anti-inflammatories, such as ibuprofen,[14] polyunsaturated fatty acids,[15] and beta-blockers[16] have been shown to decrease REE, which may allow patients to more easily meet the caloric requirements to maintain or increase LBM. Accurate measurements of REE can only be obtained by indirect calorimetry, and these measurements are used by dieticians to prevent underfeeding, resulting in cachexia, or overfeeding. In critically ill patients, overfeeding can lead to hyperglycaemia, hepatic dysfunction, and respiratory distress.[17]

In cachectic patients with advanced cancer, the symptom burden was significant but weakly associated with elevated REE. In patients with hyperthyroidism, hypermetabolism has been associated with symptoms of fatigue and muscle weakness, increased heat sensitivity or excessive sweating, anxiety, and insomnia.[18] In advanced cancer patients, symptoms, such as fatigue or cachexia, are often multifactorial, and hypermetabolism may be only one of the multiple factors that contributes to weight and muscle loss. In addition to treating elevated REE, clinicians need to simultaneously treat other etiologies, secondary nutritional impact symptoms, including adequate treatment of pain, early satiety, and nausea, and underlying constipation to adequately reverse weight loss in cancer patients.

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One of the limitations of our study is the small sample size. To avoid excessive burden on our patient population, a handheld indirect calorimeter, MedGem, was used to measure REE. A recent small study comparing the handheld device with traditional indirect calorimeters reported inferior accuracy, which often underestimated REE.[19] This limits our findings; however, the associations noted in the study are consistent with other research evaluating the frequency of hypermetabolism in cancer cachexia. Of the 151 patients referred to our cachexia clinic, only 60 patients (40%) were able to complete the indirect calorimetry. Arguably, a selection bias for cancer patients who had a better prognosis or were less frail may limit the findings and may also underestimate the frequency of hypermetabolism. More research is needed.

Conclusion

Hypermetabolism is common in cancer patients with weight loss and noted to be more frequent in non-Caucasian patients. No strong associations among velocity of weight loss, symptom burden (composite score including fatigue, insomnia, anxiety, and anorexia), C-reactive protein, and survival were noted in advanced cancer patients with elevated REE. Cachexia in advanced cancer patients is a multifactorial process. Interventions targeting elevated REE may be inadequate to maintain or reverse weight loss, and a multimodal treatment is required in cancer patients.

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Conflict of interest

None declared.

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