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Original article

Dietary energy density, inflammation and energy balance in palliative care cancer patients

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SUMMARY

Background & aims: Diet energy density is correlated with energy intake in patients with advanced cancer. Little information is available about the effects of energy density on energy balance, nor about the influence of other factors, such as systemic inflammation and disease stage. We assessed whether dietary energy density or energy intake predict energy balance over 4 months in patients with advanced cancer. We examined also the influence of systemic inflammation and survival time.

Methods: Energy balance was calculated from the change in body energy content by repeated dual-energy X-ray scans in 107 patients for a total of 164 4-month measurement periods. A linear mixed model was used to investigate relationships between diet energy density (kcal/g), energy intake (kcal/day) and energy balance with systemic inflammation and survival as covariates.

Results: In an unadjusted model, the energy density of solid food and energy intake were positive predictors of energy balance ($P < 0.03$). A 1-SD increase in energy density and energy intake increased energy balance by 38 and 41 kcal/day, respectively. The total diet energy density did not predict energy balance ($P > 0.05$). Survival was positively ($P < 0.001$), and systemic inflammation negatively ($P = 0.005$) associated with energy balance. Only energy intake remained a significant predictor of energy balance after adjustment for survival and inflammatory status.

Conclusions: Dietary energy density is positively associated with energy balance in patients with advanced cancer. Relations between energy intake, energy density and energy balance are affected by systemic inflammation. Thus, targeting systemic inflammation may be important in nutritional interventions in this patient group.

1. Introduction

Weight loss is a cardinal feature of cachexia in advanced cancer and has a negative effect on outcome.[1–3] Weight loss reflects a negative energy balance, in which dietary energy intake is less than energy expenditure. A reduced energy intake (EI) due to anorexia and metabolic abnormalities, including hypermetabolism driven by systemic inflammation, are considered the primary causes of the weight loss.[1,3,4] Other procachectic mechanisms may, however, be involved.

Many dietetic strategies have been used to increase oral EI in malnourished cancer patients, including increasing the intake of energy-dense food and beverages, increasing the frequency of meals, enhancing flavor and modifying texture.[5,6] Dietary counseling can either increase or prevent a decline in energy and nutrient intake in cancer patients.[5,7–10] However, little well supported dietary advice aimed at increasing the EI of cancer patients with self-selected diets in free living conditions is available.[5,7–9]

Energy density (ED) is positively correlated with energy intake in healthy and obese people, both in experimental studies and in studies of people eating self-selected diets in free living conditions.[11–14] We have previously shown that ED is positively correlated with energy intake in patients with advanced cancer, both in a between-subject and in a within-subject analysis.[15,16] Cross-sectional epidemiological studies have shown that ED and body mass index (BMI) are correlated, and that ED is associated with weight change.[17,18] This result, while not a general finding, implies that ED is associated with long-term energy balance.[17,18]

Abbreviations: BMI, body mass index; BW, body weight; CRP, C-reactive protein; E%, percentage of energy intake; ED, energy density; ED_{food}, energy density of solid food; EI, energy intake; ESR, erythrocyte sedimentation rate; REE, resting energy expenditure.

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The effect of dietary advice aimed at increasing energy density in patients with advanced cancer eating self-selected diets in free living conditions has not been studied. Dietary counseling to increase the intake of energy-dense foods may be inappropriate for patients with advanced cancer, if it does not result in increased energy intake and an improved energy balance. This may be the case, for example, if the patient makes compensatory changes. Clarification of the association between energy density, energy intake and energy balance in patients with advanced cancer is, therefore, necessary to improve dietary advice. The aim of the present study was to investigate the associations between energy density, energy intake and energy balance in patients with advanced cancer, and the possible influence of systemic inflammation on these relationships.

2. Materials and methods

Patients referred to a palliative care program at the Department of Surgery at Sahlgrenska University Hospital (Gothenburg, Sweden) between 1993 and 2005 were included in the study. This was a secondary analysis of longitudinal data from intervention studies of anti-inflammatory treatment with indomethacin, of anemia with erythropoietin, insulin (NCT00329615), dietary counseling and nutritional support in an outpatient palliative care program. Informed consent was obtained from all patients, and the Committee for Ethics at the Faculty of Medicine, University of Gothenburg, approved the studies.[19–22] Patients were invited to participate in follow-up measurements that included biochemical tests, measurement of body composition and dietary intake every 4 months. Inclusion criteria were the presence of generalized malignant disease with a solid tumor type without efficient or established tumor treatment available, expected survival of more than six months at first visit, and the completion of at least two measurements of body composition and food records separated by 4 months. None of the patients received radio- or chemotherapy during follow-up or had received any of these therapies within 6 months of the start of our evaluations. The only exclusion criterion was treatment with parenteral or enteral nutrition. Thus, our results do not reflect alterations in energy balance and dietary intake during disease progression that were fully spontaneous: they present an integrative view over time, according to the evidenced-based treatment offered to unselected and heterogeneous groups of cancer patients.[19–22]

