



Randomized control trials

Tight Calorie Control in geriatric patients following hip fracture decreases complications: A randomized, controlled study[☆]

R. Anbar^{a,d}, Y. Beloosesky^b, J. Cohen^c, Z. Madar^d, A. Weiss^b, M. Theilla^c, T. Koren Hakim^a, S. Frishman^a, P. Singer^{c,*}

^a Nutrition Unit, Rabin Medical Center, Petah Tikva, Israel

^b Department of Geriatrics, Rabin Medical Center, Petah Tikva and Sackler School of Medicine, Tel Aviv University, Israel

^c Department of General Intensive Care, Rabin Medical Center, Petah Tikva and Sackler School of Medicine, Tel Aviv University, Israel

^d School of Nutritional Sciences, The Robert H Smith Faculty of Agriculture, Food and Environmental Quality Sciences, Hebrew University, Jerusalem, Israel

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SUMMARY

Background & aims: Optimizing nutritional intake has been recommended for geriatric patients undergoing hip-fracture surgery. Whether nutritional support guided by repeated measurements of resting energy requirements (REE) improves outcomes in these patients is not known.

Methods: A randomized, controlled, unblinded, prospective, cohort study comparing provision of energy with a goal determined by repeated REE measurements using indirect calorimetry, with no intervention. Oral nutritional supplements were started 24 h after surgery and the amount adjusted to make up the difference between energy received from hospital food and measured energy expenditure.

Results: 50 Geriatric patients were included in the study. Patients in the intervention group ($n = 22$) received significantly higher daily energy intake than the control group ($n = 28$) (1121.3 ± 299.0 vs. 777.1 ± 301.2 kcal, $p = 0.001$). This was associated with a significantly less negative cumulative energy balance (-1229.9 ± 1763 vs. -4975.5 ± 4368 kcal, $p = 0.001$). A significant negative correlation was found between the cumulative energy balance and total complication rate ($r = -0.417$, $p = 0.003$) as well as for length of hospital stay ($r = -0.282$, $p = 0.049$).

Conclusion: We have demonstrated that nutritional support actively supervised by a dietician and guided by repeated measurements of REE was achievable and improved outcomes in geriatric patients following surgery for hip fractures. Clinicaltrials.gov Identifier: NCT017354435.

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1. Introduction

Hip fractures remain a significant health risk in the elderly population in western society. Thus, in the United States, the mean annual number of hip fractures in 2005 was 957.3 per 100 000 for women and 414.4 for men.¹ These injuries degrade quality of life and increase both morbidity and mortality.^{1,2} One of the factors

which might influence the outcome of these patients is their nutritional status. In this regard, up to half of elderly patients with hip fractures are already malnourished on admission to hospital and protein energy malnutrition appears to be more common in older patients with hip fractures than age-matched controls.^{3,4} In addition to the effects of preexisting under nutrition, lean body mass may be further depleted by the inflammatory response to injury, which leads to a catabolic state characterized by nitrogen loss and insulin resistance. This is evident immediately after the injury and may continue for up to 3 months after surgery. Finally, under nutrition may be further aggravated by lower than required intake of energy during the hospital stay.

This state of under nutrition may impact on outcome. Negative effects include muscle wasting and weakness, impairing mobility and predisposition to decubitus ulcers and pulmonary complications (including atelectasis and pneumonia) as well as impaired immune responses further predisposing to an increase in post-operative infections.^{5,6}

Non-standard abbreviations: IC, indirect calorimetry; ONS, oral nutritional supplements; MAC, mid-arm circumference; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; CCI, Charlson's comorbidity index; FIM, Functional Independence Measure; MMSE, Mini-Mental State Examination; MNA, mini-nutritional assessment; CAM, Confusion Assessment Method.

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* Corresponding author. Department of General Intensive Care, Rabin Medical Center, Petah Tikva 49100, Israel. Tel.: +972 3 9376521; fax: +972 3 9232333.

E-mail address: psinger@clalit.org.il (P. Singer).

It is therefore important to determine whether these adverse outcomes may be modified by active nutritional interventions. In this regard, a recent Cochrane review of nutritional supplementation for hip fracture aftercare in older people concluded that there was only weak evidence for the effectiveness of protein and energy feeds.² In these studies, energy requirements were typically based on the use of weight-based formulae which may not necessarily capture the different metabolic profile seen in patients following injury compared to those undergoing elective procedures.

