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YAN, KOCHING

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AN EXPERIMENTAL STUDY ON PARENTERAL NUTRITION IN SEPSIS: EFFECT OF COMBINED HYPERTONIC CARBOHYDRATES OR AMINO ACIDS INFUSION ON POSTINJURY METABOLISMS

KOCHING YAN, HARUMASA OHYANAGI, AND YOICHI SAITOH

1st Department of Surgery
Kobe University School of Medicine

INDEXING WORDS

total parenteral nutrition; combined use of carbohydrates; amino acids rich TPN; sepsis; glucose metabolism; lipid metabolism; $F2,6P_2$; immune defense mechanism

SYNOPSIS

The present study was undertaken experimentally to reveal the appropriate formula of total parenteral nutrition (TPN) under septic conditions.

Rabbits with perforated diffuse peritonitis and consequent sepsis were nourished with four types of nutrients, namely, low calory infusion, conventional TPN (C-TPN), TPN with glucose, fructose and xylitol solution (GFX-TPN) and TPN with high concentrations of amino acids (AA-TPN).

In looking at the general conditions and immune defense mechanism, each parameter seemed to confirm that TPN played an important role in improving malabsorptive status and depressed immune defense mechanism in sepsis. However, no definite pieces

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Authors' names in Chinese and Japanese : 楊 国慶　大柳 治正　斉藤 洋一

of evidence were obtained in these studies to show the best TPN composition to combat sepsis.

Routine nutritional assessment revealed that GFX-TPN and AA-TPN were of metabolic advantage.

In addition to the results of blood glucose and insulin levels, $F2,6P_2$ content and F6P2K activity in the liver suggested that glycolysis would be maintained better in GFX-TPN than in both C-TPN and AA-TPN in situations of severe stress such as sepsis.

Changes of serum TG, FFA and keton body and of liver TG content suggested that lipogenesis was enhanced by TPN while lipid utilization was depressed due to high blood glucose and insulin in C-TPN and not depressed due to the relatively low blood glucose and insulin in GFX-TPN and AA-TPN.

In view of glucose and lipid metabolism, therefore, GFX-TPN and AA-TPN were superior to C-TPN, whereas no differences between former two could be found.

INTRODUCTION

Recent advances in immunological techniques have demonstrated that the proteins of the complementary system appear to be quite sensitive to nutritional stress.[18, 38] Alexander et al.[1, 2] reported that high protein diet not only corrects depressed post-operative neutrophil function, opsonin activity and complementary strength but also accelerates post-operative recovery of cellular immunity. Therefore, appropriate nutritional support[10, 14, 25, 26, 34] plays a key role in reducing post-operative infections and complications by improving the immune defense mechanism in surgical patients. In fact, Mullen et al.[22] reduced post-operative infection by pre- and post-operative nutritional management.

During the septic or post-traumatic situation, metabolism is generally augmented and patients tend to become malnourished.[11, 17] Nutritional management is especially important in these cases, and if it is initiated, myocardial metabolism is improved causing hemodynamic improvement, too.[7, 14, 20, 36]

However, the therapeutic procedures and values of nutritional management still remain unclear in the septic condition.

The concept of simple caloric supplementation alone is not

necessarily acceptable for undernourished patients faced by sepsis since various sequential metabolic changes take place: impaired glucose utilization because of increased insulin resistance,[7, 9, 20, 35, 37] accelerated proteolysis in the peripheral muscle and enhanced utilization of branched chain amino acids (BCAA),[5, 7, 19, 20] impaired lipid utilization[3, 30, 32] as an outcome of depressed hormone sensitive lipase activity due to increased insulin secretion and impaired endogenous fat mobilization in the peripheral tissue.[4, 19]

Recently Blackburn et al.[4] emphasized the role of amino acid solutions in such cases, but the optimal form of calory supply is still subject to controversy.

We have prepared animal models of perforated diffuse peritonitis and consequent severe infection. Animals were nourished with various compositions of hyperalimentation solutions, and the clinical effectiveness of each solution was assessed by examining both systemic improvement and immunological functions.

These results suggest that septic status may benefit from hypertonic combined carbohydrates solutions or a large amount of amino acid infusion in the feeding regimen.

MATERIALS AND METHODS

Male white rabbits weighing about 2.5 kg were fed with standard solid food (Oriental Yeast ORC4). After 24 hrs fasting, animals were anesthetized with intravenous nembutal at 25 mg/kg and laparotomized. The vermiform appendix was extirpated partially without ligation to induce perforated diffuse peritonitis and consequent severe general infection.

As a preliminary experiment, some of the animals were fed orally, and on the 1st and 2nd days white blood cells (WBC) were counted, the Limulus Test was performed and blood and ascites were sampled and cultured.

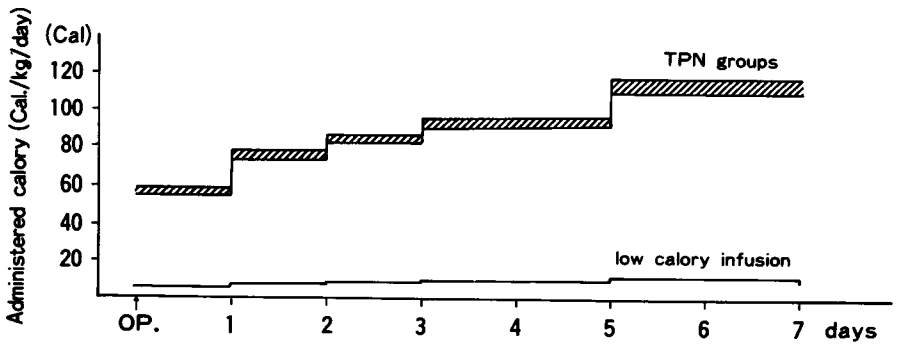
In the main experiment, a silicon rubber catheter (Dow Corning, Inc. Fr. 5) was inserted into the superior vana cava via the jugular vein for infusion of total parenteral nutrition (TPN).

