Combining enteral with parenteral nutrition to improve postoperative glucose control

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The provision of parenteral nutrition (PN) to 'stressed' patients often results in hyperglycaemia, which may be detrimental. In animal models limited amounts of enteral nutrition (EN) improve intestinal integrity and stimulate intestinal incretin production, which may lead to improved glucose control. We set out to assess if combining EN with PN results in improved glucose homeostasis rather than PN given alone. We conducted a randomised trial in a university teaching hospital of patients undergoing a 'curative' oesophagectomy for adenocarcinoma. Differences between the two intervention groups were assessed for continuous glucose measurement, insulin sensitivity using insulin tolerance tests (ITT) and homeostasis model analysis (HOMA), the incretin glucose-dependent insulinotropic polypeptide (GIP) and intestinal permeability. The combination of PN with EN resulted in lower interstitial glucose concentrations ($P=0.002$), reduced insulin resistance, improved insulin sensitivity (HOMA-insulin resistance (IR) $P=0.045$; HOMA β $P=0.037$; ITT $P=0.006$), improved intestinal permeability ($P<0.001$) and increased GIP ($P=0.01$) when compared with PN alone. The combination of EN with PN, when compared with PN alone, results in reduced glucose concentrations, reduced insulin resistance, increased incretins and improvements in intestinal permeability.

Glucose: Insulin: Nutrition: Parenteral nutrition: Enteral nutrition

Under normal homeostasis, euglycaemia is normally maintained by a combination of metabolic, neural, hormonal and hepatic autoregulatory mechanisms, but can be disrupted in various pathophysiological states. Among these, stress hyperglycaemia occurs in critically ill patients and is associated with worse outcome[1,2]. Stress-induced hyperglycaemia represents a complex neuroendocrine response to inflammation and is characterised by inappropriately enhanced gluconeogenesis, glycogenolysis, relative insulin deficiency, and impaired glucose utilisation. Indeed, in such patients, it has been shown that maintaining normoglycaemia improves outcome[1–4], though this may result in hypoglycaemia and associated metabolic disturbance[4].

Poor glycaemic control is a particular problem in postoperative patients receiving parenteral nutrition (PN) and is associated with poorer outcome[5]. In this context, there is considerable data in both human subjects and animals to show that PN is less beneficial than enteral nutrition (EN), being associated with increased intestinal atrophy[6], enhanced intestinal permeability[7–9], a heightened inflammatory response[10], increased serum glucose concentrations[11], impaired wound healing[12] and worse outcome[13–15]. The poorer clinical outcome associated with PN is reportedly related to increased septic complications[16–18] and, if these could be reduced by improved nursing care, the benefits of EN over PN might be negated. However, in some patient groups nutritional requirements cannot be met using EN alone; in this situation animal work suggests that combining EN with PN may result in better outcomes than using PN alone[19,20]. In animals, this improvement is unlikely to be related to better clinical care and the mechanism is open to speculation. One possibility is that glucose homeostasis is better maintained (perhaps via secretion of incretins such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 from intestinal K- and L-cells) and reduced insulin resistance reduced during combined EN and PN nutrition but, to date, there have been no controlled human studies examining this combination.

In the present study we have explored the effect of combining EN with PN on glucose homeostasis in a well-defined

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group of patients. By providing postoperative patients with their full nutritional requirement we placed a stressor on their glucose homeostasis system, thus allowing us to test the hypothesis that combination feeding may result in enhanced insulin secretion via an incretin effect.

Subjects and methods

Study population

Consecutive patients with oesophageal cancer over the age of 18 years who were scheduled for a 'curative' Ivor-Lewis oesophagectomy for carcinoma were invited to participate. Patients were ineligible if they: had a preoperation fasting glucose greater than 7 mmol/l, had a diagnosis of diabetes, had other significant co-morbidity, or were taking steroids or immunosuppressants. Written informed consent was obtained. The study was approved by Plymouth Local Research Ethics Committee.

Study design

Preoperative baseline clinical data were recorded, patients weighed and tests done, and POSSUM scores calculated (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity). POSSOM scores are designed to predict surgical outcome; higher scores relate to a higher risk of mortality and morbidity[21].

