Metabolic alterations in dogs with osteosarcoma

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Objective—To evaluate changes in resting energy expenditure (REE) as well as protein and carbohydrate metabolism in dogs with osteosarcoma (OSA).

Animals—15 weight-stable dogs with OSA that did not have other concurrent metabolic or endocrine illness and twelve 1-year-old sexually intact female Beagles (control dogs).

Procedures—Indirect calorimetry was performed on all dogs to determine REE and respiratory quotient (RQ). Stable isotope tracers (\(^{15}N\)-glycine, 4.5 mg/kg of body weight, IV; \(6,6\)-deuterium-glucose, 4.5 mg/kg, IV as a bolus, followed by continuous-rate infusion at 1.5 mg/kg/h for 3 hours) were used to determine rate of protein synthesis and glucose flux in all dogs. Dual-energy x-ray absorptiometry (DEXA) scans were performed to determine total body composition.

Results—Accounting for metabolic body size, REE in dogs with OSA was significantly higher before and after surgery, compared with REE of healthy control dogs. The RQ values did not differ significantly between groups. Dogs with OSA also had decreased rates of protein synthesis, increased urinary nitrogen loss, and increased glucose flux during the postoperative period.

Conclusions and Clinical Relevance—Alterations in energy expenditure, protein synthesis, urinary nitrogen loss, and carbohydrate flux were evident in dogs with OSA, similar to results documented in humans with neoplasia. Changes were documented in REE as well as protein and carbohydrate metabolism in dogs with OSA. These changes were evident even in dogs that did not have clinical signs of cachexia. (Am J Vet Res 2001;62:1234–1239)

Humans and other domestic animals affected by cancer have alterations in protein and carbohydrate metabolism, including impaired carbohydrate utilization, altered lipid patterns, catabolism of endogenous proteins, and changes in resting energy expenditure (REE).\(^{11}\) Indirect calorimetry has become standard for use in human and veterinary research to determine REE and metabolic energy requirements (MER).\(^{12-16}\) Metabolic energy requirements for healthy dogs have been known for many years;\(^{17-19}\) however, MER have only recently been determined directly from animals with neoplasia.\(^{19,20}\) Assessment of total body composition is important for determining MER. Techniques to assess MER include evaluation of markers of muscle metabolism, measurement of total body potassium concentration, densitometry, isotope dilution procedures, and anthropometry. These techniques can be time-consuming, invasive, and subjective in nature.\(^{20}\) The newer technique of dual-energy x-ray absorptiometry (DEXA) analysis is considered the standard for determining total body composition in human medicine.\(^{21}\) Dual-energy x-ray absorptiometry scans are gaining popularity among researchers involved with animals because of the ease for rapid, noninvasive, precise, and repeatable measurements of total body composition.\(^{22}\) Precise measurement of body fat, muscle, and bone content can be used to determine lean body mass. These measurements then can be used to calculate more accurate estimates of REE and MER.

Reports of increased energy requirements attributable to critical illness, neoplasia, or trauma have led to the use of arbitrary multiplication factors to adjust REE and to account for a presumed hypermetabolic state. However, conflicting reports exist in human and veterinary literature regarding increases in REE attributable to disease. Several studies in human\(^{23-25}\) and veterinary\(^{12-14,26}\) patients have found little or no difference in REE of patients with critical illness or neoplasia. For example, Ogilvie et al\(^{26}\) observed a decrease in REE and oxygen consumption in dogs with lymphoma. Furthermore, Walton et al\(^{26}\) had equivocal results when determining REE in more than 100 animals that required critical care. Differences in REE were not observed in dogs that had surgical trauma, acquired trauma, or neoplasia, compared with 20 healthy control dogs. However, dogs with documented sepsis were found to have increased REE, compared with control dogs.

Increases in REE in tumor-bearing humans have been documented. Fredrix et al\(^{27}\) found significantly higher REE in 60% of people with newly diagnosed non–small-cell lung cancer. The same study documented hypermetabolism in only 14 of 104 (13%) patients with gastric or colorectal cancer. Therefore, 87% of patients with colorectal or gastric cancer and 40% of patients with non–small-cell lung cancer were eumetabolic or hypometabolic. Dempsey et al\(^{24,25}\) also documented increases in REE in humans with gastrointestinal or colorectal neoplasms. Peacock et al\(^{26}\) documented similar results in humans with sarcoma. Therefore, not all people with neoplasia are hypermetabolic, as previously believed. In fact, metabolic changes may represent a continuum of normometabol-
ic, hypometabolic, and hypermetabolic states, depending on the type and degree of illness at the time of diagnosis.