As shown in table 1, experimental animals were divided into four groups and given different types of infusions, respectively: (1) low calory infusion, (2) conventional TPN (C-TPN), (3) TPN

Table 1 Formula of each transfusion.

	low calory infusin	conventional TPN (C-TPN)	GFX-TPN	amino acids rich TPN (AA-TPN)
original fluids	2.6% glucose and electrolyte solution	31.3% glucose and electrolyte sol. +10% amino acid sol. 200mℓ	glucose, fructose, xylitol (4:2:1) and electrolyte sol. 400mℓ(Total carbohydrate 116.8g)+10% amino acid sol. 200mℓ	50% glucose and electrolyte sol. 200mℓ +10% amino acid sol. 400mℓ
final amino acid conc. (W/V %)	2.6 %	21 %	19.5 %	17 %
final carbohydrate conc. (W/V %)	0	3.3 %	3.3 %	6.7 %
mean administered dose (Cal/kg/day)	9.8	92.3	86.6	90.1
administered N (g/kg/day)	0	0.41	0.41	0.81
non protein calory/N		195	181	75

Schedule for calory administration.



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with glucose, fructose and xylitol solution (GFX-TPN) and (4) TPN with amino acids in high concentration (AA-TPN). Control animals were treated with conventional TPN solution without laparotomy (control group). The infusion volume was uniformly 95 ml/kg/day, and it was maintained for 7 days.

Blood was sampled on the 2nd, 4th and 7th post-operative days, and all animals were killed and necropsied on the 7th day after operation.

Clinical effects of the nutrient solutions were assessed on the basis of the survival rate, Limulus Test and necropsy findings. The Limulus Test was performed using Wako's Limulus Test Kit after removing plasma inhibitory substances by the heat method.[8] The function of the reticuloendothelial system (RES) was determined by the congo red method[24] as one of the immunological indexes. Fibronectin levels were monitored by the method[16] using latex on each of the blood samples taken during the course. The strength of the complement was determined in term of hemoglobin amount in sheep red blood cells (RBC) lyzed by antibody compliment binding.[5] Non-activated random mobility of leucocytes was measured by an agarose plate method.[33]

Body weight, nitrogen balance, total protein, albumin, blood sugar, insulin, free fatty acid (FFA), triglyceride (TG) and keton body were determined and analyzed as nutritional and metabolic indexes. Urinary nitrogen was determined by Microkjeldahl-indophenol method,[6] blood sugar by glucose-oxidase method, insulin by double antibody method using a Dinabot RI Laboratories' Insulin RIA Kit, FFA using a Wako NEFA C-Test Kit, TG using a Wako Triglyceride G Test Kit, ketone body using a Sanwa Chemicals' acetoacetic acid and β-hydroxybutyric acid assay reagent.

Liver specimens were rapidly frozen and stored at -80C for the subsequent assays. Glycogen content was determined by Pfieiderer's method, $F2,6P_2$ content by the method of Richards et al.,[29] F6P2Kinase (F6P2K) activity by the method of Furuya et al.,[13] TG content using a Wako TG Kit (acetyl-acetone method) after extraction by Folch's method.[12]

RESULTS

Preliminary experiment

The WBC count was significantly increased to 6,550 ± 311/mm^3 on the 2nd day after vermiform appendix extirpation, whereas it was 3,614 ± 733/mm^3 before the operation.

Blood cultures done at 24 and 48 hrs revealed infection initially with candida and bacteroides species followed in time by E. coli, streptococci and pseudomonas aeruginosa before death. The ascites culture also indicated the presence of E. coli and streptococci (Table 2). The Limulus Test turned positive in 4 of 5 animals at 48 hrs after operation. All 5 animals died within 3 days. Necropsy revealed extensive development of peritonitis and abscess. Thus, it was demonstrated that perforated diffuse peritonitis and consequent sepsis could be experimentally prepared by the procedures taken.

Main experiment

1. General condition

The survival rate of surgical animals was determined by experimental groups. All five animals died on the 3rd post-operative day in the diet group. The rate for the low calory group was 58.8%, whereas the rates for the GFX-TPN, AA-TPN and C-TPN groups were 88.2%, 76.0% and 71.4%, respectively. The life prolongation in the GFX-TPN group was significant as compared to that in the low calory group (Fig. 1).

Animals that survived for 7 days were necropsied and the abscess formation was detected in 70.0% of animals in the low calory group but in only 18.5% on the average in other TPN groups. But there were no statistically significant differences in the rate among those three TPN groups.

As to the formation of inflammatory tumor, all of the animals in the low calory group fell into a pathologic state without any signs of recovery, whereas it was observed only in 37% of the other three TPN groups while the remaining 63% of the animals showed adhesion of the cut surface of the vermiform appendix to the peritoneum, mesentery and intestinal serous membrane as a sign of recovery (Fig. 2).

The Limulus Test turned positive by the 4th day in all 5 animals of all groups. But it became negative again in 20% of the animals in the low calory group and as many as 60% of the animals in the TPN groups on the 7th day after the operation (Table 3).

Table 2
Results of blood culture.

	1 st Postop. Day		2 nd Postop. Day	
	AM	PM	AM	PM
NO. 1	Candia Bacteroides sp.	(−)	(−)	Streptococcus Pseudomonas aeruginosa
NO. 2	Bacteroides sp.	E. coli	(−)	Streptococcus Pseudomonas aeruginosa
NO. 5	Bacteroides sp.	E. coli	Bacteroides sp. Streptococcus	Staphylococcus Pseudomnas aeruginosa

Distal one third of the vermiform appendix was amputated without closure to induce purulent peritonitis in rabbit.

Results of culture of the ascites.