Patients underwent an Ivor-Lewis oesophagectomy with placement of a feeding jejunostomy, central venous catheter and a urethral catheter. Standardised anaesthetic protocols were followed. Epidural catheters were placed for pain control. Immediately postoperatively (in recovery) APACHE II (Acute Physiology and Chronic Health Evaluation II[22]) scores were calculated (this is a measure of severity of disease classification commonly used in critical care settings). Non-steroidal anti-inflammatory drugs were not used during the study period. All operative and perioperative management was undertaken by the patients' attending surgical staff as clinically indicated, except where stated within the methods section.

On the first postoperative day, if a 'curative' resection had been completed, each patient was randomly allocated to receive all their calculated nutritional requirements (using actual preoperative body weight) by the Schofield method[23] as either PN (Baxter, Newbury, Berks, UK) or a combination of PN (70%) and EN (30%) (Osmolite®; Abbott, Maidenhead, Berks, UK) via the patient's jejunostomy. Both nutritional regimens were isonitrogenous, isoenergetic and had a similar glucose content. The PN bags were formulated to give 0·64 g N/100 kcal (0·153 g N/100 kJ) of energy, which was identical to the EN used. Nutrition was commenced from 19.00 hours on the first postoperative day and continued until 15.00 hours the following day – a total of 20 h. After a 4 h fasting period (to enable measurement of fasting glucose, insulin and to perform insulin tolerance tests) a further cycle of nutrition was given and this was repeated until postoperative day 4. Patients underwent a gastrograffin swallow on postoperative day 4, and if satisfactory were encouraged to start oral intake.

At 10.00 hours on the first postoperative day a subcutaneous glucose probe, Medtronic® continuous glucose monitoring system (CGMS) (Medtronic, Inc., Minneapolis, MN, USA), was placed on each patient's thigh or abdominal wall. In this device, interstitial glucose is measured by the glucose oxidase method every 10 s and the monitor then records an average value every 5 min. A minimum of four capillary blood glucose measurements was fed into the recorder each day to maintain calibration, as recommended by the manufacturer. Glucose measurements were continuously recorded until postoperative day 5.

Preoperatively and on postoperative days 1, 2, 3 and 4, blood was drawn for measurement of C-reactive protein (CRP), GIP, fasting insulin, glucose and determination of insulin tolerance (administration of 0·1 units/kg of Actrapid®, with venous blood drawn for laboratory glucose measurement at 90 s intervals for 15 min)[24].

C-reactive protein was measured using a competitive turbidometric immunoassay (Alpha Laboratories, Eastleigh, Hants, UK); internal controls had a CV of < 5%. Insulin was measured using a solid-phase two-site chemiluminescent immunometric assay (Immulite 2000; Siemens, Llanberis, Gwynedd, UK) at 0·56 µIU/ml (CV 7·3%), 1·32 IU/ml (CV 5·0%) and 15·5 IU/ml (CV 5·0%). Total GIP was measured using a commercial ELISA method for human GIP (Linco Research, St Charles, MO, USA) according to the manufacturer's instructions. Samples were analysed in duplicate, and compared against standard human GIP diluted in parallel with patient samples. Positive controls provided with the kit were always within the stated range; the CV was < 6·5%.

Small-bowel permeability was assessed using the dual markers mannitol (5 g) and lactulose (10 g) dissolved in 200 ml water and injected into each patient's jejunostomy at time zero (09.00 hours). Urine was collected over a 6 h period, the volume recorded and stored frozen before analysis. Measurement of lactulose and mannitol was performed using high-pressure anion exchange chromatography as previously described[25], with the CV < 5%. The percentage excretion of each sugar was calculated and expressed as a lactulose: mannitol permeability ratio. The test was performed preoperatively and postoperatively on days 1, 2, 3 and 4.

Fluid balance and energy content (nutrition as well as supplements of 5% dextrose) were recorded. Only 0·9% saline was permitted during the patients' 'fasting' periods and for 4 h before. The length of postoperative hospital stay was recorded. Clinical complications and both patient visits to a doctor or by a nurse were recorded to postoperative day 30. Nutrition was managed by a dietitian, and the study data was collected by a research fellow.

Statistics

Randomisation codes were computer generated and held in sealed envelopes. Patients were actively allocated according to their randomisation on the first postoperative day by a study coordinator who had no contact with the patients. Patients, their attending surgeon and the researcher collecting the clinical data were not blinded to study intervention. The calculation and delivery of nutrition were managed by a ward dietitian according to protocol. All randomised patients

were analysed on an intention-to-treat basis by a trialist blinded to which intervention the patient received. Analysis of data was done using SPSS software (SPSS, Inc., Chicago, IL, USA). Continuous, normally distributed data are expressed as mean and 95 % CI, and other quantitative data are expressed as median and interquartile range. Comparisons between groups were assessed using Student's t test, χ^2 tests or repeated-measures ANOVA (general linear model, with the pre-feeding measurements taken on the first post-operative day used as a covariant). Correlations between variables were assessed using Pearson's correlation method, and the results are presented as P values and Pearson's correlation coefficient r.

