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ORIGINAL ARTICLE

# Preoperative oral supplementation with carbohydrate and branched-chain amino acid-enriched nutrient improves insulin resistance in patients undergoing a hepatectomy: a randomized clinical trial using an artificial pancreas

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**Abstract** Glucose metabolism is adversely affected in patients following major surgery. Patients may develop hyperglycemia due to a combination of surgical stress and postoperative insulin resistance. A randomized trial was conducted to elucidate the effect of preoperative supplementation with carbohydrates and branched-chain amino acids on postoperative insulin resistance in patients undergoing hepatic resection. A total of 26 patients undergoing a hepatectomy for the treatment of a hepatic neoplasm were randomly assigned to receive a preoperative supplement of carbohydrate and branched-chain amino acid-enriched nutrient mixture or not. The postoperative blood glucose level and the total insulin requirement for normoglycemic control during the 16 h following hepatic resection were determined using the artificial pancreas STG-22. Postoperative insulin requirements for normoglycemic control in the group with preoperative nutritional support was significantly lower than that in the control group ($P = 0.039$). There was no incidence of hypoglycemia (<40 mg/dL) observed in patients, including those with diabetes mellitus, when the STG-22 was used to control blood glucose levels. STG-22 is a safe and reliable tool to control postoperative glucose metabolism and evaluate insulin resistance. The preoperative oral administration of carbohydrate and branched-chain amino acid-enriched nutrient is of clinical benefit and reduces postoperative insulin resistance in patients undergoing hepatic resection.

**Keywords** Branched-chain amino acids · Carbohydrate · Artificial pancreas · Insulin resistance · Hepatectomy

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## Introduction

Strict control of blood glucose levels in patients following major surgery reduces both morbidity and mortality (Van den Berghe et al. 2001, 2003). In addition, adverse effects on glucose metabolism are prevented in patients undergoing a hepatectomy and in whom liver function is inevitably compromised by providing perioperative nutritional support (Fan et al. 1994). Postoperative parenteral nutrition with intensive insulin therapy is, therefore, provided for patients while they are in a surgical intensive care unit (ICU). However, it is difficult to strictly control blood glucose levels, and thus postoperative hyperglycemia is commonly seen in critically ill patients (Cely et al. 2004; McCowen et al. 2001), even in those without glucose intolerance (Capes et al. 2000). Surgical stress is a major causative factor of hyperglycemia (Huo et al. 2003), as is disruption in liver metabolism and in the immune system, resulting in impaired recovery of patients (Little et al. 2002). Hypoglycemia is often also encountered in patients following high-risk surgery (Van den Berghe et al. 2001, 2003), since there is no reliable technique for avoiding this

condition during intensive insulin therapy (Brunkhorst et al. 2008).

Hyperglycemia can also result from insulin resistance, a central feature of postoperative metabolism, as glucose uptake by skeletal muscle, adipose tissue and liver is inhibited (Svanfeldt et al. 2008). Insulin resistance after major surgery has been well documented and its development is related to the magnitude of surgery (Thorell et al. 1993). Insulin infusion support to maintain normal glucose levels reduces morbidities and mortality rates in critically ill patients. Since postoperative glucose metabolic disturbance further worsens because of insulin resistance, the preoperative improvement of whole-body insulin resistance should be required. Interestingly, preoperative oral administration of carbohydrate reduces postoperative insulin resistance in patients with colorectal resection (Svanfeldt et al. 2008). Furthermore, a short-term infusion of amino acids following colorectal surgery appeared to reduce insulin resistance, since endogenous glucose production and glucose clearance were decreased (Donatelli et al. 2006). However, it is uncertain whether preoperative supplementation of carbohydrate and branched-chain amino acids (BCAA) improves postoperative insulin resistance. To address this question, a randomized clinical trial was performed in which patients received a supplement of carbohydrate and BCAA prior to undergoing a hepatectomy. An artificial pancreas was then used to precisely quantify the exogenous insulin that was required to maintain normoglycemic status in postoperative patients at a surgical ICU.