Rabbit NO.	Results of culture	
NO. 1	E. coli	Staphylococcus
NO. 2	〃	〃
NO. 3	〃	〃
NO. 5	〃	〃

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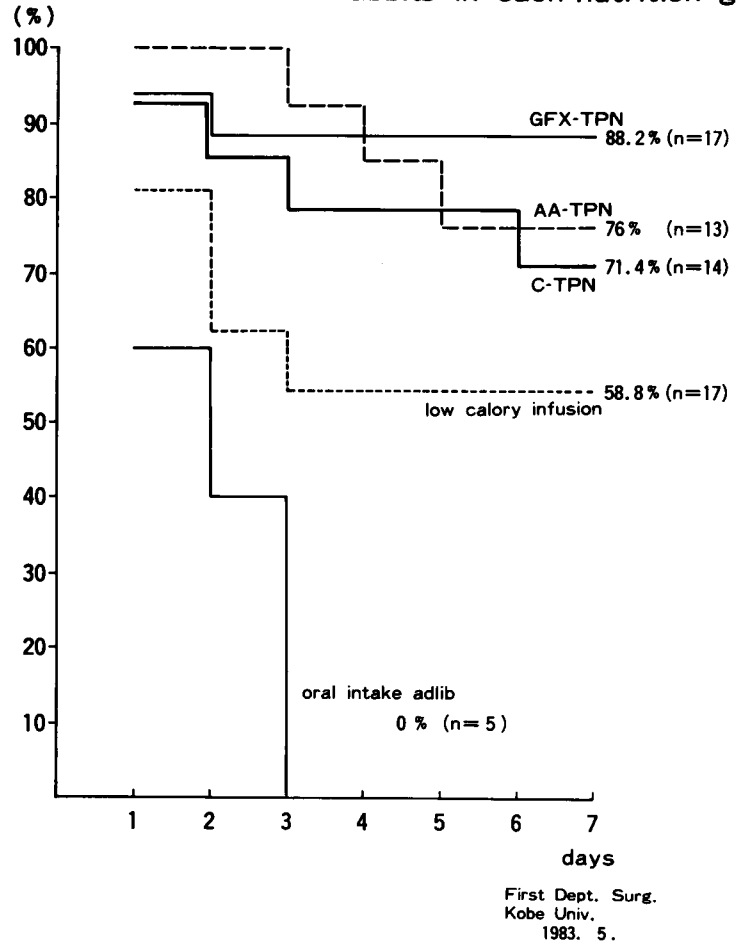
2. RES and immune alterations

Rates of blood clearance of congo red (K value) at 48 hrs after operation were $5.55 \times 10^{-3} \pm 1.06 \times 10^{-3}$, $10.6 \times 10^{-3} \pm 2.2 \times 10^{-3}$, $9.16 \times 10^{-3} \pm 0.37 \times 10^{-3}$, $6.04 \times 10^{-3} \pm 2.4 \times 10^{-3}$ and $2.7 \times 10^{-3} \pm 1.9 \times 10^{-3}$ in normal control, GFX-TPN, AA-TPN, C-TPN and low calory group, respectively. As compared to low calory group, K value of C-TPN tended to increase, while the values of GFX-TPN and AA-TPN group showed significant increases (Fig. 3).

At 48 hrs after operation the random mobility of leucocytes was measured to be 1.13 ± 0.48 mm in the GFX-TPN group and 1.03 ± 0.6 mm in the AA-TPN group, not significantly different from the normal control value (1.4 ± 0.7 mm). But the values were significantly lowered in the C-TPN group (0.88 ± 0.44 mm) and in the low calory group (0.62 ± 0.43 mm) (Fig. 4).

On the 2nd day after operation, the fibronectin level reached

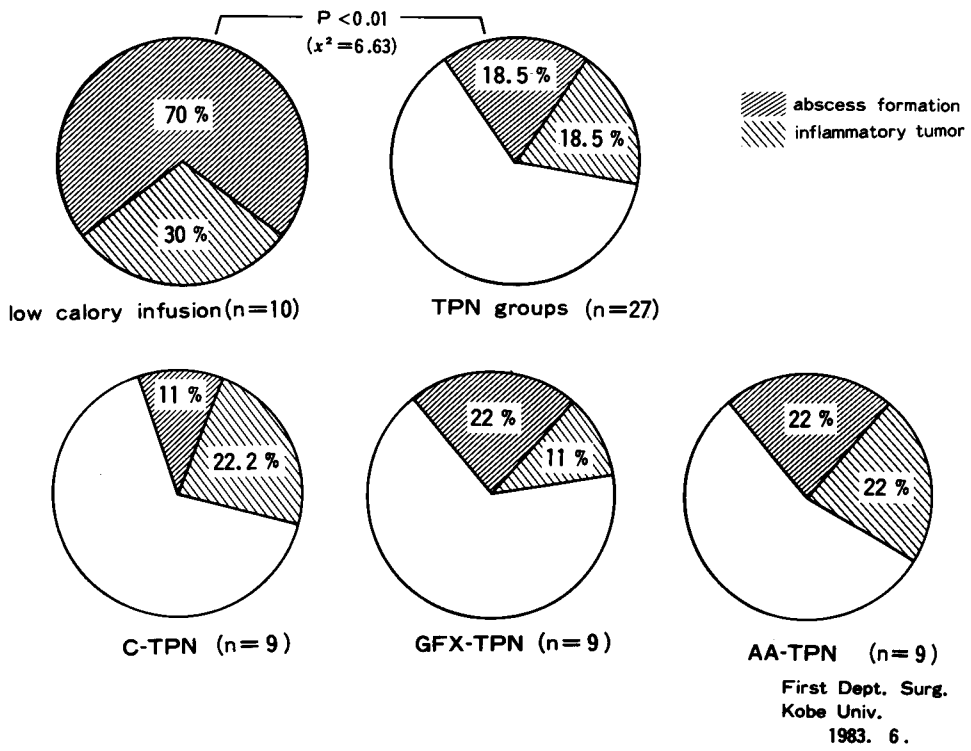
Fig. 1 Survival rate of rabbits in each nutrition group.



289.7 ± 80.8 % in the GFX-TPN group and 177.9 ± 64.4 % in the AA-TPN group. The level was not altered (104.6 ± 6.0 %) in the C-TPN group. But the level in the low calory group was found decreased to 25.7 ± 13.8 % which was significantly lower than in the TPN groups. On the 4th and 7th day, levels in the TPN groups were not significantly different to each other, but still significantly higher than that in the low calory group (Fig. 5).

Blood complement level was 13.78 ± 0.82 CH_{50}/ml in the normal control group. In almost all animals of the low calory group, the levels were lower than the detection limit (< 3CH_{50}/ml). The mean

Fig. 2 Macroscopic findings in the abdomen at sacrifice in each case.



blood complement levels of the TPN groups on the 2nd, 4th and 7th day were 12.28 ± 4.45 CH_{50}/ml, 10.62 ± 3.06 CH_{50}/ml and 12.14 ± 2.31 CH_{50}/ml respectively. No significant fluctuations of these values were seen throughout the experimental period and differences among the TPN groups were negligible.

