Hypermetabolism Following Moderate to Severe Traumatic Acute Brain Injury: A Systematic Review

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Abstract

Elevations of metabolic rate following traumatic brain injury (TBI) have been reported previously, with estimates ranging from 32% to 200% above normal values. The aim of this systematic review was to describe the pattern of energy expenditure during the first 30 days following TBI. We searched six databases for trials that measured the energy expenditure at least once during the first 30 days post-injury and compared that value to one that would be predicted in the non-injured state. We identified 24 studies, three of which were randomized controlled trials (RCTs). The sample sizes of the included studies ranged from 6 to 80 (mean, 24.7), and the mean Glasgow Coma Scale (GCS) score of subjects was 4.8. Mean energy expenditure, expressed as a percentage of a predicted value, ranged from 75% to 200%. The lowest values were reported in patients admitted in brain death. Several factors were found to have modulating effects on energy expenditure. The administration of paralyzing agents, sedatives, or barbiturates reduced metabolic rate by approximately 12–32%. Propranolol and morphine were associated with smaller decreases in energy expenditure. Factors that do not appear to augment the hypermetabolic response included the administration of steroids and method of feeding (enteral vs. parenteral). Based on our results, it was unclear if elevated temperature, the presence of extracranial injury, or the severity of injury further exacerbate hypermetabolism. We conclude that energy expenditure following TBI is highly variable, and the use of standard factors to estimate the energy needs of individual patients are inappropriate and should be discouraged.

Key words: energy expenditure; head injury; nutrition; review

Introduction

THE HYPERMETABOLIC STATE that accompanies traumatic brain injury (TBI) has been well documented (Loan, 1999; Long et al., 1979; Ott et al., 1989; Pepe and Barba, 1999; Roberts, 1995; Wilson and Tyburski, 1998; Yanagawa et al., 2002). Although our understanding of the etiology of this phenomenon is not complete, the release of various cytokines and counter-regulatory hormones, mediated through the acute phase response, is believed to be contributory (Chiolero et al., 1989a; Young et al., 1988, 1992). Wide variations in both the magnitude and time course of metabolic perturbations have been reported, with energy expenditures ranging from 32% (Long et al., 1979) to 200% (Haider et al., 1975) above that which would be predicted in the non-injured state. The length of time that metabolic rate remains elevated following head injury is also uncertain. Work by Long et al. (1979) suggested that hypermetabolism resolves within the first 20 days, while

other investigators have reported elevations in metabolic rate that have persisted at 1 year following head injury (Haider et al., 1975).

The present state of uncertainty regarding both the extent and duration of hypermetabolism following head injury limits clinicians' ability to effectively guide nutritional interventions. The task of estimating caloric requirement may be less problematic in the early stages of recovery, where indirect calorimetry is often easily and routinely performed. However, in some circumstances, such as in the absence of this technology, estimating energy expenditure becomes more difficult. Increased mortality, infections, and complications have been associated with caloric deficit (Rapp et al., 1983; Villet et al., 2005), while feeding in excess of requirement may lead to hepatic steatosis and difficulty weaning from mechanical ventilation (Wilson and Tyburski, 1998). Since negative outcomes have been associated with both under- and overfeeding, it is important to estimate caloric requirement thoughtfully.

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In 2000, citing insufficient data upon which to base standards regarding the nutritional care of patients with severe brain injury, the Brain Trauma Foundation, the American Association of Neurological Surgeons, and the Joint Section on Neurotrauma and Critical Care (2000) collectively released guidelines recommending that 140% and 100% of resting metabolic expenditure be replaced in nonparalyzed and paralyzed patients, respectively; these guidelines were recently revised (2007b). Although the recommendations for caloric replacement remain unchanged (100–140%), a distinction is no longer made between these two groups of patients, since energy expenditures are now thought to be 20–30% above pre-injury values, even with paralysis. We sought to define energy expenditure more precisely, by considering the contribution of additional factors. Therefore, the aim of this systematic review was to (i) describe the pattern of energy expenditure during the first 30 days following TBI and (ii) examine the effects of possible mediating factors such as the use of commonly used medications, the presence of extracranial injury, elevated temperature, method of feeding, and severity of injury, in order to support a more informed process of clinical decision-making.

Methods

Search strategy and selection criteria

A systematic review of the literature was conducted to identify all studies measuring energy expenditure within the

first month following acute TBI. Six electronic databases were searched: Cumulative Index to Nursing and Allied Health Literature (Cinahl), Medline, Embase, ISI Web of Science, and Cochrane Library. Search dates depended on the database, but ranged from 1966 to December 2007. Search terms varied slightly across databases and are presented in Table 1. Selecting suitable search terms was challenging given that hypermetabolism and energy expenditure are not indexed terms in any of the databases. The reference lists of all potentially included articles, as well as those from review papers, were hand searched for studies not identified through the original literature search.

The titles and abstracts of each of the citations retrieved through the search process were reviewed independently for potential inclusion by two investigators (N.F. and K.S.). The original articles were retrieved if (a) it was unclear if the subjects had suffered from acute brain injury or (b) energy expenditure had been measured based on the information provided in the abstract. Consensus following discussion was used to resolve conflicts over eligibility of identified articles. Following the initial selection process, all studies found to be potentially suitable were reviewed and assessed for final inclusion.

Inclusions and exclusions

This review was restricted to original research articles, written in the English language, published in peer-reviewed

TABLE 1. LITERATURE SEARCH RESULTS

Database	Search terms	Hits	Duplicates	Exclusions					Potential inclusions
				Not TBI	EE not measured	Non-human	Non-English	Review/opinion	
MEDLINE	Brain injuries [Mesh] Craniocerebral trauma [Mesh] Hypermetabolic/hypercatabolic Protein-energy malnutrition [Mesh] Metabolism [Mesh]	130	—	44	28	9	11	10	28
EMBASE	Brain injury Diet therapy	72	6	26	31	1	3	2	3
ISI Web of Science	Brain injury Hypermetabolism	37	3	2	5	24	0	3	0
CINAHL	Brain injury Hypermetabolism Energy metabolism	6	5	0	1	0	0	0	0
EBM Reviews	Brain injury Energy metabolism Metabolism Hypermetabolism	5	3	0	1	0	0	1	0
Psycinfo	Traumatic brain injury Head injury Metabolism Brain metabolism Hypermetabolism	2	0	0	1	1	0	0	0
Total		252	17	73	67	35	14	16	31

EE, energy expenditure; TBI, traumatic brain injury.

journals conducting subject-level investigations. Included trials were limited to those in which either all, or an identified subgroup of the subjects, had suffered from acute (injury occurring within 2 weeks) traumatic, moderate to severe brain injury, as defined by the study's authors. Trials that recruited subjects with or without extracranial injuries were included. To be eligible for inclusion, subject energy expenditure had to be measured at least once within the first 30 days of injury, and the value expressed as a percentage of predicted energy expenditure (PEE). The latter requirement was included to enable comparability among trials. Trials which did not present summary statistics of the outcomes of interest were still included if sufficient patient level data were available, either in text or figure format to enable a reasonable estimation or calculation of energy expenditure. Studies that included subjects who were less than 18 years of age were also included, provided this group did not comprise more than 50% of the total sample. There were no restrictions based on study design.

Non-English language studies, reviews, letters to the editor, commentaries, and other non-investigational publications were excluded. Abstracts were excluded because of lack of reporting detail. Trials in which the sample was composed entirely of subjects recovering from non-traumatic intracerebral haemorrhages were also excluded. Studies with sample sizes of less than three were excluded.