## Methods

### Patients

The present study employed 26 patients who underwent elective liver resection for the treatment of hepatocellular carcinoma or adenocarcinoma (Fig. 1). Patient exclusion criteria were body weight loss greater than 10% during the 6 months prior to surgery, the presence of distant metastases, or seriously impaired function of vital organs due to respiratory, renal or heart disease. The patients were informed of the purpose and details of the study, and written consent was obtained from them prior to enrollment. The study was approved by the local ethics committee at the Kochi Medical School and carried out in accordance with the Helsinki Declaration. All studies were performed at the Kochi Medical School between April 2007 and December 2007.

### Laboratory investigations and operative parameters

A complete physical examination was undertaken and the clinical history obtained from all patients. Laboratory tests included the measurement of serum levels of albumin, total bilirubin, total cholesterol, and alanine and aspartate aminotransferases, as well as peripheral blood cell counts, prothrombin time and the retention of indocyanine green at 15 min (ICG15). Infectious status with hepatitis B and C viruses (HBV and HCV) were examined in all patients by

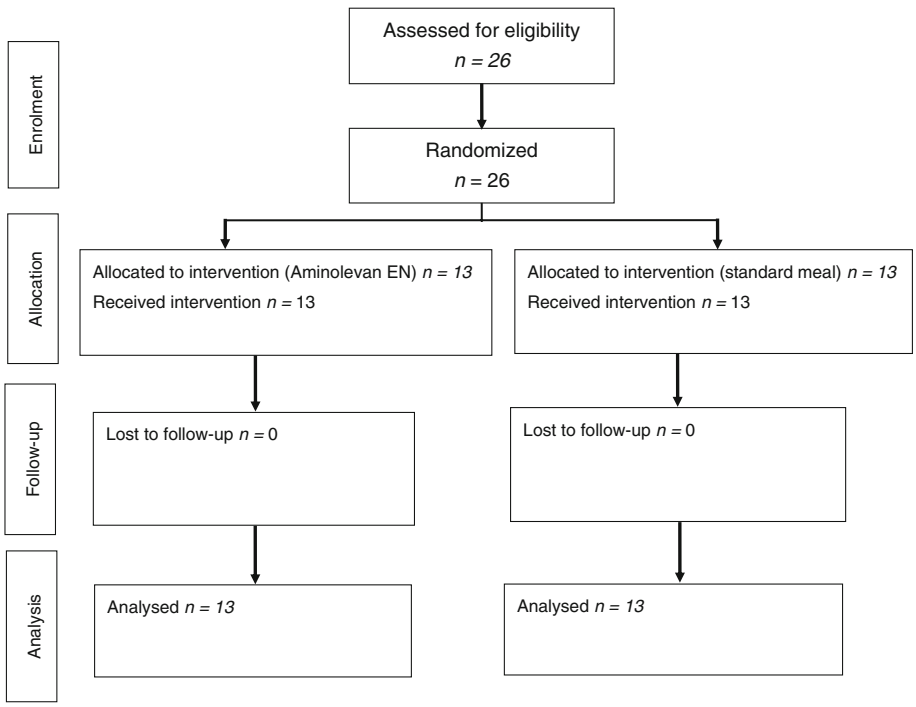


**Fig. 1** Recruitment for randomized trial

**Table 1** Preoperative clinical parameters of patients

| Parameters | AEN group ($n = 13$) | Control group ($n = 13$) | $P$ value |
|---|---|---|---|
| Profile | | | |
| Age (years) | 68.2 ± 5.7 | 63.5 ± 11.0 | 0.191 |
| Gender: male (%) | 9 (69.2) | 8 (61.5) | 0.802 |
| Etiology of hepatic disease | | | 0.920 |
| HBV and/or HCV (%) | 8 (61.5) | 7 (53.8) | |
| Alcoholic (%) | 3 (23.1) | 3 (23.1) | |
| Other (%) | 2 (15.4) | 3 (23.1) | |
| Child-Pugh class | | | 0.619 |
| Class A (%) | 10 (76.9) | 11 (84.6) | |
| Class B (%) | 3 (23.1) | 2 (15.4) | |
| Laboratory data | | | |
| Total bilirubin (0.3–1.1 mg/dL) | 0.6 ± 0.4 | 0.8 ± 0.3 | 0.138 |
| Albumin (3.8–5.1 g/dL) | 3.7 ± 0.5 | 3.9 ± 0.3 | 0.331 |
| Cholinesterase (200–440 unit/L) | 234 ± 53 | 241 ± 75 | 0.792 |
| Aspartate aminotransferase (5–40 U/L) | 25 ± 9 | 30 ± 14 | 0.284 |
| Aspartate aminotransferase (10–35 U/L) | 28 ± 5 | 37 ± 18 | 0.127 |
| Thrombocyte count (14.5–34 × $10^4$/μL) | 18.0 ± 5.5 | 19.5 ± 7.8 | 0.605 |
| Prothrombin time (%) | 85.6 ± 21.9 | 87.8 ± 15.6 | 0.779 |
| ICG 15 (%) | 13.0 ± 5.8 | 14.3 ± 8.2 | 0.663 |