3. Metabolic alterations

The increase of body weight in the control group (treated with C-TPN without laparotomy) was 2.6% during the experimental period. There was a 18.2% weight loss in the low calory group, but only 7.2% in the C-TPN group, 5.8% in the GFX-TPN group and 4.3% in the AA-TPN group. The values for the TPN groups were significantly higher than that for the low calory group.

Nitrogen balance was positive in the control group (treated

Table 3 Limulus Test.

groups / rabbit No / POD (day)	low calory infusion					C-TPN					GFX-TPN					AA-TPN				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
2 POD	+	−	+	+	+	−	+	+	+	+	+	−	−	+	−	+	+	not sampled	−	−
4 POD	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+	+	+	+	+
7 POD	+	+	−	+	±	+	+	−	−	−	−	+	−	−	−	+	−	−	+	+

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Fig. 3 RES activity of rabbit in each case.

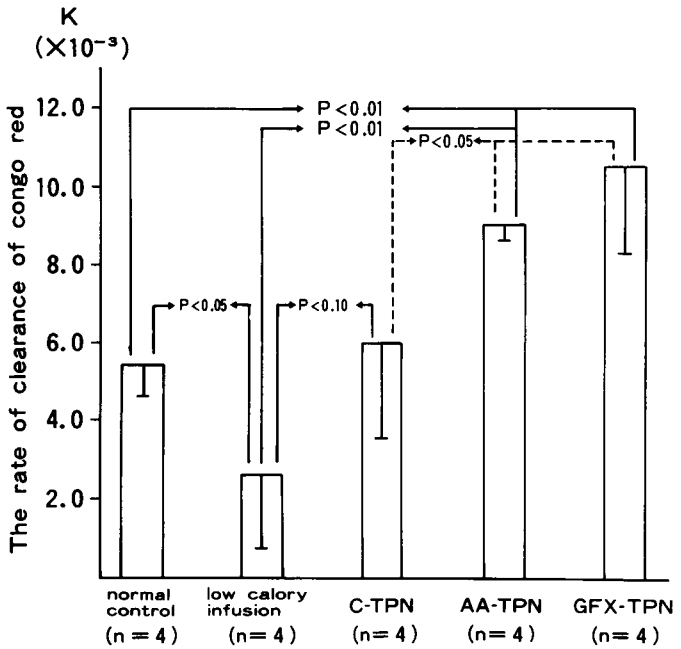

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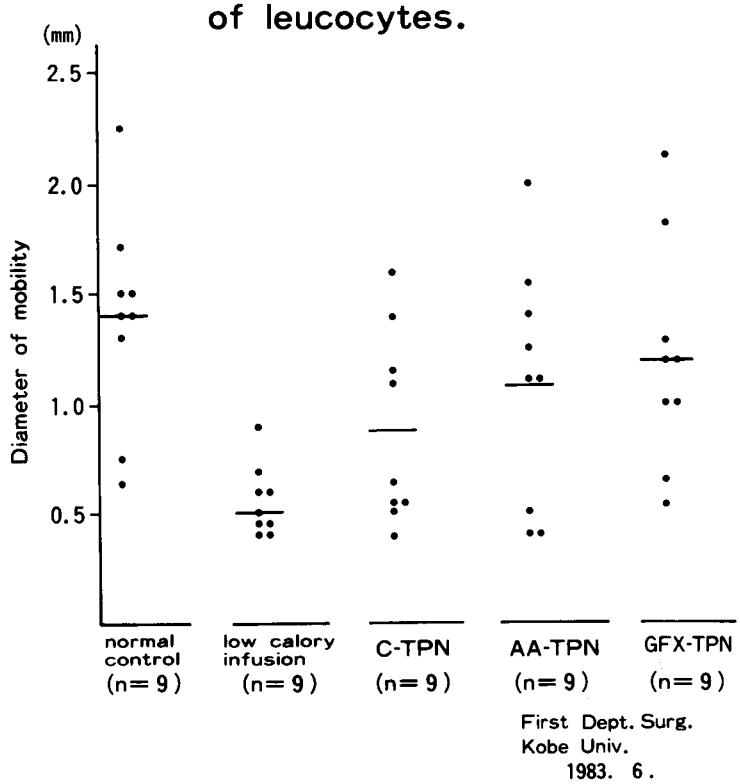
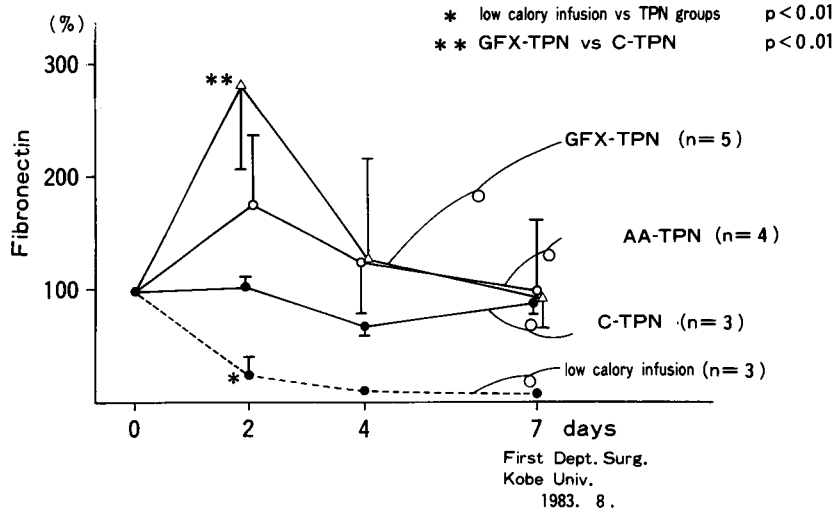
Fig. 4 Non-activated random mobility of leucocytes.



with C-TPN without laparotomy) and AA-TPN group but slightly negative in the two other TPN groups, whereas it was markedly negative in the low calory group. The 7 day cumulative value was decreased to -9.69 ± 0.75 g in the low calory group, but the decrease was significantly slight in the C-TPN group (-3.70 ± 0.55 g) and the GFX-TPN group (-1.69 ± 0.45 g), compared to the low calory group. The value in the AA-TPN group was +3.79 ± 1.95 g (Fig. 6).