We have recently demonstrated encouraging results on the outcome of critically ill patients whose energy requirements were determined by repeated measurements of resting energy expenditure (REE).⁷ To our knowledge, no study has examined longitudinal REE in the immediate postoperative course in this patient population. We therefore undertook the present study to evaluate whether nutritional support guided by repeated measurements of REE improved outcomes in geriatric patients following surgery for hip fractures and compared this to usual nutritional therapy.

2. Subjects and methods

2.1. Subjects

This study was conducted in the ortho-geriatric unit of the Department of Geriatrics, at the Rabin Medical Center in Petah Tikva, Israel, over a period of 20 months (from May 2010 to December 2011). The study was approved by the local institutional review board and written informed consent was obtained from all participants prior to randomization. Consecutive patients older than 65 years who were admitted to the unit following hip fracture within 48 h of the injury and in whom orthopedic surgery was considered the treatment of choice. Patients were excluded if they presented to hospital >48 h after the injury, were receiving steroids and/or immunosuppression therapy; in the presence of active oncologic disease, multiple fractures, diagnosed dementia or in the event that patients required supplemental nasal oxygen which precludes the measurement of REE.

2.2. Interventions

In this unblinded study, eligible patients were randomly assigned to 2 groups, within 48 h of the injury and prior to surgery: the tight calorie (intervention) group and the control group. Randomization was performed using a concealed, computer-generated program. RA enrolled participants and assigned them to interventions while YB enrolled patients but was blinded to the intervention. The tight calorie group received calories with an energy goal determined by repeated REE measurements using indirect calorimetry (IC) (Fitmate, Cosmed, Italy) which was based on hospital-prepared diets (standard or texture-adapted). Oral nutritional supplements (ONS) were started 24 h after surgery and the amount adjusted to make up the difference between energy received from hospital food and measured energy expenditure. These ONS were provided in the form of Ensure plus (Abbott Laboratories) containing 355 kcal/237 ml and 13.5 g protein or Glucerna (Abbott Laboratories) containing 237 kcal/237 ml and 9.9 g protein/237 ml. The patient, family and caregivers were educated regarding the importance of nutritional support and more attention was given to personal food preferences. The control group received usual hospital food (standard or texture-adapted) and a fixed dose of ONS if already prescribed prior to hospitalization. Hospital prepared diets provide a mean of 1800 kcal and 80 g of protein in the event that the meals are completely eaten by the patients.

All patients were treated in the same unit and perioperative care including antibiotic and thrombosis prophylaxis was identical in both groups.

2.3. Measurements

All patients underwent IC measurements after a fasting period of at least 6 h at three time periods: on admission to the study, between 24 and 48 h following surgery and on the 7th day of the study. Measurements were performed by an experienced nurse or dietician, the device was automatically calibrated before each measurement and the REE was recorded after 15 min.

The nutrient intake of each patient was monitored by the research team on a daily basis. Twenty-four hour food diaries were filled in by the medical staff, family and caregivers. All meals had a known energy and protein content and the proportion of each component consumed was calculated using a food data base program. In addition, the amount of ingested ONS was noted by the medical staff. Before surgery, grip strength in the dominant arm was measured with a hand-grip dynamometer (JAMAR[®]) with the highest of 3 measurements being recorded. Midarm circumference (MAC, cm) was measured on the first day of the study using a non-stretchable flexible tape perpendicular to the long axis of the non-dominant arm.

2.4. Data collection

On admission and during hospitalization, demographic, laboratory and clinical data were collected from patients, caregivers and patient files, where appropriate. The BMI was derived from body weight which was measured during hospitalization using seat scales, and height which was calculated according to measured recumbent knee height.⁸ Biochemical parameters including serum glucose, albumin, lymphocyte count and creatinine levels, were collected at 3 time points: before surgery, 24 h after surgery and on the 7th study day. Energy balances were assessed daily by calculating the difference between the most recently measured REE and the same day energy intake. Cumulative energy balance was assessed at either day 14 or at discharge from the geriatric department and included the preoperative period. Comorbidity was assessed retrospectively with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)⁹ and the Charlson's Comorbidity Index (CCI).¹⁰ The Functional Independence Measure (FIM) scale was used to assess pre-fracture functional ability¹¹ and the Mini-Mental State Examination (MMSE) was used for the assessment of cognitive function.¹² Nutritional status of the patient was assessed on the first day of the study using the Mini Nutritional Assessment (MNA),¹³ a validated, sensitive, reliable tool for use in the elderly. The MNA score distinguishes between elderly patients with adequate nutritional status (MNA > 23.5), those at risk of malnutrition (MNA between 17 and 23.5) and those with protein-calorie malnutrition (MNA < 17).