| Diabetic status | | | |
| Body mass index (kg/m$^2$) | 22.5 ± 2.8 | 22.3 ± 3.6 | 0.883 |
| Previous medication for diabetes (%) | 3 (23.1) | 4 (30.8) | 0.658 |
| Hemoglobin A1c (4.3–5.8%) | 5.2 ± 0.7 | 5.5 ± 0.7 | 0.252 |
| Fasting insulin (pmol/L) | 5.8 ± 3.9 | 7.2 ± 3.7 | 0.398 |
| Fasting blood glucose (70–110 mg/dL) | 103 ± 11 | 121 ± 38 | 0.121 |
| HOMA-IR | 1.50 ± 1.03 | 2.25 ± 1.68 | 0.210 |

*HBV* hepatitis B virus, *HCV* hepatitis C virus, *ICG 15* the retention of indocyanine green at 15 min, *HOMA-IR* insulin resistance using the homeostasis model assessment

testing for HBV antigen and HCV antibodies. Positive test results were confirmed by PCR analysis for the presence of viral nucleic acid in sera.

The patients' clinical history of glucose metabolism, including medication for the treatment of diabetes, the monitoring of hemoglobin A1c levels in plasma and the determination of insulin resistance, was evaluated using the homeostatic model assessment (HOMA-IR). These results were compared with measurements of insulin sensitivity in both diabetic and non-diabetic subjects using a hyperinsulinemic normoglycemic clamp (Emoto et al. 1999; Bonora et al. 2000). Operation-related parameters and pathological findings of the liver were also evaluated.

### Supplementation with carbohydrate and branched-chain amino acid-enriched nutrient mixture

The present study used carbohydrate and BCAA-enriched soft-powder nutrient mixture (Aminolevan EN, Otsuka Pharmaceutical, Tokyo) for preoperative supplementation. Supplementation with Aminolevan EN (100 g per day) started at 2 weeks prior to surgery with careful monitoring of compliance. A 100 g dose of Aminolevan EN contains 13.0 g of free amino acids, 13.0 g of gelatin hydrolysate, 1.0 g of casein, 62.1 g of carbohydrate, 7.0 g of lipid, glycyrrhizin and other components, yielding 420 kcal. The patients were subdivided into two groups. One group was administered Aminolevan EN (AEN group; $n = 13$), while the other group was given no additional dietary supplementation (control group; $n = 13$). The patients in the AEN group were given 50 g of Aminolevan EN orally twice a day during the day and in the late evening. These patients were also educated by a dietician to adjust their total caloric energy intake by subtracting the equivalence of 420 kcal of food from their standard meals per day. Thus, the total caloric energy intake per day during the study period was assumed to be equal between the two groups.