Plasma protein and albumin levels decreased for the first 4 days after the operation. These levels became worse in the order: GFX-TPN, AA-TPN, C-TPN and low calory infusion. In particular, the albumin level was high on the 2nd and 4th days in the TPN groups as compared to the low calory group. Among the TPN groups, on the 2nd and 4th days those levels in the GFX-TPN (3.6 ± 0.33

Fig. 5 Chronological changes of plasma fibronectin in each case.



and 3.7 ± 0.31 g/dl) and AA-TPN groups (3.4 ± 0.22 and 3.6 ± 0.32 g/dl) were significantly higher than those in the C-TPN group (3.1 ± 0.3 and 3.0 ± 0.41 g/dl) (Fig. 7).

Blood sugar levels reached a peak on the 2nd day when infection was severest during the experimental period. The increase was lowest in the low calory group (115.9 ± 31.7 mg/dl) followed by the AA-TPN (164.3 ± 37.8 mg/dl) and GFX-TPN groups (168.1 ± 52.8 mg/dl). The increase in these groups were significantly small than the marked increase in the TPN group (255.5 ± 106.4 mg/dl). The increase on the 4th and 7th days was not significant among the TPN groups.

Blood insulin level patterns were similar to blood glucose levels. The increase was greatest on the 2nd day. The increase in the TPN groups was significantly greater than in the low calory group (15.6 ± 6.0 μU/ml), but the level for the C-TPN group (219 ± 96.8 μU/ml) was greatest and the increase in the GFX-TPN and the AA-TPN groups tended to depress (130.7 ± 53 and 111.4 ± 39.3 μU/ml, respectively (Fig. 8).

Blood TG level on the 2nd day were highest in the C-TPN group (197.9 ± 80.8 mg/dl), somewhat high in the GFX-TPN and AA-TPN groups (106.2 ± 54.0 and 121.7 ± 68.9 mg/dl, respectively) and low in the low calory group (80.0 ± 26.3 mg/dl).

Fig. 6 Cumulative nitrogen balance in each case.

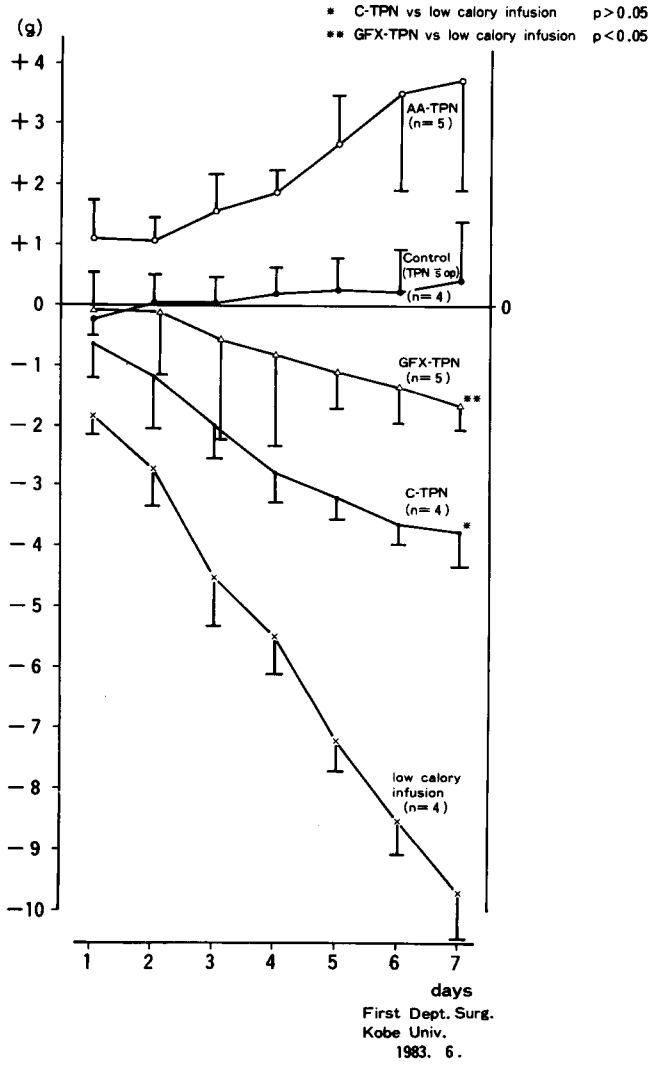


Fig. 7 Chronological changes of serum protein and albumin in each case.