Data abstraction

One investigator (N.F.) abstracted the following information, which was verified for accuracy by a second investigator (K.S.): sample size, patient characteristics, details of medical/surgical/feeding management, time (hours/days) when energy expenditure assessments were obtained, details of indirect calorimetry measurements, the method that was used to predict estimates of subjects' energy expenditure, the presence of fever or infections, and whether subjects were in a fed or unfed state at the time metabolic measurements were performed. The type of energy expenditure that was measured was also noted. Resting energy expenditure (REE) is a term used to describe the number of calories required to sustain all metabolic processes in an inactive, post-prandial, thermo-neutral state during a 24-h period. Additional energy requirements associated with absorption and digestion are estimated to be approximately 10% of total energy expenditure (Elwyn, 1980). Basal energy expenditure (BEE) differs from REE only in that it does not include the metabolic demands of absorption and digestion.

Due to the heterogeneity of methods and outcomes recorded, pooled analyses were not possible. Consequently, results are reported descriptively. Means $\pm$ standard deviations are reported. Measured energy expenditure (MEE) was expressed as a percentage of the predicted energy expenditure ($MEE/PEE \times 100\%$). Values which fell outside of the range of normal (90–110%) (Long et al., 1979) were assumed to be the result of injury. Subjects with values greater than 110% and less than 90% were considered to be hypermetabolic and hypometabolic, respectively. We accepted the authors' choice of method to estimate PEE, which is typically calculated using models that include variables such as sex, height, weight, and age.

Results

The formal search strategy yielded 252 hits. Following the initial review process, 221 articles were excluded leaving 31 articles for possible inclusion. Reasons for initial exclusions are presented in Table 1. From hand searching, an additional 25 potentially eligible articles were identified. From this pool of 56 articles, 32 were excluded (Table 2). Following final review, 24 articles remained which comprised the final sample (Bitzani et al., 1999; Borzotta et al., 1994; Bruder et al., 1991, 1994, 1998; Chiolero et al., 1989b; Clifton et al., 1984, 1986; Dempsey et al., 1985; Dickerson et al., 1990; Esper et al., 2006; Hadfield et al., 1992; Haider et al., 1975; Kolpek et al., 1989; McCall et al., 2003; Moore et al., 1989; Ott et al., 1994; Petersen et al., 1993; Raurich and Ibanez, 1994; Robertson et al., 1984, 1985; Weekes and Elia, 1996; Young et al., 1985, 1996).

Study characteristics

Mean sample size of all included studies was 24.7 ± 21.5 subjects (range, 6–80). Four trials included a percentage of subjects [50% (Hadfield et al., 1992; Kolpek et al., 1989; Petersen et al., 1993) and 70% (Esper et al., 2006)] who had not suffered from TBI, although data for these subjects were presented separately. Details of the inclusion/exclusion criteria were provided in six of the trials (Borzotta et al., 1994; Bruder et al., 1998; Chiolero et al., 1989b; Esper et al., 2006; McCall et al., 2003; Moore et al., 1989). The characteristics of a cohort of patients, recruited conveniently or consecutively, without establishing eligibility criteria, were described in the remainder of trials. There were four randomized controlled trials (RCTs) (Borzotta et al., 1994; Young et al., 1985, 1996) or quasi-randomized controlled trials (Robertson et al., 1985) evaluating routes of feeding (parenteral versus enteral) and zinc administration. One single group intervention study assessed the effect of propranolol as an intervention unrelated to usual care (Chiolero et al., 1989b). The remaining trials measured the energy expenditure of patients during the natural course of their recovery, subject to medical practices that were common at the time of publication. Three studies included data that was collected retrospectively (Esper et al., 2006; Hadfield et al., 1992; Moore et al., 1989).

Patient characteristics

The mean ages of patients enrolled in all studies ranged from 21 (Bruder et al., 1991; Moore et al., 1989) to 47 (Bitzani et al., 1999) years. Eight trials included a proportion of subjects (up to 40%) who were less than 18 years (Clifton et al., 1984, 1986; Dempsey et al., 1985; Dickerson et al., 1990; Haider et al., 1975; Moore et al., 1989; Robertson et al., 1984). Generally, gender ratios were unequal, such that a greater proportion of males were enrolled.

Subjects in the majority of trials suffered from acute TBI due to motor vehicle accidents, falls and gunshot wounds. A portion of the subjects included in five trials suffered brain injuries that may have not been traumatic in nature, including intracerebral hematomas, diffuse brain injury, or cerebral thrombosis (Clifton et al., 1984, 1986; Haider et al., 1975; Robertson et al., 1984, 1985). Mean Glasgow Coma Scale (GCS) scores ranged from 4.8 (Dickerson et al., 1990) to 9 (Petersen et al., 1993) among the 18 trials where the value was reported or could be calculated. In four cases where a mean

TABLE 2. DETAILS OF EXCLUSIONS FROM FORMAL LITERATURE AND MANUAL SEARCHING

<i>Exclusions</i>	<i>Studies identified through literature search (n = 31)</i>	<i>Studies identified through hand searching (n = 25)</i>
Energy expenditure not measured	7 (Clifton et al., 1981; Dahlberg et al., 1985; Fell et al., 1984; Godbole et al., 1991; Kaufman et al., 1987; Nataloni et al., 1999; Stechmiller et al., 1994)	3 (Bivins et al., 1986; Chioloro et al., 1989a; Fife and Jagger, 1984)
Energy expenditure not compared with a predicted value	6 (Bucci et al., 1988; Deutschman et al., 1986; Feldman et al., 1993; Hatton et al., 1997; Hatton et al., 2006; Krakau et al., 2007)	3 (Ott et al., 1999; Suchner et al., 1996; Waters et al., 1986)
Energy expenditure measured >30 days after injury	1 (Denes, 2004)	1 (Aquilani et al., 2000)
>50% of subjects <18 years	1 (Lazarov, 1999)	0
Review, commentary, or other	4 (Anderson, 1987; Cruz, 1997; Hadley, 1989; Robertson, 1991)	1 (Gadisieux et al., 1984)
Subject-level data presented in graphical form—individual data points undecipherable	1 (Sunderland and Heilbrun, 1992)	0
Duplication	Presented in Table 1	2 (Fried et al., 1989; Hadfield and Little, 1992)
90% of subjects suffered from mild TBI	0	1 (Piek et al., 1989)
Insufficient reporting detail	0	1 (Long et al., 1979)
Total number of excluded studies	20 11	12 13
Total studies remaining		24

GCS score was not provided, scores ranged from 3 to 8 (Bitzani et al., 1999; Clifton et al., 1986), 4 to 7 (Robertson et al., 1984), or were all below 7 (Robertson et al., 1985). The authors of one trial (Hadfield et al., 1992) reported that the Abbreviated Injury Scores for the head and neck were all either 4 or 5, indicating severe to critical injury (Baker et al., 1974). Haider et al. (1975) did not use a scale to assess the severity of head injury, although they described the subjects as having suffered from "severe brain damage." The percentage of patients within individual trials suffering from extracranial injuries ranged from 21% (Clifton et al., 1984) to 100% (Petersen et al., 1993). Only one study included subjects suffering exclusively from isolated head injury (Bitzani et al., 1999). It was unclear whether subjects with extracranial injuries had been included in six trials (Clifton et al., 1986; Esper et al., 2006; Haider et al., 1975; Kolpek et al., 1989; Robertson et al., 1984, 1985).

Three publications recruited subjects from the same institution during overlapping recruitment periods (Clifton et al., 1984, 1986; Robertson et al., 1984); therefore, it is likely that there is some duplication of results.