### Evaluation of insulin resistance by artificial pancreas STG-22

Following surgery, all patients were given parenteral nutrition. The total caloric requirement was calculated according to the Harris–Benedict equation (Harris and

**Table 2** Operation-related parameters and pathological findings of the liver

| Characteristics | AEN group ($n = 13$) | Control group ($n = 13$) | $P$ value |
|---|---|---|---|
| Operative procedure | | | |
| Major hepatic resection (%) | 7 (53.8) | 5 (38.5) | 0.694 |
| Minor hepatic resection (%) | 6 (46.2) | 8 (61.5) | |
| Operative time (min) | 331 ± 117 | 291 ± 49 | 0.263 |
| Estimated blood loss volume (mL) | 1252 ± 1205 | 669 ± 575 | 0.129 |
| Underlying liver diseases[a] | | | |
| Chronic hepatitis (%) | 3 | 4 | 0.658 |
| Liver cirrhosis (%) | 10 | 9 | |
| Histological type of liver tumor | | | |
| Hepatocellular carcinoma (%) | 8 (61.5) | 7 (53.8) | NS |
| Adenocarcinoma (%) | 5 (38.5) | 6 (46.2) | |

[a] Based on the histological findings from the resected specimens

*NS* not significant

Benedict 1918). To evaluate the insulin requirement, an artificial pancreas with a closed loop system, STG-22 (Nikkiso, Tokyo, Japan), was employed. In this system, blood is sampled continuously from a peripheral vein at a rate of 2 mL/h and the glucose concentration monitored. The STG-22 has previously been validated and is a reliable device for measuring the blood glucose concentration (Yamashita et al. 2008). It maintains blood glucose levels at a target zone by regular, automatic infusion of insulin or glucose into the blood circulation (Hanazaki et al. 2001; Okabayashi et al. 2008). In this study, the target blood glucose level was set between 80 and 110 mg/dL, and the requirements for insulin to maintain this glucose level for 16 h following hepatic resection was quantified using the artificial pancreas STG-22 within the ICU (Van den Berghe et al. 2001). The incidence of hypoglycemia (blood glucose level <40 mg/dL) was also assessed.

### Statistical analysis

Continuous variables are given as mean ± standard deviation, and dichotomous variables are given as a number with percentage. Continuous variables were analyzed using the Student's $t$ test (two-tailed). Dichotomous variables were analyzed by the $\chi^2$ test (two-tailed) or Fisher's exact test (two-tailed). All statistical analyses were performed using SPSS® (Chicago, Illinois, USA) and $P < 0.05$ was considered to be significant.

## Results

### Preoperative clinical parameters of patients

The preoperative clinical parameters of the 26 patients enrolled in the study are shown in Table 1. There were no significant differences in patient characteristics between the two groups (Table 1). There was also no difference in the laboratory data, including nutritional parameters, liver function, fasting insulin concentration, fasting blood glucose level and HOMA-IR between the two groups. The presence of a previous medical history for diabetes mellitus (DM) was equally distributed between the two groups.

All patients underwent a hepatectomy consisting of curative resection of hepatic tissue for the removal of a tumor. Twelve patients underwent a bisegmentectomy or a more extended hepatectomy (major hepatic resection) and 13 patients underwent a segmentectomy (minor hepatic resection). There was no significant predisposition to these operative procedures in the two groups (Table 2). The operation time and estimated blood loss volume did not differ significantly between the two groups. The final diagnoses of the liver tumor in the AEN group were hepatocellular carcinoma in eight patients and adenocarcinoma in five patients, and in the control group hepatocellular carcinoma in seven patients and adenocarcinoma in six patients. Furthermore, there were no significant differences in the pathological findings following examination of the background liver of the resected specimens between the two groups.

### Side effects of Aminolevan EN and operative mortality

The Aminolevan EN supplement was well tolerated in all patients. Although dextrin was included in the supplement, blood glucose levels were stable during the preoperative study period in all patients, including those with DM. The postoperative clinical course was monitored in all patients until February 2008, and there were no differences observed in the all-cause mortality rate. Operative mortality at 30 days following hepatic resection was 0% in both groups.

### Postoperative blood glucose levels

Figure 2 shows the postoperative blood glucose levels in patients in the two study groups for 16 h following surgery.