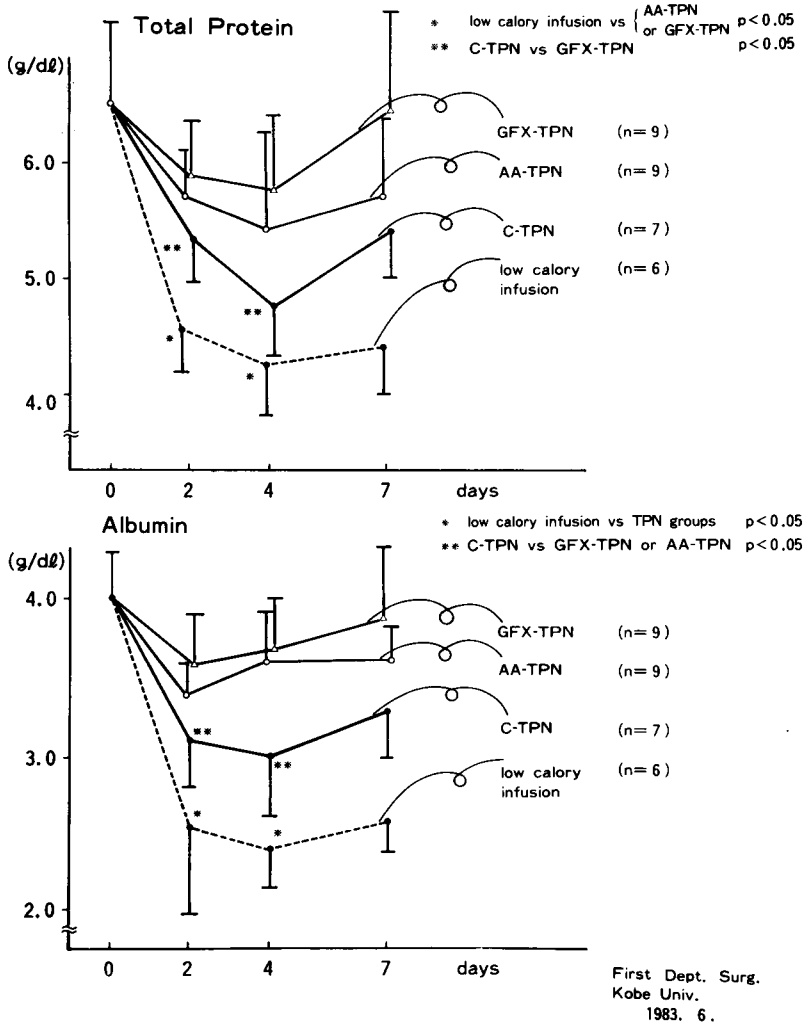


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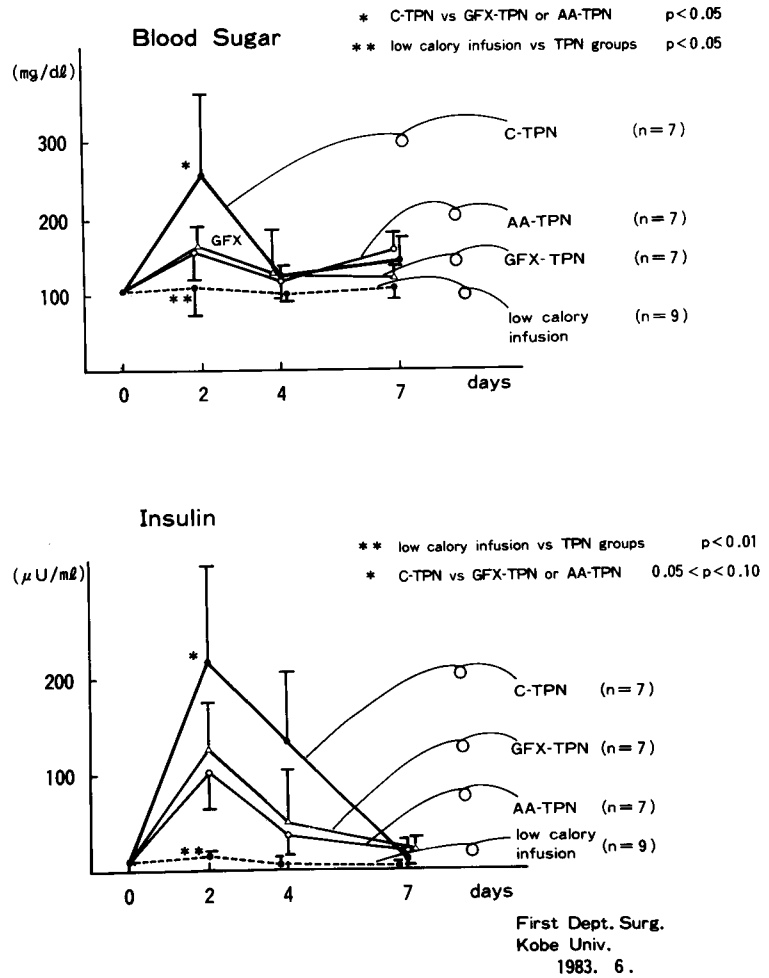
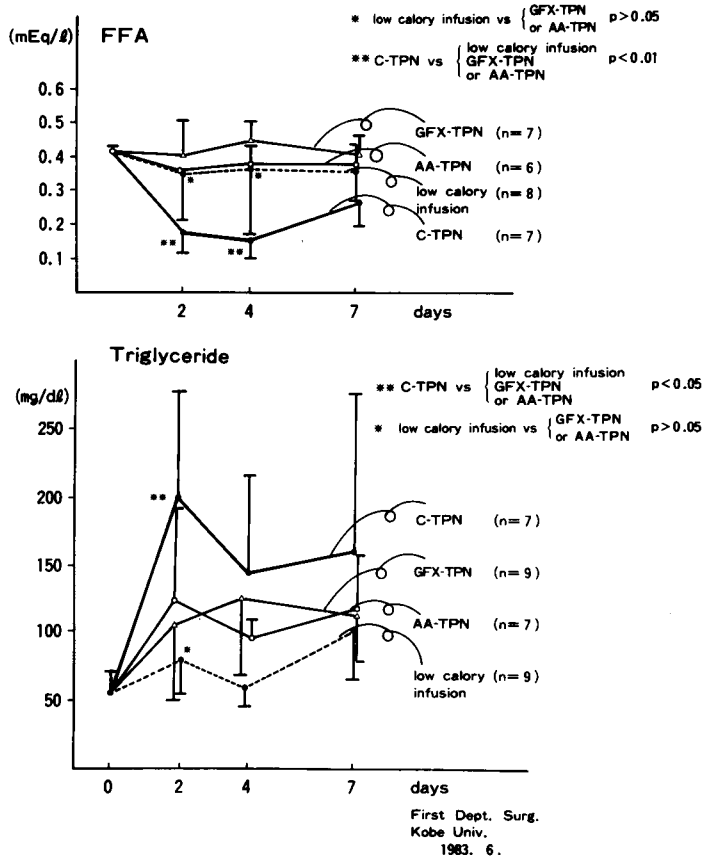
Fig. 8 Chronological changes of serum glucose and IRI in each case.



Blood FFA levels were determined to be 0.41 ± 0.10 and 0.46 ± 0.06 mEq/l (2nd and 4th days) in the GFX-TPN group and 0.36 ± 0.04 and 0.38 ± 0.07 mEq/l (2nd and 4th days) in the AA-TPN group, not much different from the respective initial levels, but the figures were markedly lower in the C-TPN group (0.18 ± 0.05 and 0.15 ± 0.05 mEq/l on the 2nd and 4th days). The decrease in the C-TPN group was significantly lower than other groups (Fig. 9).

Fig. 9 Chronological changes of serum free fatty acids and triglyceride in each case.