The primary outcome is subcutaneous interstitial glucose concentration. Data from the continuous glucose recorders were downloaded and transferred to Microsoft Excel (2007 version; Microsoft Corp., Redmond, WA, USA) spreadsheets. Mean values were calculated for consecutive 4 h periods of feeding and the final 1 h of the 'no nutrition' period. Differences between the two interventions were assessed using repeated-measures ANOVA (general linear model).

No data from previous studies were available. In-house data (using Accu-Chek; Roche, Burgess Hill, UK) suggested that on the first postoperative day mean glucose concentrations on PN were 8·4 (SD 0·81) mmol/l. A study size of fifteen patients in each group (power = 0·8, $\alpha = 0.05$) will enable the detection of a 10 % reduction in glucose concentration, which we felt would be clinically significant.

Ethical approval

The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the South West Local Research and Ethics Committee (study 2011). Written informed consent was obtained from all patients.

Results

Baseline characteristics

A total of thirty-six patients consented to participate in the study, of which thirty were randomly allocated to receive nutritional support as either PN alone or as a combination of PN and EN. Of the patients not entered into the study, five were found at operation to have an 'unresectable' tumour and one developed significant immediate post-operative complications (before randomisation). There was no difference between the two groups of patients for the baseline characteristics (Table 1), POSSUM (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) scores, operative details, anaesthetic management, postoperative APACHE II (Acute Physiology and Chronic Health Evaluation II) score, post-operative management (including fluid balance and energy requirement) or postoperative TNM (tumour–lymph nodes–metastasis) staging.

Table 1. Baseline preoperative patient characteristics, and operative and postoperative details*

(Median values and interquartile ranges)

	Parenteral nutrition only		Parenteral and enteral nutrition	
	Median	IQR	Median	IQR
Subjects (n)	14		16	
Age (years)	67	56, 76	69	56, 73
Sex (n)				
Male	11		14	
Female	3		2	
Baseline BMI (kg/m²)	23·6	21·9, 26·9	27·2	23·3, 28·8
Preoperative weight loss (n)				
> 10 %	3		3	
5–10 %	3		6	
< 5 %	8		7	
Calculated energy requirements				
kJ/d	6941	6280, 7431	6402	6063, 7732
kcal/d	1659	1501, 1776	1530	1449, 1848
Actual energy delivery (includes intravenous 5 % dextrose)				
kJ/d	7084	6364, 7519	6602	6163, 7870
kcal/d	1693	1521, 1797	1578	1473, 1881
POSSOM physiology score	15	14, 16	15·5	14, 17
POSSOM morbidity/mortality score	7·98	3·55, 12·59	9·54	3·95, 12·91
Duration of surgery (min)	325	259, 366	294	266, 354
Duration of anaesthesia (min)	369	302, 415	343	312, 430
APACHE II score POD 1	7·0	4·8, 9·0	7·0	6·0, 8·5
Duration of epidural anaesthesia (d)	5·0	4·0, 5·0	4·0	4·0, 5·0
Duration of PCA (d)	5·0	4·0, 6·3	6·0	5·0, 7·0
Fluid balance POD 1 (ml)	2187	1024, 2930	2028	1532, 3378
Fluid balance POD 2 (ml)	1459	982, 1926	1275	870, 2135
Fluid balance POD 3 (ml)	1401	595, 1762	985	423, 1366

IQR, interquartile range; POSSUM, Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity; APACHE II, Acute Physiology and Chronic Health Evaluation II; PCA, patient-controlled analgesia; POD, postoperative day.

* No difference between groups for any parameter.

Clinical progress and outcomes

Patients in both groups received all their PN and EN prescribed according to protocol and without complication. No evidence of refeeding syndrome was seen. There was no difference between the two groups of patients for clinical course, removal of lines, fluid balance (and energy content), analgesia use, weight loss or length of postoperative hospital stay. Five postoperative complications were seen in those patients receiving PN only ($1 \times$ anastomontic leak, $1 \times$ cardiac failure, $3 \times$ wound infection) and seven in those receiving the combination of EN and PN ($1 \times$ cardiac failure, $2 \times$ pneumonia, $1 \times$ wound infection, $1 \times$ diarrhoea, $2 \times$ superficial wound dehiscence); this difference was not significant and there was no mortality.