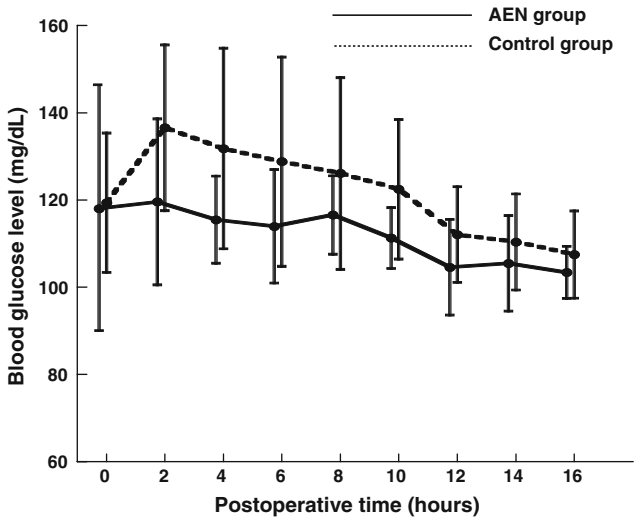


**Fig. 2** Postoperative blood glucose levels monitored by using the STG-22 closed-loop system in the control (*broken line*) and AEN groups (*solid line*) ($n = 13$ in each)

The artificial pancreas STG-22 gradually decreased the blood glucose levels in patients from both groups to the target zone (80–110 mg/dL). During the study period, the blood glucose levels in patients in the AEN group tended to be lower than those in patients in the control group (Fig. 1), although this observation was not of statistical significance. No patient in either group showed a hypoglycemic event.

Total insulin requirement after hepatic resection

The total caloric intake of patients did not significantly differ between the AEN group and the control group (1,700 ± 178 and 1,651 ± 301 calories/person per day, respectively). Figure 3 shows the total insulin requirement of patients during glucose clamping, using the artificial pancreas STG-22, for 16 h following surgery. The average total insulin requirement for all patients was 114 IU (range: 22–370 IU). However, a significant difference ($P = 0.039$) in insulin requirement was observed between the control group (150 ± 103 IU, range: 51–370 IU, $n = 13$) and the AEN group (78 ± 51 IU, range: 22–230 IU, $n = 13$).

## Discussion

The present study shows that oral supplementation with Aminolevan EN for 2 weeks prior to surgery significantly reduces the postoperative insulin requirement for normoglycemic control in patients with a hepatectomy. Especially, HCV infection causes insulin resistance. Because increased insulin resistance is a risk factor for the development of hepatocellular carcinoma and reduced long-term

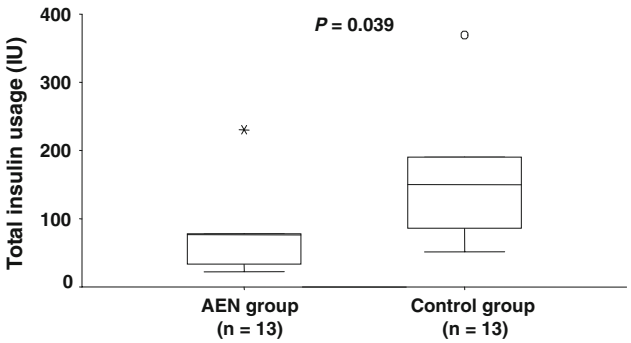


**Fig. 3** Significant differences in total insulin usage during 16 h following hepatic resection between the control and AEN groups ($P = 0.039$)

survival, insulin resistance should be a therapeutic target in patients with HCV infection. HCV should be divided from HBV, and the limitations of this study include the associated errors and biases inherent in a small study design. Large randomized control trials are recommended to further evaluate the benefit of branched-amino acids-rich nutrient support on the survival of patients after hepatic surgery for HCC. Since Aminolevan EN is rich in carbohydrates and BCAA as major energy sources, the findings observed in this study strongly indicate that preoperative administration of one or both of these two nutritional components reduces insulin resistance.