Blood keton levels altered like blood FFA levels. The increase was smallest in the C-TPN group (124.7 ± 30.4 and 156.7 ± 94.8 μmol/l on the 2nd and 4th days), while the level in the low calory group almost doubled (290.5 ± 151.9 and 369.5 ± 140.6 μmol/l on the 2nd and 4th days). The increase was intermediate in the GFX-TPN (170 ± 50.3 and 199.4 ± 40.2 μmol/l on the 2nd and 4th days) and AA-TPN groups (202 ± 74.4 and 188.6 ± 42.8 μmol/l on the 2nd and 4th days).

Liver glycogen was significantly depleted in the low calory group but remained in the normal range in the TPN groups.

Control liver TG level was 38.2 ± 7.3 mg/g liver. The level in the low calory group (34.1 ± 4.1 mg/g liver) was almost the

Table 4 Content of liver glycogen and triglyceride in each case.

Group	liver glycogen (mg/g liver)	liver triglyceride (mg/g liver)
normal control	32.6±19.0 (4)	38.2±7.3 (5)
low calory infusion	8.3±3.1 (6)	34.1±4.1 (5)
C-TPN	31.7±15.8 (6)	96.5±25.1 (5)
GFX-TPN	38.4±16.0 (6)	58.6±7.1 (5)
AA-TPN	30.3±15.5 (6)	51.0±21.3 (5)

P<0.01 (low calory infusion vs C-TPN)
P<0.01 (normal control vs low calory infusion)
P<0.01 (C-TPN vs GFX-TPN)

Mean ± SEM
(number)

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Table 5 Content of fructose 2, 6 bisphosphate and activity of fructose 6 phosphate 2-kinase of rabbit liver in each case.

	liver F2, $6P_2$ (n moles/g liver)	liver F6P2K (μU/mg prot)
normal control	5.08±1.70 (4)	2.7±1.1 (4)
low calory infusion	0.45±0.28 (4)	0.2±0.2 (4)
C-TPN	2.46±0.54 (4)	1.1±0.7 (4)
GFX-TPN	3.57±0.29 (4)	4.2±1.3 (4)
AA-TPN	0.33±0.20 (4)	1.3±0.9 (4)

P<0.01 (normal control vs low calory infusion)
P<0.05 (low calory infusion vs C-TPN)
P<0.01 (normal control vs C-TPN)
P<0.05 (C-TPN vs GFX-TPN)
P<0.01 (GFX-TPN vs AA-TPN)
P<0.01 (normal control vs low calory infusion)
P<0.05 (normal control vs C-TPN)
P<0.01 (C-TPN vs GFX-TPN)
P<0.01 (GFX-TPN vs AA-TPN)

Mean ± SEM
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same as this value, but the level was high in the TPN groups, particularly in the C-TPN group (96.5 ± 25.1 mg/g liver) (Table 4).

Liver F2,6P2 level was 5.08 ± 1.70 nmol/g liver in the control group. The level was significantly low in the low calory group (0.45 ± 0.28 nmol/g liver). Among the TPN groups, the GFX-TPN group showed a comparable value of 3.57 ± 0.29 nmol/g liver, but the C-TPN and AA-TPN groups showed significantly lower values of 2.46 ± 0.54 and 0.33 ± 0.20 nmol/g liver, respectively.

Liver F6P2K activity was 2.7 ± 1.1 μU/mg protein in the control. The level was significantly low in the low calory group (0.2 ± 0.2 μU/mg protein). The level in the GFX-TPN group (4.2 ± 1.3 μU/mg protein) tended to rise, while the level in the TPN was significantly low and that in the AA-TPN group tended to be low (1.3 ± 0.9 μU/mg protein) (Table 5).

DISCUSSION

Though both parenteral and enteral nutritional support has already been established to be indispensable for treating patients with severe infection,[1, 2, 17, 22, 23, 31] compositional analysis of energy sources in TPN has not been well documented yet in such cases. In this paper, therefore, the appropriate formula of TPN in septic status is discussed experimentally in order to improve patient care with TPN and to alleviate adverse effects.

On the basis of bacterial appearance in blood and ascites, positive Limulus Test, increased leucocyte count in blood and markedly decreased survival rate of the orally fed rabbits in our preliminary experiment, it would be natural to expect that perforated diffuse peritonitis and consequent sepsis occurred throughout all the experiments.

To find a better TPN formula for sepsis we assessed two new candidates - namely GFX-TPN and AA-TPN, and compared them with C-TPN for the following reason. We[27, 28] have already shown that the combined use of glucose, fructose and xylitol at the ratio of 4:2:1 as carbohydrate source in TPN is of metabolic advantage in depressed glucose metabolism. Blackburn et al.[4] revealed the superiority of amino acids over glucose in sepsis because of the resulting better utilization of amino acids and reduced secretion of insulin. Thus we discuss three compositions of TPN and a low

calory infusion as a control in this study.

Aspects of general conditions and immune defense mechanism

The effect of each form of nutrition on general conditions is compared using the survival rate and Limulus Test. The rapid decrease of survival rate in rabbits fed per os shows that intestinal absorption of various nutrients may be extremely impaired by diffuse peritonitis and subsequent sepsis. Though decreased survival was also observed in the low calory infusion group, it was significantly improved in the TPN groups by contrast, indicating that TPN plays an important role in improving malabsorption and immune defense response.[20, 31, 38] The Limulus Test change from positive to negative in TPN groups also suggests that TPN is superior to low calory infusion in sepsis.

The significantly decreased incidence of abscess formation and inflamatory tumor in TPN groups is considered to be concomitant of improved wound healing and immunocompetence against infection.[17, 23, 25, 31, 34, 35]

Therefore, we examined congo red clearance rate as one of the indexes by which RES function could be monitored. These results - namely, a decrease in the low calory group, no apparent decrease in C-TPN group and a significant increase of congo red clearance in GFX-TPN and AA-TPN groups, strongly suggest that sufficient caloric supplementation is required to maintain intact immune defense against bacterial infection[1, 17, 35, 38] further improvement in RES function can be expected with GFX-TPN and AA-TPN as compared to C-TPN.

Non-activated random mobility of leukocytes is also investigated as one protective response to infection.[33] Decreased mobility of leukocytes in the low calory group and no significant change in TPN groups suggest that sufficient calory administration is important to keep leukocyte activity intact.