Patient management

Patients were all managed according to established institutional protocols or at the discretion of the attending physicians. Routine care often included measures to prevent intracranial hypertension (controlled hyperventilation, sedation, barbiturates, analgesics, muscle relaxation, paralyzing

agents, salt and water restrictions, or diuretics (Table 3). Details regarding routine management, with emphasis on medications that could alter metabolic rate, were often lacking, or it was unclear what individual patients had received. The authors of one trial stated that subjects did not receive any medications known to alter metabolic rate (Kolpek et al., 1989). A portion of the subjects, ranging from 33% to 100%, reported from 10 studies underwent either craniotomy or surgical debridement (Table 3). No details of surgical procedures were provided in the remaining studies. All subjects in all trials were mechanically ventilated upon admission to hospital.

Metabolic measurements

Indirect calorimetry was performed using a portable metabolic cart in all but six studies (Clifton et al., 1984; Dempsey et al., 1985; Haider et al., 1975; Raurich and Ibanez, 1994; Robertson et al., 1984), most of which were published before this technology became commercially available (around 1984). In the remainder of studies, other analytical techniques were used to collect and measure oxygen consumption and carbon dioxide production. In one study, a portion of the metabolic measurements were obtained using a metabolic cart, which became available during the study's duration (Robertson et al., 1984). Among the studies that used a metabolic cart, the sampling period varied from less than 30 min (Esper et al., 2006; Hadfield et al., 1992; Kolpek et al., 1989; Moore et al., 1989; Petersen et al., 1993; Young et al., 1985), to

TABLE 3. RESULTS (ARRANGED CHRONOLOGICALLY)

<i>Author</i>	<i>Study type and objective(s)</i>	<i>Subject characteristics / details of management</i>	<i>Number / time of assessments</i> <i>Mean % of measured energy</i> <i>Expenditure (MEE) compared with</i> <i>predicted energy expenditure (PEE)</i>
Haider et al., 1975	Noninterventional study examining energy expenditure following acute brain injury	<p>$n = 11$ (8 M / 3 F)</p> <p>55% intracranial hematomas, 27% concussion, 9% GSW, 9% cerebral thrombosis</p> <p>Mean GCS: not reported</p> <p>Mean age: 32 yrs (3 subjects < 18 yrs)</p> <p>Oxygen consumption was measured once subjects were able to breathe spontaneously</p> <p>Craniotomy: not reported</p> <p>Medications: antibiotic cover, diuretics and aldosterone antagonists</p> <p>Feeding: enteral if tolerated, otherwise parenteral</p> <p>Infections: no details</p>	<p>30 measurements were obtained during the first 30 days, after the subjects were able to breath spontaneously</p> <p>200 $\pm$ 99% day 1 ($n = 2$)</p> <p>168 $\pm$ 55% days 3–5 ($n = 6$)</p> <p>161 $\pm$ 30% days 6–8 ($n = 4$)</p> <p>188 $\pm$ 50% days 9–12 ($n = 6$)</p> <p>200 $\pm$ 49% days 13–20 ($n = 8$)</p> <p>156 $\pm$ 21% days 21–30 ($n = 4$)</p>
Clifton et al., 1984	Noninterventional study measuring increases in energy expenditure and protein catabolism following TBI and to assess adequacy of nutrient intake	<p>$n = 14$ (12 M / 2 F), 3 with extracranial injuries</p> <p>Subjects were selected randomly from a group of 115 patients</p> <p>50% intracranial hematomas, 29% GSW, 21% DBI</p> <p>Mean GCS at admission: 6.2</p> <p>Mean age: 28 yrs (1 subject < 18 yrs)</p> <p>Inclusions: absence of major systemic injuries, survival for the first 48 h and coma lasting > 24 h</p> <p>~ 80% of subjects received craniotomy or surgical debridement.</p> <p>Routine medications included phenytoin, dexamethasone, cimetidine, antibiotics</p> <p>Morphine and pancuronium were used as necessary</p> <p>Enteral feeding initiated within 24 h</p> <p>Infections: no details</p>	<p>Daily measurements were obtained in the absence of gross motor activity and averaged over first 9 days of injury</p> <p>134 $\pm$ 29% for all subjects</p> <p>Subjects at rest without sedation or paralysis: 138 $\pm$ 27%</p> <p>Subjects who were heavily sedated / paralyzed or in barbiturate coma (3 subjects, 10 sampling events): 89 $\pm$ 3%</p>
Robertson et al., 1984	Noninterventional study examining factors that influence the hypermetabolic state following TBI	<p>$n = 55$ (49 M / 6 F)</p> <p>Subjects were selected randomly from a group of 122 patients</p> <p>45% intracranial hematomas, 34% DBI, 21% GSW</p> <p>Mean GCS: Not reported. All 4–7</p> <p>Mean age: Not reported, 49% 21–30 yrs. (11% > 18 yrs)</p> <p>Same patient management as Clifton et al. (1984)</p> <p>Craniotomy: Not reported</p> <p>Enteral feeding initiated within 24 h of injury</p> <p>Infections: no details</p>	<p>188 measurements were taken over the first 5 days</p> <p>152% for all subjects</p> <p>GCS 4–5: 168 $\pm$ 53%</p> <p>GCS 6–7: 129 $\pm$ 31%</p> <p>GCS 8: 150 $\pm$ 49%</p>

(continued)

TABLE 3. RESULTS (ARRANGED CHRONOLOGICALLY) (CONTINUED)

<i>Author</i>	<i>Study type and objective(s)</i>	<i>Subject characteristics/details of management</i>	<i>Number/time of assessments Mean % of measured energy Expenditure (MEE) compared with predicted energy expenditure (PEE)</i>
Dempsey et al., 1985	Noninterventonal study comparing the degree of hypermetabolism exhibited by patients requiring barbiturate therapy when required through medical management and those who did not require barbiturates following TBI	<i>n</i> = 10 (6M/4F), 3 with associated extracranial injuries 80% CHI, 20% GSW Mean GCS at admission: 5.2 Mean age: 27 yrs (4 subjects < 18 yrs) Excluded subjects with sepsis 3 patients required craniotomy Steroids barbiturates, ICP bolt per MD Feeding: No details Infections: no details	30 measurements were obtained within the first 7 days 104 ± 37% for all subjects 86 ± 28% (16 measurements with barbiturates) 126 ± 36% (14 measurements without barbiturates) Mean measurement was significantly lower during barbiturate administration (<i>p</i> < 0.01)
Robertson et al., 1985	Quasi-randomized trial assessing the effect of steroids on nitrogen balance following the first 3 weeks of severe TBI	<i>n</i> = 20 (17M/3F) 75% intracranial hematomas, 20% DBI, 5% GSW GCS score of < 7 on admission Mean age: 36 ± 20 yrs. Same patients management protocol as Clifton et al. (1984) Craniotomy: Not reported Enteral feeding began on day 4 Patients receiving steroids had more infections (2 vs. 0 pneumonia, 3 vs. 2 urinary tract infection)	Daily measurements averaged over days 1–3 123 ± 30% (<i>n</i> = 10:steroid group) 124 ± 16% (<i>n</i> = 10: no steroid group) No significant between group differences
Young et al., 1985	Randomized controlled trial evaluating enteral (EN) versus parenteral nutrition (PN) following TBI	<i>n</i> = 16 (15M/1F), 6 with extracranial injuries 31% CHI, 25% intracranial hematomas, 25% skull fracture, 19% GSW Mean GCS at admission: 6.3 Mean age: 40 yrs. 10 subjects required craniotomy No routine meds—no steroids given, phenytoin only if seizures occurred. Appears elevated ICP was treated conservatively. Enteral feeding initiated when bowel sounds were present Infections: no details	107 measurements (<i>n</i> = 2–12) obtained over 22 + days (data from both groups combined and estimated from figure) 0–3 days: 151% 4–7 days: 138% 8–14 days:137% 15–21 days:140% 22 + days:116% No significant differences in MEE/PEE between EN and PN groups No significant differences in MEE/PEE over the study period