Analysis of results of studies reveals that critically ill dogs or dogs with neoplasms may not differ substantially from those of clinically normal dogs, suggesting that previously used methods for predicting energy requirements may overestimate actual needs of these dogs. An adequate understanding of the nutrient and energy requirements of cancer patients is necessary when considering nutritional therapy. Alterations in metabolic pathways exist before the onset of clinical signs of cachexia. Use of stable isotope tracers has allowed researchers to obtain valuable information about metabolic derangements in patients with neoplasia. The purpose of the study reported here was to determine changes in REE or respiratory quotient (RQ) in dogs with osteosarcoma (OSA), using indirect calorimetry techniques, and to determine whether the same dogs had measurable alterations in protein or carbohydrate metabolism prior to the onset of clinical signs of anorexia or cachexia.

Materials and Methods

Dogs with OSA—Fifteen client-owned dogs with OSA were included in the study. The OSA involved a single limb of each dog. Each owner consented to inclusion of their dog in the study. The study protocol was approved by a university animal care and use committee.

A CBC, serum biochemical analyses, and urinalysis were performed on each dog to rule out other underlying illness. Dogs were excluded from the study when they had concurrent hepatic, renal, or endocrine disease, had received steroid treatments or undergone anesthesia within 30 days prior to referral to our facility, or had historical or physical evidence of anorexia, weight loss, or cachexia at the time of referral.

During the study, general anesthesia was induced in each dog, and the affected limb was amputated, as described elsewhere. Dogs had ad libitum access to water and were fed a commercial prescription diet twice daily.

Healthy control dogs—Eleven healthy 1-year-old sexually intact female Beagles were selected for use as control dogs for comparison purposes. Each control dog was housed in a 2.4 × 2.4-m pen with 2 other beagles. Dogs had ad libitum access to water and were fed a commercial prescription diet twice daily.

Stable isotope tracers—Stable isotope tracers are widely used in human medicine to evaluate various metabolic pathways. Analysis of stable isotope tracers was used to observe characteristics of substrate flow in various metabolic pathways to determine carbohydrate and protein metabolism. Each dog was administered 15N-glycine (4.5 mg/kg of body weight, IV) and 6,6-(deuterium)-glucose (4.5 mg/kg, IV as a bolus, followed by constant-rate infusion at 1.5 mg/kg/h for 3 hours).

Collection and analysis of blood and urine samples—A catheter was placed in a jugular or lateral saphenous vein of each dogs for collection of blood samples. A urinary catheter was inserted and connected to a closed collection system for 10 hours after infusion of isotopes to enable collection and quantification of urine. Blood samples (3 ml) were obtained at time 0 (just prior to start of isotope infusion) and 2, 2.5, 3, 6, and 10 hours after the start of isotope infusion. Samples were allowed to clot and were centrifuged (3,000 × g), and serum was decanted. Serum samples were frozen at ~70°C and stored until analysis. Urine volume for the 10-hour period after infusion was determined. A 3-ml aliquot of pooled urine was frozen at ~70°C and stored until analysis was performed. All samples were shipped on dry ice to a laboratory at the University of Medicine and Dentistry of New Jersey and analyzed for stable isotope metabolites, using mass spectrometry.

The BUN concentration was determined by use of the urease method. For determination of isotopic enrichment of BUN, 1 ml of water and urease solution (1.0 ml, 60 μM units of urease/ml in 0.1 ml of phosphate buffer, pH 6.5) was added to 2 ml of serum. After incubation at 37°C for 30 minutes, 2 ml of K2CO3 and 0.4 ml of 2-octanol were added. The reaction results in the production of ammonia, which is removed via aeration and collected in 0.1N H2SO4. Total urinary nitrogen content was measured on 1 ml of urine, using the Kjeldahl method. Nitrogen enrichment of the BUN-derived ammonia and Kjeldahl digests were measured via isotope ratio mass spectroscopy, using a mass spectrometer.