Main outcomes

Continuous glucose measurement. Continuous glucose measurements were started on the first postoperative day and are presented in Fig. 1. Measurements were similar between the two groups until the third postoperative day; from that time point patients receiving the combination of EN and PN had lower interstitial glucose than those receiving PN alone ($P=0.009$). There was an interaction between the two interventions with time ($P=0.02$). For glucose measurements made during the final 1 h of the 'no nutrition' period, those performed in patients receiving the combination of EN and PN were lower than in those receiving PN alone ($P=0.004$).

Glucose, insulin, homeostasis model analysis and insulin tolerance tests. Serum glucose and insulin concentrations (combined groups) increased from their fasting preoperative values of 4·83 (95 % CI 4·59, 5·07) mmol/l and 9·91 (95 % CI 7·99, 11·82) mU/l, respectively, to 6·19 (95 % CI 5·76, 6·62) mmol/l and 14·64 (95 % CI 11·29, 18·01) mU/l on the first postoperative day ($P<0.001$ (95 % CI -1.77, -0.95) and $P=0.001$ (95 % CI -7.49, -2.09)) then rose still further when feeding was commenced. Neither glucose nor insulin concentrations had fallen to their preoperative values by the end of the study. Measurements of glucose and insulin were similar between the two groups preoperatively and on the fir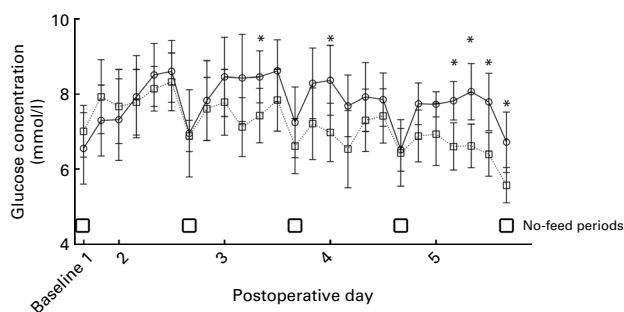st postoperative day. However, from the first postoperative day, glucose values in patients receiving the combination of EN and PN were lower than those receiving PN alone ($P=0.002$). No difference in insulin levels was seen between the groups.

Insulin resistance (combined groups) as measured by homeostasis model analysis (HOMA)-insulin resistance (IR), increased from 2·21 (95 % CI 1·69, 2·73) mUmmol/l^2 preoperatively to 4·255 (95 % CI 3·07, 5·55) mUmmol/l^2 on the first postoperative day (Fig. 2) ($P<0.001$; 95 % CI -1.05, -3.05). The reverse pattern was seen for insulin secretion (combined groups), as indicated by a decrease in the preoperative HOMA β of 188·6 (95 % CI 131·5, 245·6) mU/mmol to 116·5 (95 % CI 90·9, 142·0) mUmmol on the first postoperative day ($P=0.01$; 95 % CI 18·1, 126·1). In patients receiving the combination of EN and PN, HOMA-IR ($P=0.045$) was lower and HOMA β ($P=0.037$) higher than in those receiving PN alone.

Insulin sensitivity (combined groups), as deduced from the outcome of glucose tolerance tests, was reduced on the first postoperative day then increased with time back to preoperative values ($P<0.001$; 95 % CI 0·05, 0·10; Fig. 3). Patients receiving the combination of EN and PN demonstrated higher sensitivity to insulin than those receiving PN alone ($P=0.006$). Insulin tolerance in patients receiving the combination of EN and PN returned to preoperative levels by postoperative day 4, whilst in those receiving PN alone, values were lower, suggesting continued insulin resistance.

Glucose-dependent insulinotropic polypeptide. GIP concentrations fell (combined groups) from the preoperation value of 25·5 (95 % CI 18·2, 32·8) pg/ml to 8·3 (95 % CI 5·5, 11·1) pg/ml on the first postoperative day ($P<0.001$; 95 % CI 16·7, 23·8; Fig. 4). Concentrations then increased in those patients receiving the combination of EN and PN, achieving preoperation levels by postoperative day 4. By contrast, GIP concentrations increased more slowly in patients receiving PN alone and they had still not reached preoperation levels by the end of postoperative day 4. Patients receiving the combination of EN and PN had increased GIP concentrations compared with those receiving PN alone ($P=0.013$) (Fig. 4).