2.5. Outcome measures

The primary outcome was the presence of postoperative complications and hospital length of stay. Secondary outcomes included energy intake and calculated energy balance.

Patients were examined daily by the research nurse and attending physician for the presence of postoperative complications. These included surgical complications (such as local bleeding or the need for repeat surgery); infectious complications, including pneumonia (based on clinical symptoms and signs and positive chest radiograph), urinary tract infection (based on clinical symptoms and signs and positive urinary cultures) and wound infections

Table 1
Baseline characteristics of study participants.

Variable	Study group (n = 22)	Control group (n = 28)	p-Value
Age (yrs)	82.3 ± 6.1	83.7 ± 6.4	0.876
Gender			
Male n (%)	6 (27.3%)	11 (39.3%)	0.318
Female n (%)	16 (72.7%)	17 (60.7%)	
Weight (kg)	64.8 ± 9.5	64.3 ± 11.3	0.86
BMI (kg/m ²)	25.2 ± 3.2	24.7 ± 4.4	0.653
MAC (cm)	25.6 ± 2.5	25.3 ± 2.9	0.688
Hand grip (kg)	17.8 ± 7.1	18.9 ± 7.3	0.629
Mean serum albumin (mg/dl)	3.2 ± 0.3	3.1 ± 0.3	0.282
Mean blood glucose (mg/dl)	121.5 ± 22.5	118.2 ± 21.1	0.589
MNA	24.8 ± 2.6	24.5 ± 2.9	0.672
Well nourished n, (%)	14 (63.6%)	18 (64.3%)	0.597
At risk of malnutrition n, (%)	8 (36.4%)	10 (35.7%)	
CCI	0.8 ± 1.1	1.4 ± 1.1	0.073
CIRS-G	7.4 ± 3.6	7.4 ± 2.6	0.944
FIM	80.0 ± 17.6	79.1 ± 17.2	0.863
MMSE	25.2 ± 4.9	23.7 ± 5.2	0.375

Data are expressed as mean ± standard deviation. Abbreviations: BMI, body mass index; MAC, mid-arm circumference; MNA, mini-nutritional assessment; CCI, Charlson's comorbidity index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; FIM, Functional Independence Measure; MMSE, Mini-Mental State Examination.

(based on clinical symptoms and signs and positive wound cultures); cardiovascular complications, such as myocardial infarction (based on clinical symptoms and signs together with a positive electrocardiogram and elevated enzymes) and congestive heart failure (based on clinical symptoms and signs and compatible chest radiograph); gastrointestinal (such as gastrointestinal bleeding); delirium lasting > 4 days (based on the Confusion Assessment Method (CAM) algorithm)¹⁴; deep vein thrombosis (based on clinical features and positive doppler sonography examination) and the development of new pressure sores (stage 2 and above).

2.6. Statistical analysis

A priori power analysis was performed. In order to detect a statistically significant difference in the rate of total complications, at least 33 patients in each group were needed for a power (1 – β) of 0.9 and α of 0.05. In view of the slow rate of expected recruitment of patients meeting all the inclusion criteria, an interim analysis was planned after 50 patients. In the presence of a positive result, the study was to be discontinued. Differences between the two groups were assessed using the Student's *t* test for parametric data and Chi-square test for categorical data. Correlations between energy balance and length of stay or total complication rate were analyzed using the Pearson correlation tests. All calculations were performed using SPSS software (version 12.0, SPSS, Chicago, IL).

Table 2
Summary of energy and protein parameters during the study period.