Isotopic enrichment of serum glucose was determined as described elsewhere. Serum (0.2 ml) was deproteinized with bismuth hydroxide (4.73%) and 1 ml of zinc sulfate (5.5%). After centrifugation, the supernatant was lyophilized. The residue then was reconstituted with 1 ml of deionized water and separated through a column of Dowex 50 and Dowex 1 ion exchange resin (0.7 g of each). Glucose was eluted with 2 ml of water. The sample was frozen, lyophilized, and converted to the penta-acetate derivative by reaction with excess acetic anhydride:pyridine (2:1; final volume of 0.2 ml) at 60°C for 10 minutes. The mixture was evaporated almost to dryness under a stream of nitrogen gas and reconstituted with 0.2 ml of dichloromethane. Isotopic enrichment can be calculated using the following equation. Ions at 200/202 were monitored.

Whole-body protein synthesis rate was calculated from the total amount of 15N excreted. Amount of the administered dose excreted was calculated by measuring the amount of 15N excreted during the 10-hour period and the amount of 15N remaining in the body’s urea pool at 9 hours. The latter was calculated from the blood collected at the end of the sample collection period (sample obtained at 10 hours). Size of the body’s urea pool was estimated by assuming total body water was equivalent to body weight × 0.65. The amount of isotope remaining in the BUN at 10 hours was < 5%.

Amount of 15N in the urea pool was calculated, using the following equation:

\[
15N_{\text{in urea pool}} = \text{UDS} \cdot \text{BUN} \cdot 15N_{\text{in BUN}} \cdot \text{APE} \cdot 0.01
\]

where UDS is urea distribution space, and APE is atom percent excess.

Protein synthesis rate was calculated as follows:

\[
\text{Protein synthesis rate} = \frac{\text{ET} \cdot (d \cdot e \cdot f \cdot g \cdot h \cdot i)}{1}
\]

where ET is the grams of nitrogen excreted during the 10-hour period, *d is the amount of 15N administered, and *e is the amount of 15N excreted in urine and BUN during the 10-hour period.

Rate of glucose production was calculated and used to determine glucose flux. For 6,6-(deuterium)-glucose, rate of appearance in serum was calculated, using the following formula:

\[
Ra = F \cdot (\text{APE}_{\text{infusion}} / \text{APE}_{\text{serum}} - 1)
\]

where Ra is the rate of appearance in the serum, F is the isotope administration rate, and APE_{infusion} and APE_{serum} are amount of isotopic enrichment in the infusion and serum, respectively.
Calorimetry—Indirect calorimetry was performed to determine REE and RQ for healthy Beagles and for dogs with OSA before and after limb amputation. Indirect calorimetry was performed in dogs with OSA before and 24 hours after anesthesia and amputation. Each control dog was acclimated to the indirect calorimetry unit by use of once weekly sessions for 8 consecutive weeks. Food then was withheld overnight, and serial samples were obtained during a period of 10 to 15 minutes. The acclimation period and overnight withholding of food were used to decrease the potential for stress-induced or postprandial increases in REE. Values for REE were estimated, using an open-flow indirect calorimetry system. Rate of carbon dioxide production (VCO2) and oxygen consumption (VO2) were determined, and REE then was calculated using the following abbreviated Weir formula:

\[
\text{REE} = 1.44 ([9.9 \times \text{VO}_2] + [1.1 \times \text{VCO}_2])
\]

This formula does not account for incomplete oxidation of protein; however, < 2.5% of error is observed by use of this simplification. The RQ is the ratio of VCO2 to VO2 and is used to estimate the type of substrates being used for energy. Values of RQ approaching 1.0 indicate that glucose is the principal substrate for energy metabolism, whereas RQ values of 0.7 and 0.8 indicate that fat and protein, respectively, are the principal energy substrates.

All calorimetry studies were conducted by the same 2 investigators (TBH, JW). Each dog was placed in lateral recumbency in a thermonuclear (20 to 22°C) and relatively quiet environment to minimize stress. This method was similar to that described for humans and dogs in other studies. For all evaluation periods, each dog was allowed to acclimate to its environment, handling, and the collection mask for 5 to 15 minutes before sample collection.

To ensure that all expired gases were collected, the total flow of room air was 10 times estimated basal VO2. Percentage of O2 in a dried aliquot (100 ml) of effluent gas was measured continuously by use of an O2 sensor and an O2 analyzer, using electrochemical cell techniques. Percentage of CO2 in a similar aliquot also was measured by use of a CO2 sensor and a CO2 analyzer, using infrared absorption. Medical-grade 100% N2 and 10% CO2 were used to calibrate the unit immediately following each measurement. Before calibration, gas content of each tank was verified by use of mass spectrometry. A volumeter was used to calibrate flow meters each month. The VO2 was calibrated, using the Fedak nitrogen dilution technique, whereas VCO2 was calibrated by infusing a known flow of CO2 into the mask. A minimum of 10 minutes was allowed for equilibration; once the system reached a steady state after that time, data were collected for an additional 15 minutes to calculate mean VO2 and mean VCO2 for the period.