Permeability and C-reactive protein. Following surgery intestinal permeability (lactulose:mannitol ratio) increased significantly from baseline in both the PN and PN combined
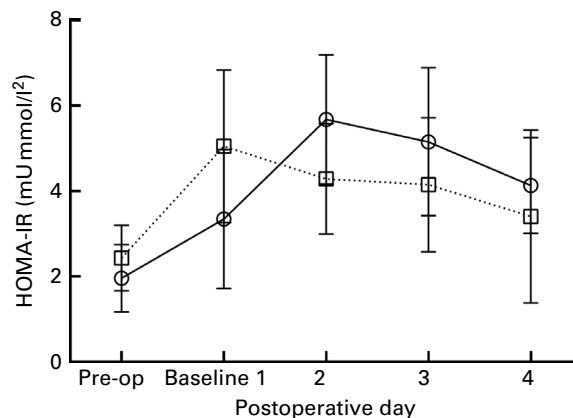

Fig. 1. Subcutaneous glucose concentrations presented in four-hourly blocks of patients given parenteral nutrition (PN) only (−○−) or enteral nutrition (EN) and PN (--□--). No-feed periods are shown. Values are means, with 95 % CI represented by vertical bars. *Mean value was significantly different from that of the patients receiving both EN and PN ($P<0.05$). ANOVA $P=0.009$.

Fig. 2. Homeostasis model analysis-insulin resistance (HOMA-IR) measurements of patients given parenteral nutrition (PN) only (−○−) or enteral nutrition (EN) and PN (--□--). Pre-op, preoperation. Values are means, with 95 % CI represented by vertical bars. ANOVA $P=0.045$.
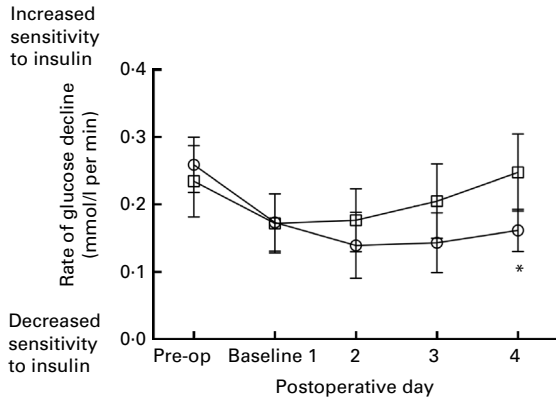
Fig. 3. Insulin tolerance tests of patients given parenteral nutrition (PN) only (−○−) or enteral nutrition (EN) and PN (--□--). Pre-op, preoperation. Values are means, with 95 % CI represented by vertical bars. * Mean value was significantly different from that of the patients receiving both EN and PN (P=0·01). ANOVA P=0·006.
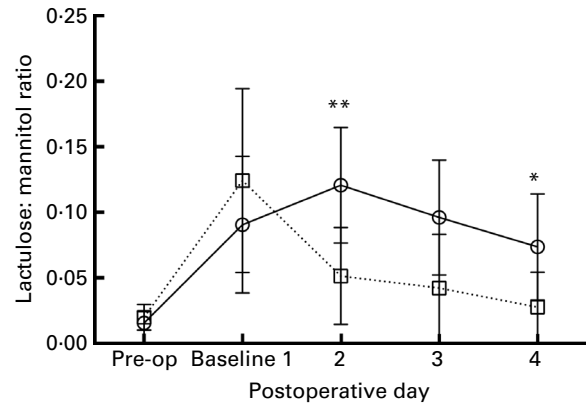

Fig. 5. Intestinal permeability of patients given parenteral nutrition (PN) only (−○−) or enteral nutrition (EN) and PN (--□--). Pre-op, preoperation. Values are means, with 95 % CI represented by vertical bars. Mean value was significantly different from that of the patients receiving both EN and PN: * P=0·05, ** P=0·016. ANOVA P<0·001.

with EN groups on day 1. Permeability decreased back towards baseline more quickly in those patients receiving PN and EN compared with those receiving PN alone (P<0·001) (Fig. 5) over the next three postoperative days. Patients in the PN and EN group achieved a lactulose:mannitol permeability ratio within the adult reference range by day 3, whilst those in the PN-only group still had an abnormal ratio at day 4 postoperatively.