Parameter	Study group (n = 22)	Control group (n = 28)	p-Value
REE measurement – day 1(kcal/day)	1292.2 ± 255.9	1262.3 ± 246.1	0.90
Mean REE during study	1274 ± 262.9	1346 ± 309.1	0.96
Mean energy delivered/day (kcal/day)	1121.3 ± 299.1	777.1 ± 301.2	0.001
Mean enterally and ONS delivered energy/day (kcal/day)	220.3 ± 147.2	94.6 ± 233.8 ^a	0.845
Preoperative days of fast	1.7 ± 0.5	1.4 ± 0.7	0.635
Mean protein delivered/day (g/day)	55.9 ± 18.1	37.4 ± 12.4	0.001
Mean daily energy balance (kcal)	–176.9 ± 273.2	–490.7 ± 355.2	0.104
Cumulative energy balance (kcal)	–1229.9 ± 1763	–4975.5 ± 4368	0.001

Data are expressed as mean ± standard deviation. Abbreviations: REE, resting energy expenditure; kcal, kilocalories; ONS, oral nutritional supplements.

^a Included 1 patient who required mechanical ventilation and who received 1500 kcal/day via tube-feeding.

Results are expressed as mean ± standard deviation. A *p* level < 0.05 was considered statistically significant.

3. Results

A total of 230 patients were screened, of whom 51 were found eligible for the study. Reasons for non-inclusion included the presence of dementia (*n* = 80), presence of oncologic disease (*n* = 17), presentation to hospital > 48 h after the injury, (*n* = 14), patients who refused to participate in the study (*n* = 21) and others (*n* = 47). A patient initially recruited to the study group did not undergo surgery and was therefore excluded. There were thus 50 patients included in the study, 22 in the intervention and 28 in the control group. All patients completed the study, with no drop-outs.

There were no significant differences between the groups regarding baseline characteristics (Table 1). In particular, there was no significant difference in the nutritional assessment between the 2 groups, with 63.6% of patients in the intervention group and 64.3% in the control group being well nourished, 36.4% of patients in the intervention group and 35.7% in the control group being at risk for malnutrition, while there were no malnourished patients in either group (i.e. MNA < 17). Three patients in the intervention group and 5 in the control group had MAC measurements below the 15th percentile (*p* = NS).

Surgical procedures included the following: repair of peritrochanteric (11 in the control and 9 in the intervention group), sub-capital (3 in the control and 7 in the intervention group) subtrochanteric (1 in the control and 2 in the intervention group) and other unspecified fractures. There was no significant difference in type of procedure between the 2 groups. The waiting time between admission to the study and performance of surgery was not significantly different between the 2 groups (1.4 ± 0.5 days for the intervention group vs. 1.4 ± 0.7 days for the control group, *p* = 0.635). During this time patients were kept in a semi-fasting state while awaiting surgery.

3.1. Nutritional intake

Table 2 summarizes mean energy and protein values for the study period, from recruitment prior to surgery and up to 14 day. Patients in the intervention group had a significantly higher mean daily intake of energy and protein compared to the control group during the first 11 postoperative days (*p* = 0.001). ONS accounted for a mean of 19.6% of total energy delivered in the intervention group. Three patients in the control group received additional enteral energy sources: one patient required mechanical ventilation and received tube feeding while the other two received ONS at

home prior to the present admission on a regular basis and which were continued in hospital.

3.2. Primary outcomes

The incidence of complications and length of hospital stay are shown in Table 3. The total complication rate was significantly lower in the intervention group compared to the control group (27.3% vs. 64.3%, $p = 0.012$). This was mainly due to a reduction in the number of infectious complications in the intervention group (13.6% vs. 50%, $p = 0.008$). In particular there were 9 cases of pneumonia in the control group compared to none in the intervention group. There was a trend for shorter length of hospitalization in the intervention group (10.1 ± 3.2 days vs. 12.5 ± 5.5 days for the control group, $p = 0.061$). Finally regarding mortality, 2 patients in the control group died (one from sepsis and the other following a cerebrovascular accident) while none died in the intervention group. This difference was not significant ($p = 1.0$).

3.3. Secondary outcomes

The calculated daily energy balance was significantly more positive in the intervention group ($p < 0.05$) from the 3rd to the 10th day of the study. This was associated with a significantly less negative cumulative energy balance (-1229.9 ± 1763 vs. -4975.5 ± 4368 kcal, $p = 0.001$), as shown in Table 2. The mean daily energy delivered was significantly higher in the intervention group (1121.3 ± 299.1 kcal vs. 777.1 ± 301.2 kcal, $p = 0.001$). For the whole group, a significant negative correlation was found between the cumulative energy balance and total complication rate ($r = -0.417$, $p = 0.003$) as well as for length of hospital stay ($r = -0.282$, $p = 0.049$).