Dual-energy x-ray absorptiometry—A DEXA scan was performed on each dog with OSA while it was anesthetized for surgery to determine total body composition. Description and validation of DEXA analyses have been reported elsewhere. Each control dog was anesthetized by administration of propofol (4 to 7 mg/kg, IV as a bolus, followed by constant-rate infusion to achieve the desired effect). For dogs that weighed < 10 kg, infant whole-body software was used, whereas for larger dogs, software for adult humans was used.

Statistical analyses—Data were determined to be normally distributed by use of the Kolmogorov-Smirnov test, and differences between dogs with OSA and healthy control dogs were analyzed by use of the Student t-test. Values for REE in dogs with OSA and healthy control dogs in our study were compared with values obtained for control dogs in a study conducted by Walton et al. Those differences were evaluated by use of an ANOVA, followed by the Fisher least-significant difference test for comparison of means. A value of P < 0.05 was used to define significant differences. All results were reported as mean ± SD.

**Results**

**Age and sex of dogs with OSA**—The 15 dogs represented 8 breeds (3 Rottweilers, 3 Golden Retrievers, 3 Labrador Retrievers, 2 Doberman Pinschers, 1 Irish Setter, 1 Bernese Mountain Dog, 1 Australian Shepherd, and 1 Greyhound). Age at the time of diagnosis ranged from 4 to 11 years (mean ± SD, 9.07 ± 1.87 years). Eight dogs were spayed females, 1 was a sexually intact female, and 6 were neutered males. Breed distribution of these dogs was representative of the population of dogs with OSA typically seen at the Colorado State University Veterinary Teaching Hospital during a year.

**Body weight and composition**—Dogs with OSA weighed 33.1 ± 9.1 kg and had a significantly (P = 0.001) higher percentage of body fat than control dogs. Body fat of dogs with OSA ranged from 10 to 40% (24 ± 8.62%), whereas for control dogs, it ranged from 6.4 to 17.2% (10.17 ± 3.25%).

**Results of calorimetry**—The REE of dogs with OSA was significantly higher before (120%; P = 0.01) and after (112%; P = 0.04) surgery, compared with values for control dogs (Table 1). Also, REE of dogs with OSA reported here was significantly (P = 0.006) higher than that of control dogs published elsewhere. The REE for our control dogs did not differ significantly (P = 0.900) from that of control dogs published elsewhere. When corrected for lean body mass, REE obtained before surgery for dogs with OSA was still significantly (P = 0.02) higher (115%) than that of control dogs. However, REE obtained after surgery for dogs with OSA did not differ significantly (P = 0.35), compared with values for control dogs. The RQ values for control dogs following withholding of food did not differ significantly from that for dogs with OSA following withholding of food before (P = 0.26) or after (P = 0.50) surgery.

**Protein synthesis rate**—Protein synthesis rate of dogs with OSA during the postoperative period was 59.7% of the rate of healthy control dogs. Mean value for dogs with OSA after surgery (7.97 ± 1.90 g/kg/d) was significantly (P < 0.001) less than for control dogs.

<table>
<thead>
<tr>
<th>REE</th>
<th>Group</th>
<th>kcal/kgd</th>
<th>kcal/kgd</th>
<th>RQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs with OSA</td>
<td>Before surgery</td>
<td>92.6 ± 16.2*</td>
<td>53.2 ± 4.3*</td>
<td>0.74 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>After surgery</td>
<td>98.1 ± 10.0</td>
<td>48.6 ± 7.9*</td>
<td>0.75 ± 0.07</td>
</tr>
<tr>
<td>Control Beagles</td>
<td>Before surgery</td>
<td>76.8 ± 8.3*</td>
<td>45.8 ± 4.3*</td>
<td>0.77 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>After surgery</td>
<td>75.8 ± 18.2*</td>
<td>41.3 ± 9.4*</td>
<td>0.84 ± 0.06</td>
</tr>
<tr>
<td>Other control dogs</td>
<td>Before surgery</td>
<td>76.8 ± 8.3*</td>
<td>45.8 ± 4.3*</td>
<td>0.77 ± 0.06</td>
</tr>
</tbody>
</table>

*Within each column, values with different superscript letters differ significantly (P < 0.05).
(13.35 ± 3.33 g/kg/d). Correcting for metabolic body size, protein synthesis rate of dogs with OSA was 72.4% of that observed for control dogs. Mean value for dogs with OSA after surgery was 16.25 ± 7.99 g/kg−0.75/d, which was significantly (P = 0.048) less than the value for control dogs (22.46 ± 6.03 g/kg−0.75/d). Urinary nitrogen excretion was 165% higher in dogs with OSA after surgery than in healthy control dogs. Mean value was significantly (P = 0.003) higher in dogs with OSA after surgery (0.76 ± 0.15 g of protein/kg−0.75/d), compared with the value for control dogs (0.46 ± 0.26 g of protein/kg−0.75/d).