Studies on the effect of preoperative oral intake of carbohydrate by patients with colorectal resection on glucose and protein kinetics using the hyperinsulinemic normoglycemic clamping method have previously provided evidence that preoperative supplementation of carbohydrate reduces postoperative insulin resistance (Svanfeldt et al. 2005). It was observed that postoperative insulin-stimulated endogenous glucose release was significantly higher in patients with preoperative oral administration of a low dose of carbohydrates (25 mg/day) than in patients with preoperative oral administration of a high dose of carbohydrates (125 mg/day) (19 ). Preoperative oral carbohydrate treatment enhances glucose disposal in peripheral tissue and increases the glucose oxidation rate, resulting in the attenuation of insulin resistance (Soop et al. 2001).

Aside from carbohydrate, the other main component of Aminolevan EN, BCAA may also play an important role in improving postoperative insulin resistance. In experimental studies using rodents, BCAA induced glucose uptake in skeletal muscle, adipocytes and hepatocytes. In a rat model of liver cirrhosis induced by $CCl_4$, leucine and isoleucine promoted glucose uptake in the skeletal muscle (Nishitani et al. 2005). This effect might occur as a result of upregulation of the glucose transporters 4 and 1 (GLUT4 and GLUT1) and also by rapamycin-dependent activation of

glucose synthase in skeletal muscle. In a recent human study (Kawaguchi et al.2007), oral supplementation of BCAA for 4 and 6 weeks reduced HOMA-IR in two cases with HCV-related liver disease. However, there have been no studies evaluating the effect of BCAA on insulin resistance in patients with major surgery.

Previous studies of postoperative insulin resistance employed the hyperinsulinemic normoglycemic clamping method (Donaldson et al. 2006). Although this method is reliable for the assessment of insulin resistance, it is technically troublesome. In addition, there is a risk of hypoglycemia, since a nonphysiological hyperinsulinemic condition is necessarily produced. In the artificial pancreas STG-22, the energy supplementation level is fixed and the insulin infusion rate is varied according to blood glucose concentration. Blood glucose levels were gradually, rather than rapidly, reduced to the ideal glucose level (80–110 mg/dL), avoiding unnecessary disturbances in metabolic homeostasis, such as hypoglycemia, in postoperative patients. STG-22 allows the physiological restoration of blood glucose homeostasis and is therefore a safer method for controlling insulin resistance. Notably, the postoperative blood glucose level was reasonably well controlled even in patients with DM. The postoperative insulin requirement of patients following hepatectomy was monitored using the artificial pancreas STG-22. In this study, it is evidenced that the amount of insulin in the AEN group required to maintain tight glycemic control after hepatic surgery was significantly lower than that in the control group. Namely, insulin plays a vital role not only in blood glucose control, but also as an anti-inflammatory and anti-oxidant agent. However, postoperative high-dose insulin therapy was a significant factor contributing to hepatocellular carcinoma recurrence after treatment (Komura et al. 2007). Our clinical findings suggested that preoperative oral supplementation with carbohydrate and branched-chain amino acid-enriched nutrient was of clinical benefit in the reduction of postoperative total insulin usage after liver resection and might be a chance to review the perioperative management for patients with liver neoplasm.

In summary, preoperative oral administration of carbohydrate and BCAA-enriched nutrient might help to improve postoperative insulin resistance in patients with chronic liver disease who are undergoing hepatic resection. Furthermore, STG-22 is a safe and reliable tool to control postoperative glucose metabolism and evaluate insulin resistance.

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## References

Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB et al (2000) Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 36:57–63. doi:10.2337/diacare.23.1.57

Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N et al, German Competence Network Sepsis (SepNet) (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125–139. doi:10.1056/NEJMoa070716

Capes SE, Hunt D, Malmberg K, Gerstein HC (2000) Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 355:773–778. doi:10.1016/S0140-6736(99)08415-9

Cely CM, Arora P, Quartin AA, Kett DH, Schein RM (2004) Relationship of baseline glucose homeostasis to hyperglycemia during medical critical illness. Chest 126:879–887. doi:10.1378/chest.126.3.879

Donaldson S, Villanueva G, Rondinelli L, Baldwin D (2006) Rush University guidelines and protocols for the management of hyperglycemia in hospitalized patients: elimination of the sliding scale and improvement of glycemic control throughout the hospital. Diabetes Educ 32:954–962. doi:10.1177/0145721706294918