4. Discussion

We have shown that elderly patients who underwent surgery for fracture of the hip and achieved near-target energy intakes as assessed by measured energy expenditure, had significantly fewer postoperative complications and a trend to shorter hospital length of stay compared to a control group.

Previous studies have revealed conflicting results regarding the effect of nutritional interventions in these patients. Thus some studies have reported improved nutritional status, decreased length of stay and fewer postoperative complications while others have not.² This may be the result of a variety of factors including differing baseline nutritional status of the patient populations and varying compliance with the nutritional intervention. However, another factor which has not been fully assessed relates to the adequacy of the energy intake, i.e. does energy intake meet energy

demands. To date, the amount of energy provided has been based on either predictive formulae such as the Harris-Benedict equation¹⁵ or on a basal demand of 25 kcal/kg body weight/day.¹⁶ In this regard a recent systematic search of the relevant literature revealed that these equations are not adequate to predict REE in this specific patient population,¹⁷ especially for malnourished older patients.

Studies of energy expenditure in the elderly have revealed on one hand a reduction in basal metabolic rate as lean body mass declines¹⁸ while on the other, a more hyperdynamic and hyper-metabolic host response than those of young patients in situations of stress such as after major abdominal surgery.¹⁹ These findings, together with evidence that meeting energy requirements may improve outcomes in critically ill patients,⁸ provide a rationale for more precisely and directly measuring REE, i.e. using indirect calorimetry, in this patient population in order to avoid both under and overfeeding. Nutritional studies in patients following hip fracture have revealed that energy expenditure predicted by equations either underestimated measured REE by between 8 and 30%²⁰ or overestimated REE by up to 25%, in particular where an adjustment is made for stress.²¹ However, these studies were performed on admission to a rehabilitation center and not in the immediate perioperative period.

In our prospective study, the intervention group received significantly more calories over the study period compared to the control group (1121.3 ± 299.0 kcal/day vs. 777.1 ± 310.2 kcal/day, $p = 0.001$). This represented 88% of measured energy expenditure in the intervention and 58% in the control group ($p = 0.001$). The improved energy delivery appeared to translate into improved clinical outcomes, namely significantly fewer complications, in particular those related to infections and a trend for a shorter hospital stay.

Apart from the determination of a defined and dynamic energy goal, we believe that measuring REE yielded other important advantages. Firstly, it allowed us to accurately assess the cumulative energy balance which may be more important to document than the mean energy intake. Thus, we have previously shown a correlation between measured large energy deficits and increased infections, as well as prolonged hospital and ICU stay, in critically ill patients.²² Indeed, in the present study, the cumulative energy balance was significantly less negative in the intervention compared to the control group (-1229.9 ± 1763 kcal vs. -4975.5 ± 4368 kcal, $p = 0.001$). Secondly, measuring REE may be important for another reason. By using a formula to assess energy expenditure, viz, 25 kcal/kg/day, the basal energy expenditure in our study would have been calculated at 1613.7 kcal/day, significantly higher than the measured REE, further demonstrating the discrepancies between measured and calculated energy requirements. This gap would have been further aggravated had we used a multiplier for physiological stress, as is commonly recommended.²³ While preventing underfeeding appears to be important, overfeeding may also be associated with adverse effects. These include an increase in oxidative stress, in intracellular lipid content, decrease in insulin sensitivity and metabolic flexibility which may lead to mitochondrial dysfunction.²⁴

The improved energy delivery in the intervention group was also a function of the intensity of the nutritional intervention generated by the defined and dynamic energy goal. Thus, it was possible to achieve near-target energy intakes under the close supervision of the study dietician (RA). Indeed, 82% of delivered energy was derived from hospital food while supplemental ONS provided 19.6% of the total energy delivered in the intervention group. This should be compared to the control group where patients receiving usual care and not under active supervision of a dietician, incurred a significant negative energy balance. The importance of a proactive approach with the appropriate staff

Table 3
Primary outcomes: complications and duration of hospital stay.