Glucose flux—Glucose flux of dogs with OSA was 178% that of healthy control dogs. Mean glucose flux in dogs with OSA after surgery (328.8 ± 124.3 mg/kg/h) was significantly (P = 0.008) higher, compared with the mean value for control dogs (185.0 ± 94.9 mg/kg/h).

**Discussion**

Analysis of results of the study reported here revealed that changes in protein and carbohydrate metabolism, indicated by a decreased rate of protein synthesis, increased rate of urinary nitrogen loss, and increased glucose turnover, were evident in dogs with OSA. These effects were clearly evidenced by a decreased rate of protein synthesis, increased rate of urinary nitrogen loss, and increased glucose turnover, were evident in dogs with OSA even though they did not have clinical signs of cachexia. In contrast to other studies conducted by our laboratory group on dogs with lymphoma or dogs requiring critical care in which the animals were hypometabolic or normometabolic, dogs with OSA in this study were hypermetabolic before and after surgical removal of the tumor and affected limb, as determined on the basis of metabolic body size. When corrected for lean body mass, REE obtained after surgery for dogs with OSA was not significantly different from the value obtained before surgery or from the value for control dogs. Other researchers have described continuation of a hypermetabolic state even after surgical removal of tumor mass.12,14,45,47 Removal of gross tumor burden potentially may have canceled out changes in REE after surgery that were attributable to the stress of anesthesia and surgery. However, other studies conducted by our laboratory group revealed that REE did not change following removal of gross tumor burden, including OSA, or following elective surgeries.11 Furthermore, although gross tumor burden was eliminated with amputation, microscopic tumor burden is likely to persist in dogs with OSA because of the propensity of this type of tumor to metastasize.

Factors other than tumor burden alone are responsible for changes in REE and have been implicated in contributing to cancer cachexia, including tumor necrosis factor-α, interferon-γ, interleukin (IL)-1β, and IL-6.16,44,50 Because we did not detect a significant difference in REE before and after surgery, it appears that REE did not increase as a result of the stress of anesthesia and surgery. This is similar to other findings by our laboratory group in which we documented that REE did not change in healthy dogs and dogs with malignancies before and after invasive surgery.11 One consideration is that dogs with OSA were not compared with age-matched control dogs. The healthy control dogs were younger and also had a substantially lower percentage of body fat than the dogs with OSA. However, it would be expected that younger leaner dogs would have higher REE, compared with REE in clinically affected dogs. It is possible that control dogs had lower REE because of acclimation to the calorimetry unit, and, therefore, were less stressed than dogs with OSA that were naïve to the apparatus. However, REE for our control population did not differ significantly from the REE of other control dogs. Furthermore, variables that were dependent on body size were analyzed relative to metabolic body size, using indexing on the basis of kg0.75 and lean body mass. These are accepted methods for minimizing effects of differences in mass and body composition that may be breed- or age-dependent effects. The control population used in another study26 was slightly older large-breed dogs. When corrected for lean body mass, REE in the study reported here was higher in dogs with OSA during the preoperative but not postoperative period. Therefore, the discrepancy in REE of dogs with OSA before surgery cannot be explained on the basis of age and body composition alone. Analgesics were required after surgery and may have contributed to the decrease in REE observed in dogs with OSA. Alternatively, REE (when corrected for lean body mass) may have been significantly higher before surgery in dogs with OSA as a result of some degree of discomfort or pain and the initial stress of hospitalization. Because REE increases with stress, the decrease in REE in the postoperative period, compared with REE values for the preoperative period, could have been associated with acclimation to the calorimetry unit. However, other research conducted by our laboratory group has not detected significant differences in REE or RQ in dogs with nonhematopoietic malignancies before and after tumor removal.13 Because a difference was not detected in that group of dogs following repeated calorimetry over time, it seems unlikely that acclimation to the calorimetry unit and decreased stress caused the decrease in REE observed after surgery in dogs with OSA in the study reported here.