Donatelli F, Schricker T, Mistraletti G, Asenjo F, Parrella P, Wykes L et al (2006) Postoperative infusion of amino acids induces a positive protein balance independently of the type of analgesia used. Anesthesiology 105:253–259. doi:10.1097/00000542-200608000-00007

Emoto M, Nishizawa Y, Maekawa K, Hiura Y, Kanda H, Kawagishi T et al (1999) Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes Care 22:818–822. doi:10.2337/diacare.22.5.818

Fan ST, Lo CM, Lai EC, Chu KM, Liu CL, Wong J (1994) Perioperative nutritional support in patients undergoing hepatectomy for hepatocellular carcinoma. N Engl J Med 331:1547–1552. doi:10.1056/NEJM199412083312303

Hanazaki K, Nose Y, Brunicardi FC (2001) Artificial endocrine pancreas. J Am Coll Surg 193:310–322. doi:10.1016/S1072-7515(01)01014-6

Harris JA, Benedict FG (1918) A biometric study of human basal metabolism. Proc Natl Acad Sci USA 4:370–373. doi:10.1073/pnas.4.12.370

Huo TI, Lui WY, Huang YH, Chau GY, Wu JC, Lee PC et al (2003) Diabetes mellitus is a risk factor for hepatic decompensation in patients with hepatocellular carcinoma undergoing resection: a longitudinal study. Am J Gastroenterol 98:2293–2298. doi:10.1111/j.1572-0241.2003.07688.x

Kawaguchi T, Taniguchi E, Itou M, Sumie S, Oriishi T, Matsuoka H et al (2007) Branched-chain amino acids improve insulin resistance in patients with hepatitis C virus-related liver disease: report of two cases. Liver Int 27:1287–1292

Komura T, Mizukoshi E, Kita Y, Sakurai M, Takata Y, Arai K et al (2007) Impact of diabetes on recurrence of hepatocellular carcinoma after surgical treatment in patients with viral hepatitis. Am J Gastroenterol 102:1939–1946. doi:10.1111/j.1572-0241.2007.01354.x

Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y (2002) Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for

colorectal cancer. J Gastrointest Surg 6:88–94. doi:10.1016/S1091-255X(01)00019-1

McCowen KC, Malhotra A, Bistrian BR (2001) Stress-induced hyperglycemia. Crit Care Clin 17:107–124. doi:10.1016/S0749-0704(05)70154-8

Nishitani S, Takehana K, Fujitani S, Sonaka I (2005) Branched-chain amino acids improve glucose metabolism in rats with liver cirrhosis. Am J Physiol Gastrointest Liver Physiol 288:G1292–G1300. doi:10.1152/ajpgi.00510.2003

Okabayashi T, Hnazaki K, Nishimori I, Sugimoto T, Maeda H, Yatabe T et al (2008) Continuous post-operative blood glucose monitoring and control using a closed-loop system in patients undergoing hepatic resection. Dig Dis Sci 53:1405–1410. doi:10.1007/s10620-007-0010-3

Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O (2001) Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. Am J Physiol Endocrinol Metab 280:E576–E583

Svanfeldt M, Thorell A, Hausel J, Soop M, Nygren J, Ljungqvist O (2005) Effect of "preoperative" oral carbohydrate treatment on insulin action: a randomised cross-over unblinded study in healthy subjects. Clin Nutr 24:815–821. doi:10.1016/j.clnu.2005.05.002

Svanfeldt M, Thorell A, Hausel J, Soop M, Rooyackers O, Nygren J et al (2008) Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. Br J Surg 94:1342–1350. doi:10.1002/bjs.5919

Thorell A, Efendic S, Gutniak M, Häggmark T, Ljungqvist O (1993) Development of postoperative insulin resistance is associated with the magnitude of operation. Eur J Surg 159:593–599

Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M et al (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367. doi:10.1056/NEJMoa011300

Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M et al (2003) Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med 31:359–366. doi:10.1097/01.CCM.0000045568.12881.10

Yamashita K, Okabayashi T, Yokoyama T, Yatabe T, Maeda H, Manabe M et al (2008) The accuracy of a continuous blood glucose monitor during surgery. Anesth Analg 106:160–163