Plasma fibronectin content has never been discussed with TPN for septis in spite of its essential role against infection, as demonstrated recently.[16, 21] The decreased fibronectin content in the low calory group coincides with depressed RES function activities and non-activated random mobility of leukocytes in the same animals. On the other hand, all TPN groups apparently show detectable improvement. Of particular note is the signifi-

cant increase of fibronectin obtained in the GFX-TPN group on the 2nd day.

According to Alexander et al.,[1, 2] high protein diet corrects depressed complementary system after operations. A significantly higher level of serum complement in TPN groups than those observed with low calory infusion suggests that blood complement level is easily affected by nutritional status and that TPN is superior to low calory infusion for maintaining complement capacity.

Thus, these results together support the idea that TPN plays an important role in improving malabsorption and reviving the depressed immune defense mechanism in sepsis. However, no definite evidence has been obtained yet to show the best TPN composition for septis.

Nutritional assessment

The increase of body weight after one week on C-TPN in normal control rabbits shows that sufficient calories are supplied by TPN for normal controls. The positive nitrogen balance in this group is compatible with the increase of body weight. The slight decrease of body weight and negative nitrogen balance in the C-TPN group laparotomized to induce severe infection suggest that C-TPN did not meet the caloric requirement of septis and that it was not always the best formula which was avilable for TPN in sepsis.[17, 20] On the basis of body weight change and improved nitrogen balance, GFX-TPN and AA-TPN appear superior to C-TPN in sepsis, but further study is warranted to clarify more details.

Plasma protein and albumin levels decreased gradually for 4 days after operation. The levels in the GFX-TPN and AA-TPN groups were significantly higher at the 2nd and 4th days than those in C-TPN, indicating that nutritional status can be maintained better by GFX-TPN and AA-TPN than C-TPN.

Glucose metabolism, we[27, 28] have already proved that massive glucose administration as carbohydrate source in TPN for more than 2 weeks induces diabetic changes of enzymatic activities in the liver without clinical manifestation. Furthermore, Blackburn et al.[4] suggested that in sepsis serum high glucose level due to deteriorated glucose utilization results in plasma high insulin levels which prevent endogenous fat utilization.

Serum glucose level peaked on the 2nd day when infection seemed to be at its severest during the experimental period. Plasma insulin and serum glucose levels showed similar patterns, reflecting the good secretory response of pancreatic islets in sepsis. The influence on serum glucose and plasma insulin by infection during TPN management was negligible in GFX-TPN and AA-TPN groups as compared to the C-TPN group, where these levels were affected markedly. Thus, it is concluded that GFX-TPN and AA-TPN are of metabolic advantage because of the easy glucose control affected as well as their amino acid content alone.[4)]

Recently, it has been shown that fructose-2,6-bisphosphate is the most potent activator of phosphofructokinase in the liver and that fructose-6-phosphate2-kinase catalyzes the synthesis of fructose-2,6-bisphosphate from fructose-6-phosphate and ATP.[13)] These key substances of the liver in glycolysis are studied to elucidate the glucose metabolism more precisely in each method of nutrition for combatting septis. A normal blood glucose level, remarkable decrease of $F2,6P_2$ content and F6P2K activity in the liver in the low calory group were observed, indicating that glycolysis in the liver would be depressed due to fasting and severe sepsis. The significant decrease in both $F2,6P_2$ and F6P2K with AA-TPN is considered to be due to not only to septis but also increased gluconeogenesis at massive amino acids supplementation. The moderate decrease in both $F2,6P_2$ and F6P2K of the liver with high blood glucose level in the C-TPN group suggests that glycolysis was depressed by the additional effect of sepsis[3), 9), 35)] and massive glucose administration for a certain period.[27), 28)] On the other hand, the slight decrease of $F2,6P_2$ and compensated increase of F6P2K in GFX-TPN apparently suggest that glycolysis would be maintained better in GFX-TPN than both C-TPN and AA-TPN in severe stress such as sepsis.

Nutritional support often affects lipid metabolism. Blackburn et al.[4)] reported that a high insulin level depresses endogenous lipid utilization in sepsis. We[28)] have already revealed that GFX-TPN accelerates markedly hepatic lipogenesis due mainly to the included fructose. Thus, lipid metabolism is discussed for each form of nutrition. Almost no changes of serum TG and FFA and the remarkable increase in serum keton body indicates facilitated endogenous lipid mobilization and utilization as energy source due to the caloric deficit in the low calory group. Significantly

increased serum TG, decrease of FFA and only slight elevation of blood keton body seem to be due to accelerated lipogenesis and depressed lipid utilization on account of high blood glucose and insulin in C-TPN. On the other hand, serum TG and FFA in the GFX-TPN and AA-TPN groups fluctuated slightly to show no significant deviations from the preoperative levels. In addition to change of blood keton body, these results suggest that endogenous lipid utilization is enhanced to balance the lipid metabolism within normal ranges accompanying accelerated lipid synthesis in GFX-TPN and AA-TPN. As lipid metabolism depends on nutritional status, contents of liver glycogen and TG are discussed for each form of nutrition. Normal ranges of liver glycogen content in all TPN groups indicate the apparently good maintenance of nutritional status resulting from sufficient calory supplementation, whereas the differences in metabolic aspects have already been described above. Liver lipid content in the C-TPN groups was significantly higher than that in GFX-TPN and AA-TPN, though the lipogenesis has been already proved to be higher in GFX-TPN than in C-TPN.[28] This reverse relationship between hepatic lipogenesis and lipid content in C-TPN and GFX-TPN suggests that lipid utilization is suppressed by higher levels of blood glucose and insulin when highly concentrated glucose such as C-TPN is administered and that depressed lipid utilization is avoided by the relatively low levels of blood glucose and insulin in GFX-TPN. Liver lipid content in AA-TPN seems to also accompany good maintenance of lipid utilization due to the relatively low blood glucose and insulin as compared to C-TPN in sepsis. Thus, it is shown that GFX-TPN and AA-TPN are superior to C-TPN in view of lipid metabolism, though differences between the former two could not be clarified.

Thus, it is concluded that in terms of glucose and lipid metabolism, GFX solution is superior to highly concentrated glucose solution alone as a carbohydrate source of TPN for sepsis. It is also suggested that amino acid rich TPN including much glucose is superior to massive amounts of amino acids alone, because of same metabolic effects on serum glucose control and lipid utilization and of higher caloric supplementation.

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