Clifton et al., 1986	Nonintervention study designed to identify factors used to estimate nutritional requirements following TBI	<p>$n = 57$ (51 M/6 F)</p> <p>Subjects were selected from a group of 94 patients who remained eligible after excluding those who remained in a coma for < 24 hrs or who had experienced brain death ($n = 93$)</p> <p>53% intracranial hematomas, 28% DBI, 19% GSW</p> <p>Mean GCS Nor reported. All 3–8</p> <p>Mean age: Not stated, 49% 21–30 yrs. (14% < 18 yrs.)</p> <p>Same patient management as Clifton et al. (1984)</p> <p>Craniotomy: Not reported</p> <p>Enteral feeding initiated on days 3–4</p> <p>Infections: no details</p>	<p>Data only available for a 19 subgroup of subjects receiving steroids (fasted at time of measurement)</p> <p>122 ± 25% days 1–7</p>
Chiolero et al., 1989b	Single group intervention study assessing the effect of propranolol on REE following TBI	<p>$n = 12$ (10 M/2 F), 4 with extracranial injuries</p> <p>42% intracranial hematoma, 33% contusion, 25% DBI</p> <p>Mean GCS at admission: 5.5</p> <p>Mean age: 30 yrs.</p> <p>Inclusion criteria: subjects recovering from a severe head injury (GCS < 8 during first 6 h, age < 60 yrs., medically stable, extubated and free of infection)</p> <p>Managed according to standard protocol (no steroids, β-Blockers or anticonvulsants were used. No patient received barbiturates or benzodiazepines)</p> <p>Craniotomy: Not reported</p> <p>Energy expenditure was measured following extubation.</p> <p>Enteral feeding began when bowel signs were present (3–4 days)</p> <p>Infections: no details</p>	<p>A single measurement was taken between days 3 and 12 before and after administration of propranolol (patients in a fasted state at time of measurement)</p> <p>126 ± 14% at baseline</p> <p>120 ± 12% after propranolol</p> <p>Significant difference between measurement conditions ($p < 0.001$)</p>
Kolpek et al., 1989	Nonintervention study comparing energy expenditure and nitrogen loss of subjects with TBI ($n = 7$) and spinal cord injury (SCI) ($n = 7$)	<p>$n = 7$ (5 M/2 F)</p> <p>71% CHI, 29% GSW</p> <p>Mean peak GCS: 6.8</p> <p>Mean age: 34 yrs.</p> <p>3 patients required craniotomy</p> <p>No patient received any medication that is known to affect metabolic rate.</p> <p>Initiation of feeding: not reported</p> <p>Positive blood or urine cultures in 3 subjects</p>	<p>23 measurements were obtained over a 3-week period</p> <p>148 ± 9% for all measurements</p> <p>144 ± 13% week 1 (14 readings)</p> <p>165 ± 15% week 2 (6 readings)</p> <p>135 ± 12% week 3 (3 readings)</p> <p>Mean MEE/PEE for SCI subjects was significantly lower (94%, $p < 0.01$)</p> <p>(continued)</p>

TABLE 3. RESULTS (ARRANGED CHRONOLOGICALLY) (CONTINUED)

<i>Author</i>	<i>Study type and objective(s)</i>	<i>Subject characteristics /details of management</i>	<i>Number /time of assessments Mean % of measured energy Expenditure (MEE) compared with predicted energy expenditure (PEE)</i>
Moore et al., 1989	Retrospective review of the energy expenditure of a cohort of subjects recovering from severe TBI	<p>$n = 20$ (16 M/4 F), 7 with extracranial injuries 90% CHI, 10% skull fracture Mean GCS: 5.5 Mean age: 21 yrs. (7 subjects < 18 yrs.) Craniotomy: not reported Exclusion criteria: open head injuries, GCS score > 7, injuries to other organs more serious than their head injury 2 patients received a short course of steroids. No other details of medications provided Nutritional support was initiated within the first 48 h Infections: no details</p>	<p>A single measurement was taken within 48 hrs of injury 160 $\pm$ 37% for all subjects</p>
Dickerson et al., 1990	Nonintervention study to assess the contribution of protein oxidation on REE in a cohort of subjects following TBI	<p>$n = 6$ (4 M/2 F), 3 with extracranial injuries Injuries resulted from MVA 50%, falls 33% or GSW 17% Mean GCS: 4.8 Mean age: 31 yrs. (1 subject < 18 yrs.) 3 subjects with craniotomy All subjects received steroids, penobarbital 3 subjects received barbiturates Patients received no nutritional support during study period Infections: no details</p>	<p>A single measurement was taken within 2–3 days of injury 90 $\pm$ 31% for all subjects</p>
Bruder et al., 1991	Nonintervention study assessing energy expenditure and nitrogen excretion of a cohort of TBI subjects.	<p>$n = 8$ (8 M), 6 with extracranial injuries All injuries resulted from trauma Mean GCS: 5.2 Mean age: 21 yrs. Craniotomy: not reported No subject received steroids-no other details of management provided Subjects were initially sedated Subjects receiving TPN at first assessment, TPN or EN at second Infections: no details</p>	<p>2 measurements were obtained 104 $\pm$ 5% at day 4 (with sedation) 134 $\pm$ 10% at day 8 (no sedation, subjects breathing spontaneously) Significant difference between measurement conditions ($p < 0.001$)</p>