Variable	Study group (n = 22)	Control group (n = 28)	p-Value
Duration of hospital stay (days)	10.1 ± 3.2	12.5 ± 5.5	0.061
Total number of patients who developed complications	6 (27.3%)	18 (64.3%)	0.012
Infectious complications (n)	3 (13.6%)	14 (50%)	0.008
Pneumonia (n)	0	9	
Urinary tract infections (n)	3	5	
New pressure ulcers (%)	0	2 (7.1%)	0.497
Surgical complications (%)	1 (4.5%)	1 (3.6%)	0.691
Cardiovascular complications	0	2 (7.1%)	0.497
Gastrointestinal complications	0	4 (14.3%)	0.089
Delirium	1 (4.8%)	2 (7.1%)	1.00
Other	1 (4.8%)	0	

dedicated to the delivery of adequate nutrition has previously been shown by us in the setting of critically ill patients (7). In this group of patients, too, Hoekstra et al.²⁵ showed that the implementation of a multidisciplinary program (including nurses, doctors and dieticians) resulted in a higher average daily dietary intake which was associated with a lower decline in quality of life and fewer malnourished patients after 3-months follow-up.

Our findings are similar to those reported by Eneroth et al., who demonstrated that providing patients with 85% of calculated daily optimal energy intakes, based on an intake of 25 ml/kg/day, was associated with significantly fewer fracture-related complications and 3-month mortality compared to a control group who received only 54% of optimal requirements.¹⁶ Interestingly, the incidence of complications noted in their study was very similar to ours, namely 15% in the intervention group (vs. 27.3% in our study) and 70% in the control group (vs. 64.3% in our study). In addition, in both studies, the major complications noted in the control group were related to infections, in particular pneumonia (7/40 patients in the Eneroth control group vs. 9/28 in our control group, $p = 0.18$, and no cases of pneumonia in either study intervention group). It should be mentioned, however, that the energy intake in the Eneroth study was achieved with the aid of parenteral nutrition given for the first 3 postoperative days. While the use of parenteral nutrition as an adjunct to enteral nutrition is widely accepted, complications related to the therapy may occur and in fact, one patient in their series developed thrombophlebitis. In addition, the cost of providing parenteral nutrition is certainly significant compared to orally administered nutrition.

Apart from increased energy intakes, patients in our intervention group also received a significantly higher protein intake, namely 55.9 ± 18.1 g/day vs. 37.4 ± 12.4 g/day in the control group ($p = 0.001$). This corresponds to 0.9 g/kg/day of protein which is slightly below the recommendations of recent guidelines for geriatric patients, i.e. 1.0–1.2 g/kg/day.²⁶ In this regard a recent study showed better recovery of plasma proteins in normally or mildly malnourished geriatric patients undergoing hip fracture surgery who received perioperative energy-protein supplements.²⁷ In addition patients with higher protein intakes (an increase from 0.97 to 1.37 g/kg/day) had better outcomes on multivariate analysis.

There are several limitations of our study which should be mentioned. First, the present study was performed in a hospital where IC is routinely available and has been used over many years as an adjunct for assessing nutritional requirements. Second, the follow-up period was limited to the hospital stay and should ideally have ideally a longer period. Third, our patients received a relatively low protein intake; additional studies are required to assess whether target-adjusted protein requirements adds to the benefit shown by improved caloric intake alone. Finally, we did not include patients with advanced dementia who are more prone to be malnourished.

5. Conclusion

In this prospective study we have demonstrated that a program of nutritional support, actively supervised by a dietician, together with the provision of energy guided by repeated measurements of REE was achievable and improved outcomes in geriatric patients following surgery for hip fractures. Our study adds further support to the importance of an adequate nutritional intervention in this often malnourished and frail population at risk for significant postoperative complications.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

R.A. was responsible for the conception and design of the study, collection of data, interpretation of data, drafting, writing and final approval of the article; Y.B. was responsible for carrying out most of the clinical studies evaluating the patients, collection of data and also participated in the drafting and final approval of the article; P.S. and Z.M. were responsible for the conception and design of the study, interpretation of the data, drafting, writing and final approval of the article; J.C. was responsible for interpretation of the data, drafting, writing and final approval of the article; M.T., T. K-H. and S.F. were involved in the collection and interpretation of data; A.W. and S.L. provided important contributions for intellectual content and participated in final approval of the article.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.clnu.2013.03.005>.

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