C-reactive protein increased (combined groups) from the preoperative baseline measurements to 147 (95 % CI 128·3, 165·7) mg/l on the first postoperative day to a peak of 163 (95 % CI 140·9, 185·2) mg/l on the second postoperative day. No differences were seen between the two interventional groups over the study period. Intestinal permeability correlated with markers of the inflammatory response (CRP r 0·19, P=0·034; leucocyte count r 0·26, P=0·01).

Discussion

Stress hyperglycaemia has been associated with adverse outcomes in a number of medical and surgical conditions.
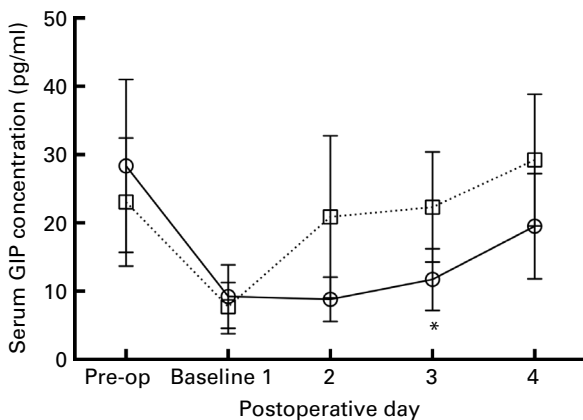

Fig. 4. Serum glucose-dependent insulinotropic polypeptide (GIP) concentrations of patients given parenteral nutrition (PN) only (−○−) or enteral nutrition (EN) and PN (--□--). Pre-op, preoperation. Values are means, with 95 % CI represented by vertical bars. * Mean value was significantly different from that of the patients receiving both EN and PN (P=0·02). ANOVA P=0·013.

We now show, in a specific postoperative situation, post-oesophagectomy, that glycaemic control can be improved by a regimen that combines enteral with parenteral feeding. The data suggest that this improvement in glycaemic control was achieved by a combination of enhanced insulin secretion and improved insulin resistance. It was associated with an increased concentration of GIP, suggesting that this hormone (and possibly other incretins, such as glucagon-like peptide-1, which were not measured in the study) may be at least partially responsible.

Baseline values measured on the first postoperative day reflected a similar inflammatory response to surgery between the two groups. However, from the second postoperative day, the progress towards preoperative values was more rapid in those patients receiving the combination of EN and PN than in those receiving PN alone, suggesting that their recovery was improved. It is likely that the addition of EN improved the integrity of the intestinal mucosa as demonstrated by the improvement in intestinal permeability and it is probable that this also accounted for the enhanced secretion of GIP, thereby promoting a rise in glucose-dependent insulin release. This may reflect a decrease in intestinal inflammation not evident in CRP measurements. CRP is an integrated systemic inflammatory marker and is not likely to be specific enough to detect changes in intestinal mucosal integrity.

Our clinical study is supported by animal data showing that the introduction of as little as 15 % of the energy requirements as EN (with the rest as PN) is nutritionally superior to PN alone, yielding improved N balance and reduced bacterial translocation[19,20]. Bacterial translocation has been identified in human studies[26] in a variety of surgical settings and is associated with septic complications[27]. However, no actual mechanism has been identified in human subjects, and as far as we are aware a direct causal relationship between intestinal permeability and translocation has not been demonstrated[28,29]. The importance of bacterial translocation in man is open to speculation. Animal studies have not examined the influence of combined EN and PN on glucose homeostasis and it is likely that the benefits seen will depend on various mechanisms, some of which are additional to the secretion of intestinal incretins. Studies in human subjects examining

the combination of EN with PN have been done in heterogeneous groups of patients, often in high-dependency units, where patients received variable amounts of EN. While these studies have provided little evidence of direct clinical benefit, no examination of glucose homeostasis or therapeutic insulin use was undertaken, thus making interpretation and comparison difficult[30].

Determining a patient's nutritional requirement in the context of a study looking at glucose homeostasis is inevitably problematic due to the abundance of variables that determine how an individual patient responds to their intake. We decided to use the Schofield equation for pragmatic reasons. All patients received their prescribed nutrition in accordance with protocol, and as both regimens were isoenergetic and isonitrogenous there were no differences in energy and N intake between the groups. Thus the present results do not reflect differences in feed composition or energy content. As all patients underwent similar surgery we were able to examine the influence of a similar large stress response on glucose homeostasis in a controlled manner. We do not believe that bias was introduced through lack of blinding, as most of the study end-points were biochemical in nature. The attending surgeons who were responsible for all patient management decisions followed 'standard' postoperative management protocols for the study patients.