Hadfield et al., 1992	Nonintervention study designed to compare the metabolic response to injury of TBI subjects (data obtained prospectively) with non-head-injured, trauma subjects ($n = 13$) (data collected retrospectively).	<p>$n = 13$ (13 M), 6 with extracranial injuries 38% intracranial hematomas, 38% contusions, 16% DBI, 8% skull fracture, all injuries resulting from accidents</p> <p>Median age: 23 yrs.</p> <p>6 subjects required craniotomy</p> <p>No steroids were used</p> <p>No feeding details</p> <p>Infections: no details</p>	<p>Measurements were obtained on 4 occasions. Data estimated from figure. (results from head-injured patients only reported)</p> <p>100% at days 1–2 ($n = 8$)</p> <p>99% at days 3–5 ($n = 11$)</p> <p>89% at days 6–9 ($n = 7$)</p> <p>87% at days 10–20 ($n = 8$)</p> <p>Energy expenditures of patients with extracranial injury only were similar.</p> <p>Measurements obtained on one occasion (48–60 h) post injury</p> <p>Head injuries with extracranial injuries: $150 \pm 5\%$</p> <p>Multiple injuries without head injury $138 \pm 5\%$</p> <p>No significant differences between groups</p> <p>9 measurement periods obtained over 27 days (data estimated from Fig. 1)</p> <p>116% at day 3</p> <p>136% at day 6</p> <p>148% at day 9</p> <p>147% at day 12</p> <p>138% at day 15</p> <p>148% at day 18</p> <p>148% at day 21</p> <p>161% at day 24</p> <p>139% at day 27</p> <p>No significant differences in MEE/PEE between EN and PN groups, therefore results combined</p>
Petersen et al., 1993	Nonintervention study to compare the metabolic responses of patients with TBI ($n = 21$) and associated injuries to patients with major trauma but without head injuries ($n = 21$)	<p>$n = 21$ (14 M/7F), all with extracranial injuries</p> <p>All injuries resulted from MVA, falls, GSW</p> <p>Mean age: 44 yrs.</p> <p>Mean GCS: 9</p> <p>Craniotomy: no details</p> <p>Medical management per MD. No patient received steroids</p> <p>Subjects not receiving nutritional support during the study period</p> <p>There were no infections.</p>	<p>Measurements were obtained on 4 occasions. Data estimated from figure. (results from head-injured patients only reported)</p> <p>100% at days 1–2 ($n = 8$)</p> <p>99% at days 3–5 ($n = 11$)</p> <p>89% at days 6–9 ($n = 7$)</p> <p>87% at days 10–20 ($n = 8$)</p> <p>Energy expenditures of patients with extracranial injury only were similar.</p> <p>Measurements obtained on one occasion (48–60 h) post injury</p> <p>Head injuries with extracranial injuries: $150 \pm 5\%$</p> <p>Multiple injuries without head injury $138 \pm 5\%$</p> <p>No significant differences between groups</p> <p>9 measurement periods obtained over 27 days (data estimated from Fig. 1)</p> <p>116% at day 3</p> <p>136% at day 6</p> <p>148% at day 9</p> <p>147% at day 12</p> <p>138% at day 15</p> <p>148% at day 18</p> <p>148% at day 21</p> <p>161% at day 24</p> <p>139% at day 27</p> <p>No significant differences in MEE/PEE between EN and PN groups, therefore results combined</p>
Borzotta et al., 1994	Randomized controlled trial evaluating enteral (EN) versus parenteral nutrition (PN)	<p>$n = 49$ (40 M/9F), 25 with extracranial injuries</p> <p>Mean age: 28 yrs.</p> <p>Mean GCS within 24 h: 5.3</p> <p>Exclusion criteria: pre-existing metabolic disorders, renal failure, inflammatory bowel disease, >72 h postinjury or immediate poor prognosis</p> <p>Medical and surgical management of subjects per MD.</p> <p>19 subjects required craniotomy</p> <p>12 subjects received barbiturates</p> <p>Enteral nutritional support was initiated within 24 h following randomization.</p> <p>A total of 90 infections were recorded</p>	<p>Measurements were obtained on 4 occasions. Data estimated from figure. (results from head-injured patients only reported)</p> <p>100% at days 1–2 ($n = 8$)</p> <p>99% at days 3–5 ($n = 11$)</p> <p>89% at days 6–9 ($n = 7$)</p> <p>87% at days 10–20 ($n = 8$)</p> <p>Energy expenditures of patients with extracranial injury only were similar.</p> <p>Measurements obtained on one occasion (48–60 h) post injury</p> <p>Head injuries with extracranial injuries: $150 \pm 5\%$</p> <p>Multiple injuries without head injury $138 \pm 5\%$</p> <p>No significant differences between groups</p> <p>9 measurement periods obtained over 27 days (data estimated from Fig. 1)</p> <p>116% at day 3</p> <p>136% at day 6</p> <p>148% at day 9</p> <p>147% at day 12</p> <p>138% at day 15</p> <p>148% at day 18</p> <p>148% at day 21</p> <p>161% at day 24</p> <p>139% at day 27</p> <p>No significant differences in MEE/PEE between EN and PN groups, therefore results combined</p>

(continued)

TABLE 3. RESULTS (ARRANGED CHRONOLOGICALLY) (CONTINUED)

<i>Author</i>	<i>Study type and objective(s)</i>	<i>Subject characteristics/details of management</i>	<i>Number/time of assessments</i> <i>Mean % of measured energy</i> <i>Expenditure (MEE) compared with</i> <i>predicted energy expenditure (PEE)</i>
Bruder et al., 1994	Nonintervention study to evaluate the effect of discontinuation of sedation on energy expenditure in a cohort of patients with TBI	<i>n</i> = 15 (7M/8F), some patients had extracranial injuries All injuries resulted from trauma Mean GCS at scene: 5.5 Mean age: 29 yrs. All deeply sedated at admission, 9 weaned successfully, 4 required further sedation Unclear if subjects were fed at the time of metabolic assessment. No details of medical management or infections provided.	Measurements were obtained within the first 48 h Patients weaned from sedation: 113 ± 10% during sedation 154 ± 20% during 12 h postwithdrawal 143 ± 30% at 24 h 129 ± 10% at 48 h Significant difference in energy expenditure between sedation and 48 h postweaning (<i>p</i> = 0.004) Patients requiring additional sedation: 115 ± 20% during initial sedation 122 ± 20% during subsequent sedation No significant difference between conditions (<i>p</i> = 0.56) Measurements were obtained on one occasion at day 3 (data estimated from figure) 145 ± 26% (<i>n</i> = 7)
Ott et al., 1994	Nonintervention study to assess amino acid flux following severe TBI	<i>n</i> = 8 (7M/1F), 4 with extracranial injuries 100% CHI Mean GCS during first 24 h: 6.8 Mean age: 35 yrs. No subject received steroids. No other details of patient management were provided All subjects received TPN 3 subjects developed an infection	Measurements were obtained on one occasion at day 3 (data estimated from figure) 145 ± 26% (<i>n</i> = 7)
Raurich and Ibanez, 1994	Nonintervention study to compare the metabolic response to injury in 3 groups of patients with severe TBI (with morphine, without morphine and patients with extracranial injuries receiving morphine)	<i>n</i> = 80 (65M/15F), 20 with extracranial injuries 88% focal injury, 12% DBI Mean GSA: 7 Mean age: 32 yrs. Craniotomy: not reported No barbiturates or β-blockers used No other details of patient management. Subjects received EN or TPN Infections: no details	Measurements were obtained on one occasion at 48–72 hrs. 126 ± 17% for subjects not receiving morphine (<i>n</i> = 34) 116 ± 11% for subjects receiving morphine (<i>n</i> = 26) 125 ± 17 % for subjects with multiple injuries receiving morphine (<i>n</i> = 20) No significant differences among groups

Weekes and Elia, 1996	Nonintervention study examining the nutritional management of patients with TBI	<p>$n = 6$ (6M), 3 with extracranial injuries 50% intracranial hematomas, 33% contusions, 17% intracerebral hemorrhage, all resulting from trauma Mean GCS at admission: 6.5 Mean age: 23 yrs. All subjects received sedating and paralyzing drugs All subjects were fasted prior to metabolic measurements Infections: no details</p>	<p>Measurements were obtained on two occasions. 125 $\pm$ 16% at days 3–5 ($n = 6$) 105 $\pm$ 11% at days 12–19 ($n = 4$)</p>
Young et al., 1996	Randomized controlled trial to examine the effect of zinc supplementation on neurological recovery and metabolic parameters following TBI	<p>$n = 68$ (55M/13F), 39 with extracranial injuries 56% focal injury, 44% DBI, all with blunt head injury Excluded subjects with gunshot injuries and severe extracranial injuries Mean GCS: 6.5 Mean age: 35 yrs. All but 2 subjects were initially mechanically ventilated 29 subjects required craniotomy No subjects received steroids, 12 received barbiturates. All subjects received TPN initially Infections: no details</p>	<p>Measurements were obtained on 6 occasions over 28 days (data estimated from figure-higher REE reported)</p> <p>163% at days 1–3 (Zn group) 155% at day 5 (both groups) 153% at day 10 (Zn group) 145% at day 15 (Zn group) 140% at day 21 (both groups) 130% at day 28 (both groups)</p> <p>No significant differences between Zn supplemented and control groups except at admission</p> <p>A total of 1,919 measurements were recorded within the first 10 days</p> <p>Grp 1) 121 $\pm$ 19% (sedated, 1,031 measurements) Grp 2) 122 $\pm$ 14% (sedated and paralyzed, 119 measurements) Grp 3) 123 $\pm$ 13% (sedated, barbiturate coma, 529 measurements) Grp 4) 140 $\pm$ 29% (no sedation, 240 measurements)</p> <p>All measurements were corrected for differences in body temperature</p> <p>Significant difference in means between groups 1 and 4 ($p < 0.05$)</p> <p>(continued)</p>
Bruder et al., 1998	Noninterventional study designed to assess the relationship between energy expenditure, body temperature and sepsis in subjects receiving differing forms of sedation following TBI	<p>$n = 24$ (19M, 5F), 9 with extracranial injuries All head injuries resulting from trauma Mean GCS on admission: 5.0 Mean age: 31 yrs. Exclusions: $\text{FI}O_2$ of > 0.6, positive end expiratory pressure of > 5 cm H_2O, or surgical procedure in the previous 24 h 4 types of sedation protocols were administered: (Grp1) fentanyl + midazolam, (Grp 2) fentanyl + midazolam + vecuronium or atracurium (Grp 3) fentanyl + midazolam + thiopental (Grp 4) No sedation No other details of medical management were provided. No details of feeding provided 13 subjects developed sepsis</p>	