Furthermore, we did not detect significant differences in RQ before and after surgery in dogs with OSA. If excitement or stress had artificially increased energy expenditure before surgery, it would be expected to shift to greater carbohydrate oxidation and a higher RQ than values obtained after surgery. After surgery, patients often are mildly overhydrated because of the use of high rates of administration of crystalloid fluids during anesthesia. This transient increase in total body water could have artifically increased lean body mass and contributed to the lack of significant differences in REE between dogs with OSA and control dogs. Finally, the decrease in REE during the postoperative period may have been associated with the body’s normal adaptive mechanisms of the thyroid gland hormone axis to down regulate metabolism and concentrate on healing. Many patients with critical illness or neoplasia have euthyroid sick syndrome. Clearly, investigation of activity of the thyroid gland axis will be required to determine whether changes can be temporally related to changes in REE.
An increase in REE can develop as a result of futile cycling of substrates for energy.3,32,33 Tumors preferentially use carbohydrates for energy, converting glucose to lactate in the process.3,32,33 In turn, lactate must be converted back to glucose by the liver via the Cori cycle. Conversion via the Cori cycle is an example of futile cycling by which the host converts 1 substance to another for energy, using an energy-consuming pathway. The process is detrimental in that there is net energy loss by the host. Daily energy requirements may increase by as much as 20% as a result of futile cycling of glucose in the Cori cycle.3,32,33 Increases in glucose flux also have been documented in humans with other types of neoplasia.1,33.35 The increase in glucose flux in our dogs with OSA after surgery suggests increased cycling of glucose, possibly within the Cori cycle or attributable to increased hepatic gluconeogenesis and the production of 3-carbon intermediates.3,36 Increased rates of glucose recycling and hepatic gluconeogenesis can lead to depletion of certain amino acids such as glutamine and alanine. An increase in glucose flux was detected after surgery. This change also was detected in dogs with OSA that lacked an increase in REE.

Values for RQ are used traditionally to document the primary substrate used for energy. The RQ values did not differ significantly between dogs with OSA and control dogs, suggesting that dogs with OSA had normal relative rates of utilization of endogenous protein, carbohydrate, and fat substrates for energy. The RQ value of approximately 0.75 suggested that lipid oxidation was the primary energy source, which is expected for animals following withholding of food overnight. Even in dogs that lacked clinical signs of cachexia or weight loss, dogs with OSA were apparently in a state of less-positive nitrogen balance. The typical adaptive response to reduced protein intake or starvation is a reduction in protein synthesis and reduction of nitrogen loss. In cancer patients, however, this normal adaptive mechanism is lost, and protein synthesis declines with concomitant increases in nitrogen loss, resulting in a negative nitrogen balance.33,35 As tumor synthesis of proteins increases, competition with protein synthesis of the host may develop, resulting in decreased synthesis of muscle protein by a cancer-bearing host.36 The protein synthesis rate of dogs with OSA was significantly lower than that of control dogs. This may have been attributable to catabolism of amino acids for oxidative purposes and may reflect a loss of muscle protein. Because anorexia was not documented in any of the dogs with OSA, the decrease in the rate of protein synthesis cannot be explained by a lack of protein intake alone. Additionally, documentation of increased urinary excretion of nitrogen in dogs with OSA reflected increased protein turnover and greater protein catabolism in those dogs, compared with control dogs. Our results are similar to those of others3,33,35 who have documented increased protein catabolism in humans with neoplasia. Urinary nitrogen excretion for dogs with OSA in the study reported here was quantitatively similar to that reported for other dogs requiring intensive care.37

To our knowledge, this is the first study to document changes in REE and metabolic pathways in dogs with OSA. Additional research must be conducted to evaluate whether the changes detected will progress with time, regress with administration of analgesic agents after surgery, or regress with chemotherapy. Because there is microscopic tumor burden even after removal of tumor mass, it is reasonable to assume that metabolic changes may continue to progress over time and, therefore, contribute to cachexia. Many factors are believed to contribute to metabolic changes, including cytokines (such as tumor necrosis factor-α, interferon-γ, and IL-1β), shifts in the thyroid gland axis, and production of acute-phase proteins. Clearly, studies must be conducted to determine the influence of these factors on metabolic changes seen in animals with neoplasia. A better understanding of the dynamic changes in metabolism in animals with neoplasia is essential for proper nutritional intervention.

References