It might be expected that during periods of 'no nutrition', intestinal stimulation of GIP would diminish and differences in glucose concentrations would be reduced. Whilst it is probable that the 4 h fasting periods were not long enough to achieve a true fasting state, it is surprising that glucose concentrations were higher in those patients receiving PN alone. This may reflect improved recovery and reduced insulin resistance in those receiving EN and PN together. As outlined above, it may also indicate that GIP secretion was enhanced in the PN group alone, due to improved mucosal condition. In retrospect it is clear that measurement of GIP concentrations during the 'feeding phase' may have helped to address this issue. We have used GIP as a surrogate for other incretins in the present study and it is acknowledged that firm conclusions about additional molecules (such as glucagon-like peptide-1) cannot be drawn. However, if, as we propose, enhanced GIP secretion results from improved intestinal mucosal integrity, then it is reasonable to speculate that glucagon-like peptide-1 levels would be similarly affected. Further studies will be required to verify this prediction.

HOMA is a tool that has been developed to examine glucose–insulin interactions at steady state. As detailed above, glucose was measured continuously in the postoperative period. The major influence on glucose concentrations in our patients was the hormone insulin. In the steady state glucose and insulin concentrations are determined by their interaction in a feedback loop. Thus glucose is influenced by insulin secretion and the degree of whole-body insulin resistance. In the postoperative period, stress responses result in marked increases in insulin resistance. We found no previous work where glucose measurement using continuous glucose monitoring system (CGMS) devices were validated in postoperative patients, and only limited data from intensive care unit patients[31]. We found that the devices performed extremely well and that readings correlated well with BM stix and, where done, blood glucose measurements.

HOMA is a commonly used tool that employs simultaneous glucose and insulin measures to predict insulin secretion and insulin resistance[32]. Our HOMA results are supported by the outcomes of insulin tolerance tests where the rate of glucose disposal in response to insulin is used as a measure of insulin sensitivity, the converse of insulin resistance. An alternative explanation for the differences in glycaemic control between the groups is that there was incomplete absorption of the enteral feed. However, during the 'fasting phase' glucose measurements fell rapidly to a baseline level where they stayed until the reintroduction of feed, suggesting that EN was promptly absorbed. One would also not anticipate a rise in GIP in response to enteral glucose if delivery of EN were inadequate. Glucose and insulin (and CRP; non-significant trend) were higher and insulin sensitivity and permeability were lower in the EN + PN-fed patients on the first and second postoperative days. After the second postoperative day mean results in the EN + PN-fed patients consistently fell below those of the patients receiving PN for the study duration. This suggests that initially (postoperative days 1 and 2) the patients receiving EN + PN had an increase in insulin resistance compared with those receiving PN alone, which would make the subsequent reversal seen (after postoperative day 2) in the measured parameters more impressive.

Hyperglycaemia within a hospital setting is associated with increased morbidity and mortality[1,33]. Reducing glucose concentrations with insulin can be problematic, with morbidity related to hypoglycaemia potentially nullifying any benefit[4]. If hyperglycaemia could be avoided without the use of insulin then this would be advantageous. Patients in many clinical settings are unable to tolerate, or do not receive, their required nutritional intake when it is delivered enterally. There is increasing evidence that failure to deliver patients' nutritional requirements is detrimental, especially in a high-dependency setting[34]. The present study was conducted in a homogeneous population of patients and not powered to look at clinical endpoints. Clearly a larger study, in a more heterogeneous population of patients, is required before clinical benefit can be established. Incretin preparations are now available for therapeutic use. Further study could examine the effect of giving exogenous incretin on glucose homeostasis in patients receiving PN. Another research question is whether the provision of exogenous incretin or EN together with PN improves glucose homeostasis without the need for insulin supplementation in patients with clinically significant hyperglycaemia.

We have shown that the combination of EN with PN, when compared with PN alone, results in reduced glucose concentrations, reduced insulin resistance, increased GIP and improvements in intestinal permeability. In a clinical setting, such as an intensive care unit, patient tolerance of EN may be suboptimal; thus the present study provides a rationale by which EN can be given with PN to not only improve N balance but also glycaemic control.

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