TABLE 3. RESULTS (ARRANGED CHRONOLOGICALLY) (CONTINUED)

<i>Author</i>	<i>Study type and objective(s)</i>	<i>Subject characteristics/details of management</i>	<i>Number/time of assessments Mean % of measured energy Expenditure (MEE) compared with predicted energy expenditure (PEE)</i>
Bitzani et al., 1999	Noninterventonal study designed to assess the effect of brain death on energy expenditure	<p>$n = 30$ (22 M/8 F), all with isolated traumatic head injury</p> <p>No details of the nature of injury reported</p> <p>Mean GCS, not stated Range, 3–8</p> <p>Mean age: 47 yrs.</p> <p>All subjects were sedated</p> <p>Grp 1: $n = 10$ no brain death</p> <p>Grp 2: $n = 20$ subjects either were admitted with brain death or progressed to it</p> <p>Standard medical protocol followed to control ICP</p> <p>Midazolam and fentanyl used as required</p> <p>No details of feeding or infections provided</p>	<p>One measurement period at 48 h</p> <p>$121 \pm 11\%$ (Grp 1)</p> <p>$75 \pm 11\%$ (Grp 2)</p> <p>Significant difference between groups ($p < 0.01$)</p>
McCall et al., 2003	Noninterventonal study designed to assess the effect of neuromuscular blockade on energy expenditure following TBI ($n = 18$) and trauma without head injury ($n = 14$)	<p>$n = 18$ (11 M/7 F), 8 with extracranial injuries</p> <p>All injuries resulting from trauma</p> <p>Mean age: 36 yrs.</p> <p>Mean GCS: 4.5</p> <p>Inclusion criteria: severe traumatic brain injury, the need for at least 5 days of mechanical ventilation, and a medical history negative for conditions that could alter metabolic rate</p> <p>All subjects underwent craniotomy and were paralyzed, sedated and receive morphine</p> <p>Enteral nutrition was initiated within 3 days of admission</p> <p>Infections: no details</p>	<p>107 measurements were taken during the first 13 days (average of 9 days). Each subject was assessed an average of 4.9 times.</p> <p>96% while paralyzed and NPO</p> <p>119% without paralyzing agents, during sedation and NPO</p> <p>Mean energy expenditure of trauma patients was significantly compared with TBI (no paralysis) (105%, $p = 0.02$)</p> <p>MEE was significantly higher without the use of paralyzing and sedating agents ($p = 0.002$)</p> <p>MEE of trauma patients was 105%</p> <p>Not explicitly stated but it appears measurements were performed on each patient once within the first 7 days following injury.</p> <p>$147 \pm 24.5\%$</p> <p>No significant difference in median MEE/PEE between traumatic and non-traumatic brain injury groups (147 % vs. 126%, $p = 0.30$)</p>
Esper et al., 2006	Comparison of the energy expenditure of subjects with non traumatic intracranial hemorrhage (data collected retrospectively) ($n = 14$) and severe traumatic brain injury (data collected prospectively) ($n = 6$).	<p>$n = 6$ (4 M/2 F)</p> <p>Mean age: 38.5 yrs.</p> <p>Mean admission GCS: 6.2</p> <p>Inclusion criteria: GCS < 9 and abnormal computed tomography scan. Exclusion: pregnancy, < 16 yrs. barbiturate coma, hemodynamic instability, agitation, seizure activity, early signs of spasticity, $\text{FIO}_2 \geq 60\%$, positive end expiratory pressure ≥ 5 cm H_2O</p> <p>4 subjects required craniotomy</p> <p>Sedation, paralyzing agents and steroids were used in 5, 0 and 0 subjects respectively.</p> <p>Enteral nutrition support was initiated within 36 hrs.</p> <p>Infections: no details</p>	

GCS, Glasgow Coma Scale score; GSW, gun shot wound; DBI, diffuse brain injury; CHI, closed head injury; ICP, intracranial pressure; FIO_2 , fraction of inspired oxygen

30 min to 2 h (Borzotta et al., 1994; Bruder et al., 1994; Chiolero et al., 1989b; McCall et al., 2003; Robertson et al., 1984, 1985), or were measured continuously over a 24-h period (Bruder et al., 1991, 1998). Weekes and Elia (1996) obtained measurements that were collected over a 24-h period on one occasion and for less than 30 min on the second occasion. Metabolic measurements were taken when subjects were both artificially ventilated and breathing spontaneously. In two studies, patients were breathing spontaneously at the time when all metabolic measurements were performed (Chiolero et al., 1989b; Haider et al., 1975). The authors of two studies stated that patients were not receiving neuromuscular blockade at the time of metabolic assessment (Haider et al., 1975; Young et al., 1985), and Chiolero et al. (1989b) stated that measurements were taken during periods when there was no significant muscular activity.

Twelve authors specified measurement of REE (Bitzani et al., 1999; Chiolero et al., 1989b; Clifton et al., 1984; Dempsey et al., 1985; Dickerson et al., 1990; McCall et al., 2003; Moore et al., 1989; Petersen et al., 1993; Raurich and Ibanez, 1994; Robertson et al., 1984, 1985) or basal metabolic rate (Weekes and Elia, 1996), while the remainder simply stated that they had measured "energy expenditure." The authors of most studies conducted metabolic measurements without feeding interruptions (Borzotta et al., 1994; Bruder et al., 1991; Clifton et al., 1984, 1986; Hadfield et al., 1992; Haider et al., 1975; Kolpek et al., 1989; McCall et al., 2003; Moore et al., 1989; Ott et al., 1994; Raurich and Ibanez, 1994; Robertson et al., 1984, 1985; Young et al., 1996), while patients in four trials were fasted prior to assessments (Chiolero et al., 1989b; Dickerson et al., 1990; Petersen et al., 1993; Weekes and Elia, 1996).

The Harris Benedict (HB) equation was used in 18 studies to predict REE. An alternate prediction equation (Elia and Livesey, 1992; Owen, 1988) was also used in two studies (Hadfield et al., 1992; McCall et al., 2003). A nomogram (Boothby et al., 1936) was used in two studies (Clifton et al., 1984; Haider et al., 1975). Finally, the method used to estimate energy expenditure was not stated explicitly in four trials (Borzotta et al., 1994; Clifton et al., 1986; Robertson et al., 1984, 1985).