2.1. Patient characteristics and energy balance

Body weight (BW) was recorded in light indoor clothing on a calibrated electronic scale. Habitual weight before the onset of disease was reported by the patients. Weight loss was calculated as the difference between the two, and expressed as percentage of habitual BW. Body height was measured using a wall-mounted stadiometer. Resting energy expenditure (REE) was measured in the morning by indirect calorimetry (Deltatrac; Datex, Helsinki, Finland) after an overnight fast. Basal metabolic rate (BMR) was predicted using the Harris–Benedict equation. Hypermetabolism was expressed as the percentage of measured REE above or below the predicted BMR.

Body composition was measured by dual-energy X-ray absorptiometry using a LUNAR DPX-L scanner (Scanexport Medical, Helsingborg, Sweden). Whole-body scans were obtained in fast-scan mode. Body fat and lean tissue mass were analyzed using the extended research mode of the LUNAR DPX-L software (Version 1.31; Scanexport Medical). Energy balance was estimated from the difference in body composition from scans separated by 4 months. Changes (gain or loss) in fat or fat-free mass were multiplied by their respective energy value (9417 kcal/kg for fat and 884 kcal/kg for fat-free mass) and divided by the number of days between scans, giving energy balance per day (kcal/day).[23] Blood tests included measurement of C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR) and serum albumin level.

2.2. Dietary intake

A dietician instructed the patients to complete a 4-day food record at home. Amounts of all food and beverages were recorded in household measures. The dietician interviewed each patient and any ambiguities were resolved upon return of the food records. The emphasis in dietary intake during our study of palliative nutritional intervention in addition to indomethacin and erythropoietin treatment had been on energy and macronutrients[19]; consequently, the recording of beverages that did not contain energy was not specifically requested. Estimation of serving sizes and conversion to weight units were aided by a previously validated meal model.[24] Intakes of energy and nutrients were calculated with KOSTSVAR (from 1993 to 2000) or with DIET32 (from 2000 to 2005) software (Aivo, Stockholm, Sweden). The National Food Composition table (PC-kost, Statens livsmedelsverk, Uppsala, Sweden) was used as nutrient database. Food records were validated by 24 h urinary nitrogen.[25]

Energy intake is reported in absolute amounts (kcal), amount per kg of BW (kcal/kg/d), and as a multiple of the measured REE (EI/REE). Macronutrient intake is reported as the percentage of energy intake (E%). Food weight, water volume and fiber weight are expressed in grams per day and as percentage of the total food weight (W%). "Energy density" is defined as the amount of energy per wet weight of food (kcal/g), and was calculated both with and without beverages, where ED is the energy density of the total diet and ED_{food} is the energy density of the diet with beverages omitted. Milk and oral nutritional supplements are not included as beverages because their nutrient compositions and energy densities are similar to those of solid food. In addition, milk and milk products may have been included in cooking and solid meals, and were thus not considered being only beverages.

2.3. Data analysis

A linear mixed model was used to investigate the relationships between energy balance (kcal/day) and ED, ED_{food}, EI, systemic inflammation and survival. Energy balance was defined as the dependent variable. The measurement period was entered as a repeated effect with a Toeplitz covariance type. If model convergence was not achieved, a first-order auto-regressive covariance was used. The last measurement period before death was considered to be common for all patients, in order to enable modeling of the natural disease progression. Thus, measurement periods were 0–4 (1st), 4–8 (2nd), 8–12 (3rd) and 12–16 (4th) months before the final follow-up appointment. ED and EI at the beginning of measurement periods were entered as continuous predictors. Additionally, models were adjusted at the beginning of each measurement period for (log transformed) survival in days, or by tertiles of survival. The presence of inflammation was defined by three criteria: the patient having an elevated level of C-reactive protein (two levels: CRP $>$ 5, CRP $>$ 10 mg/L) or having an ESR $>$ 20 mm/h. The Glasgow Prognostic Score (GPS) was also used to define whether inflammation was present.[26] Schwarz's Bayesian criterion was used to select the inflammatory marker and measure of survival (continuous or tertile-based) that yielded the best model. Differences in patient characteristics and differences in dietary characteristics between patients with or without systemic inflammation were tested with a mixed model with repeated