The number of occasions upon which energy expenditure was measured, as well as the number of subjects represented at each testing interval, varied widely among studies (Table 3). During the first 7 days following injury, mean energy expenditure expressed as a percentage of a predicted value ranged from 75% in subjects admitted in brain death, (Bitzani et al., 1999) to 200% (Haider et al., 1975). Both of these results were obtained within the first 48 h of admission. During the second week post-injury, the mean results ranged from 89% (Hadfield et al., 1992) to 161% (Haider et al., 1975), and during the third and fourth weeks, mean energy expenditure ranged from 116% (Young et al., 1985) to 200% (Haider et al., 1975) of predicted values.

Figure 1 represents the pattern of energy expenditure during the first 30 days following head injury based on data from 15 studies that reported results from measurement/assessment on specified days, or a narrow range of days, post-injury (Bitzani et al., 1999; Borzotta et al., 1994; Bruder et al., 1991, 1994; Dickerson et al., 1990; Hadfield et al., 1992; Haider et al., 1975; Moore et al., 1989; Ott et al., 1994; Petersen et al., 1993; Raurich and Ibanez, 1994; Robertson et al., 1985; Weekes and Elia, 1996; Young et al., 1985, 1996). Data from nine studies that reported only a single, combined mean value for all metabolic measurements obtained during the study period, lasting 5–13 days, were excluded (Bruder et al., 1998; Chiolero et al., 1989b; Clifton et al., 1984, 1986; Dempsey et al., 1985; Esper et al., 2006; Kolpek et al., 1989; McCall et al., 2003; Robertson et al., 1984).

Subjects receiving paralyzing agents, sedatives, or barbiturate therapy demonstrated significantly lower energy expenditures. The mean REE of sedated patients ranged from 86% to 121% of predicted values compared with non-sedated patients, which ranged from 126% to 140% (Bruder et al., 1994, 1998; Dempsey et al., 1985). The mean energy expenditures of patients who were paralyzed were also lower (89–128% of predicted) compared with samples from subjects who were not (119–159%) (Bruder et al., 1998; Clifton et al., 1984, 1986; McCall et al., 2003; Robertson et al., 1984). Propranolol administration decreased energy expenditure by 5% (Chiolero et al., 1989b) and 18% (Robertson et al., 1984). Morphine was associated with an 8% (Raurich and Ibanez, 1994) decrease in

FIG. 1. Pattern of energy expenditure during the first 30 days post-injury.

energy expenditure. There were no differences in the mean energy expenditure of patients receiving steroids compared with those who did not (Robertson et al., 1985) or between those receiving enteral or parenteral nutrition (Borzotta et al., 1994; Young et al., 1985).

Six authors examined the relationship between energy expenditure and body temperature. Of the four trials that reported the results for the whole study group, a positive correlation was reported in one study ($r=0.44$, $p<0.01$) (Clifton et al., 1984) and no association was reported in three studies (Chiolero et al., 1989b; Hadfield et al., 1992; Robertson et al., 1984). There was an association between temperature and energy expenditures reported for subjects with greater severity of head injury (Robertson et al., 1984), brain death (Bitzani et al., 1999), those receiving sedation, and/or sepsis (Bruder et al., 1998).

The results from four trials indicated that there were no differences in energy expenditures of subjects with isolated head injury compared with those who presented with accompanying extracranial injury (Borzotta et al., 1994; McCall et al., 2003; Raurich and Ibanez, 1994; Young et al., 1985), while the results from two studies comparing subjects with head injury (both with and without associated extracranial injury) and general trauma patients were conflicting. McCall et al. (2003) reported significantly increased mean energy expenditure associated with head injury, while Petersen et al. (1993) did not. The percentages of head-injured subjects suffering from extracranial injuries in the subgroups of these two studies were 44% (McCall et al., 2003) and 100% (Petersen et al., 1993). McCall et al. (2003) reported no association between energy expenditure and severity of head injury, while Robertson et al. (1984) reported that subjects with lower GCS had higher energy expenditures.

In the only study to examine the relationship, the mean energy expenditure of patients in the fed state was 9% higher than patients in the fasted state (22.3 vs. 24.6 Kcal/kg, $p=0.002$) (McCall et al., 2003). Among the studies that reported details of sepsis or infection, the relationship with energy expenditure was examined in only one (Bruder et al., 1998). The results from this study indicate that MEE was higher than predicted in subjects with sepsis compared with no infection (128% vs. 119%; $p<0.001$).

Discussion

Based on the results of this review, we can confirm that energy expenditure is increased following moderate to severe acute head injury in most patients, but the results were highly variable. Measurements for most subjects fell outside of the normal range. In subjects who were considered to be hypermetabolic, the mean percentage of MEE/PEE ranged from a low of 116% at day 3 (Borzotta et al., 1994) to a high value of 200% (Haider et al., 1975). Energy expenditures of subjects were measured serially (two to nine times) in seven trials over 10–30 days. Subjects in five of these trials were hypermetabolic at all testing occasions (Borzotta et al., 1994; Haider et al., 1975; Kolpek et al., 1989; Young et al., 1985, 1996). In only one trial were energy expenditures consistently at, or below, predicted values (Hadfield et al., 1992). Bitzani et al. (1999) reported the lowest energy expenditures following brain death, a finding which was attributed to decrease in oxygen consumption by the brain, which may be anticipated since the

brain is known to consume 20% of total caloric requirement (Pevsner et al., 1971).

We are aware of only one previous systematic review of hypermetabolism following TBI that incorporated the results from 14 trials, published from 1993 through 2003 (Krakau et al., 2006). These authors reported similar, although less variable results compared with the present study, with deviations in MEE/PEE of 96–160%. The authors attributed most of the inconsistency of results to variability in measurement procedures. Due to differences in eligibility criteria, the present study included only eight of the same studies (Borzotta et al., 1994; Bruder et al., 1994, 1998; McCall et al., 2003; Ott et al., 1994; Raurich and Ibanez, 1994; Weekes and Elia, 1996; Young et al., 1996). Since we did not impose publication date restrictions, and used patient level data or estimates from figures when summary statistics were not provided, we were able to summarize data from an additional 16 studies. We explored additional sources of heterogeneity among studies including medical management, characteristics of subjects and/or differences associated with timing, and the specifics of measurement technique.

It is difficult to define precisely the effect of medical management on energy expenditure following acute head injury since multiple interventions are commonly used. Treatments, which individually may be expected to either raise or lower energy expenditure, are often provided in combination, rendering the individual contribution from injury difficult to isolate. Patients' neurological status may change frequently and rapidly, necessitating changes in medical management; therefore, the requirement for, and effects of, medications may also be short-lived. For example, patients may require sedation for only short periods of time, during which their metabolic rate may be depressed, but may rise dramatically during withdrawal. The clinical implications of these short-term fluctuations in metabolic rate remain unclear. Nevertheless, based on the results from this review we estimated that sedatives or barbiturates reduced metabolic rate by approximately 13–32% and paralyzing agents decreased metabolic rate from 12% to 28%. While the effect of morphine appeared to be more modest, independently decreasing energy expenditure by only 8% (Raurich and Ibanez, 1994), McCall et al. (2003) reported that 16% of the variability in MEE change between the paralyzed and non-paralyzed states could be attributed to morphine, suggesting that it is a more potent mediator. Similarly, the clinical significance of the 5% reduction in energy expenditure following propranolol administration reported in one study (Chiolero et al., 1989b) is likely minimal, although Robertson et al. (1984) reported a more substantial 18% decline in a subgroup of six patients. Since 10% of REE is attributed to heart function and propranolol reduces energy expenditure by decreasing the heart rate (Chiolero et al., 1989b), some reduction in energy expenditure can be expected. Based on the results from only a single study (Robertson et al., 1984), we found no evidence that steroids, which were hypothesized to raise metabolic rate by augmenting the stress response, had the purported effect. It is worth noting that the use of steroids post-TBI is now contraindicated (2007a).

Although the route of feeding (enteral versus parenteral), type (continuous versus intermittent), nutrient composition (fat, protein, and carbohydrate), and caloric load are known to influence energy expenditure (Carlson et al., 1994; Forsberg

et al., 1994; Heymsfield et al., 1987), feeding protocols did not appear to be a major contributor to the variability observed in REE. There were no differences in the energy expenditures reported in studies that compared enteral with parenteral feeding (Borzotta et al., 1994; Young et al., 1985), a finding that has been reported previously in a small sample of healthy individuals (Vernet et al., 1986). The difference in energy expenditure between patients in the fed versus unfed state was attributed to a 10% thermogenic response to feeding in a single study where the comparison was possible (McCall et al., 2003).

Controlled mechanical ventilation reduces the metabolic cost of spontaneous breathing, which is estimated to be about 4% in healthy volunteers (Lewis et al., 1988), and up to 25% during critical illness (Bursztein et al., 1978) and weaning (Lewis et al., 1988). While mode of breathing could have contributed to some of the variability in energy expenditure, insufficient detail was provided in the majority of studies to enable further examination as it was impossible to establish whether subjects were mechanically ventilated or breathing spontaneously during measurements. Similarly, it was not possible to assess whether other manoeuvres common to the care of patients in an intensive care setting, including turning, physiotherapy or suctioning, also led to increased energy expenditure and contributed significantly to the variability among studies, particularly during the first week when interventions may be most intensive.

Differences in injury severity may have accounted for some of the variability in REE across studies. There was conflicting evidence of a relationship between severity of injury and metabolic rate. In one study, patients with GCS scores of 4–5, who exhibited posturing responses to pain, but who were not assessed during periods of posturing, had higher REE compared with patients with GCS scores of 6–7 (Robertson et al., 1984). Surprisingly, the energy expenditures of patients with GCS scores of 8 were intermediate to the other two groups, although patients were described as being restless during measurement. The same authors also noted a positive correlation between oxygen consumption and serum catecholamines. In contrast, McCall et al. (2003) and Clifton et al. (1984) both reported weak, nonsignificant correlations between GCS scores and energy expenditure.

Based on the subgroup results from three studies, the addition of extracranial injury does not appear to increase energy expenditure when compared with isolated head injury (Borzotta et al., 1994; Raurich and Ibanez, 1994; Young et al., 1985). This finding might suggest a systemic effect of the acute phase response, a hypothesis supported by the findings from Petersen et al. (1993), who reported no significant differences in the energy expenditures of patients with head and multiple injuries compared to those with multiple injuries, but no brain injury. However, Haider et al. (1975) speculated that “vegetative dysregulation”, an additional factor present in cerebral injury, could account for energy expenditures far in excess of what would be expected following common trauma.

The contribution that increased temperature makes to energy expenditure is unclear based on the results of this review. Bruder et al. (1998) suggested that the increased energy expenditure found in their two earlier publications could be explained entirely on the basis of raised body temperature in sedated patients, using Du Bois’s estimate (1954) that there is a 13% increase in metabolic rate per degree Celsius. However, Clifton et al. (1984) reported elevations in energy expenditure

far exceeding that which could be explained on the basis of increased temperature.

The lengths of time that metabolic measurements were taken and the stability of the measurements may also have contributed to the variability since shorter periods of time (i.e., less than 2 h) may not have been representative of an entire 24-h period. For example, discarded measurements indicated that energy expenditure increased from 30% above predicted values to 200% during periods of posturing (Chiolero et al., 1989b). Similarly, the energy expenditure of one patient fluctuated by more than 25% during a 24-h period in one study which was assumed to be related to body temperature fluctuations (Weekes and Elia, 1996). Metabolic measurements lasting a full 24-h period were performed in only two trials (Bruder et al., 1991, 1998).

We chose to present our energy expenditure findings in terms of a percentage of a predicted value. While this manoeuvre enabled comparisons across studies, its use may also have introduced a source of variability and error. The Harris-Benedict equation, the most frequently used prediction equation, was developed almost 100 years ago and relied on data from only 239 healthy men and women (Harris and Benedict, 1919). The individual variability in energy expenditures in this sample was substantial. For example, two female subjects weighing 106 and 176 pounds, respectively, each had a basal metabolism of 1,475 Kcals. Furthermore, the use of the HB equation to estimate energy requirements in the malnourished state, which is common following TBI, has also been questioned since the assumption of a normal body composition is violated. Malnutrition results in a loss of body cell mass and fat, while the extracellular mass expands (Roza and Shizgal, 1984).

While there was no discernable pattern of energy expenditure, the results from this study indicated that hypermetabolism persists for 30 days, although attrition of subjects in almost all studies raises doubts about the validity of this finding. Only seven trials measured the energy expenditure beyond 10 days (Borzotta et al., 1994; Hadfield et al., 1992; Haider et al., 1975; Kolpek et al., 1989; McCall et al., 2003; Young et al., 1985, 1996). Furthermore, the possibility exists that subjects with more severe injuries were over represented in trials with a longer observation period, as subjects with relatively milder injury may have been lost following transfer to other services or discharge, or alternatively, patients with the most severe injury may have died.

Several limitations of this review should be noted. We included only studies written in the English language and, therefore, may have missed relevant data published in non-English language journals. We relied on information that was supplied in the written report only where detail was frequently lacking. Sample sizes in virtually all of the included studies were small, often resulting in a lack of precision of the estimate of energy expenditure. In studies in which group comparisons were reported these small sample sizes with insufficient power may have increased the likelihood of a type II statistical error (claiming no difference between groups when one may have existed). We did not include an assessment of the methodological quality of the individual studies, as is customary, since this review included only three RCTs. The merit of assessing the quality of observational trials, which intrinsically lack rigor, has been questioned. Bias may have been introduced by including studies published over 30

years ago. Gains in knowledge and technological advances might mean that intracranial pressure, which has been shown to correlate with metabolic rate, is managed more effectively today than in previous years. Consequently, we might reasonably have expected to see a blunting of the hypermetabolic response reported in more recent studies compared with older ones. However, with the exception of the earliest study where the highest level was reported, more recently published studies reported increases in energy expenditure that were in excess of 150% of predicted values.

Conclusion

Following a review of 24 studies assessing energy expenditure following TBI, we found that metabolic rate is highly variable. The lowest value (75% of predicted) was reported in patients admitted with a diagnosis of brain death. Overall, in the remaining studies, metabolic rates ranged from 87% to 200% of predicted values at some point during the first 30 days post-injury. We estimated that paralyzing agents, sedatives, or barbiturates reduced metabolic rate by approximately 12–36%. Morphine and propranolol decreased energy expenditure by 8% and 5%, respectively. Factors that do not appear to augment the hypermetabolic response included the administration of steroids and the route of feeding (enteral vs. parenteral). It is unclear if increased severity of injury, the presence of extracranial injury, or elevated temperature contributes significantly to the hypermetabolic state. While the results of this study have implications for guiding clinical practice, particularly when indirect calorimetry is unavailable, they should not be used to estimate energy requirements for individual patients.

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