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Postoperative Lipid Levels

(surgical diabetes/postheparin lipolytic activities)

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In our group of over 50 patients, both diabetic and nondiabetic, transient hypotriglyceridemia was observed in the early postoperative period. To elucidate the mechanism of decrease in plasma triglycerides level, postheparin lipolytic activities (PHLA) were investigated, and we found that there was no difference between preoperative and postoperative PHLA. Our results suggest that the release or biosynthesis of endogenous triglycerides from liver decreases.

No elevation of free fatty acids (FFA) was observed even under low calorie intravenous nutrition. Therefore, it can be assumed that increase in liberation of FFA from adipose tissue as a response to surgical stress was prevented by the continuous administration of glucose as much as 140g per day.

The intravenous provision of calories and protein split-products is imperative in the case of severely wounded persons, postoperative patients with gastrointestinal disease or disease weakened patients. In the early postoperative period, the catabolic phase, carbohydrate stored as glycogen is consumed so rapidly that fat and protein might be degradated as fuel, and hyperglycemia can be seen under these conditions (1, 2). Therefore, the posttraumatic or postoperative catabolic state is termed "stress diabetes" or "surgical diabetes", and catabolism observed in diabetic patients develops under surgical stress.

However, there is apparently no documentation on "surgical diabetes" in diabetic patients not given insulin replacement.

In general, hypotriglyceridemia is expected to develop in "surgical diabetes" of non-diabetic subjects (3), whereas hypertriglyceridemia can be seen in diabetic subjects.

Whether or not "surgical stress" produces a hypotriglyceridemia in cases of diabetes mellitus without insulin replacement is not well understood.

It has been established that a high concentration of FFA acts as an uncoupler of the electron transport system in mitochondria and produces certain toxic effects such as hemorrhage, arrhythmia, and atelectasis (4, 5, 6). Since plasma FFA levels increase in postoperative patients, prevention of the postoperative increase in FFA in diabetic patients has to be considered (7, 8).

Therefore, one has to know whether the intravenous provision of low glucose is relevant to the recovery of "surgical diabetes" in diabetic patients, and whether the changes occur in lipids and lipoprotein lipase activity in diabetic postoperative patients under conditions of intravenous administration of glucose. In the present communication, it will be shown that increase in FFA mobilized from adipose tissue as a result of surgical stress in diabetic patients can be prevented by continuous administration of glucose at low concentrations and that the degree of hypotriglyceridemia found in diabetic patients under surgical stress was much the same as that of non-diabetic patients.

MATERIALS AND METHODS

Patients : Fifty-one Japanese patients who had undergone surgery of the alimentary tract were studied (Table I). They were divided into two groups, diabetic and control, according to either 100g oral glucose tolerance test or 25g intravenous glucose tolerance test for patients with alimentary tract stenosis or obstruction. Here diabetic patients who required preoperative insulin replacement were excluded and moreover no patient was administrated insulin postoperatively (Table II). Patients with hyperlipidemia were also excluded.

TABLE I. *Patients and Surgery*

Type of operation	No. of patients Diabetic	Control
Esophagectomy	3	3
Esophageal bypass	1	1
Total gastrectomy	1	2
Subtotal gastrectomy	6	11
Palliative gastrojejunostomy	1	0
Cholecystectomy	0	1
Pancreatoduodenectomy	0	1
Transduodenal papilloplasty	1	0
Colectomy	3	4
Rectosigmoidectomy	5	2
Ileal conduit	0	1
Graham's operation	0	1
Diversion of peritoneal adhesions	0	3
	21	30

TABLE II. *Patient Groups*

	Diabetic	Control
No. of patients	21	30
Age distribution	38–74 y. o.	25–77 y. o.
Mean±S. E.	62±10 y. o.	51±15 y. o.

TABLE III. *Postoperative Nutritive Administration*

	0–3 P.O.D.	4–5 P.O.D.	6–7 P.O.D.	8–10 P.O.D.
Intravenous administration				
Water	2100 ml/day	1300 ml/day	800 ml/day	0 ml/day
Glucose	140 g/day	110 g/day	60 g/day	0 g/day
Amino acids	48 g/day	24 g/day	24 g/day	0 g/day
Gastric tube or oral administration	0 Cal/day	160 Cal/day 480 Cal/day	800 Cal/day	1300 Cal/day

The peripheral venous routes were maintained for the first three postoperative days and postoperative nutrition was carried out in same manner as shown in Table III. The type of operation and body weight of each patient were disregarded.

Experimental Methods : Aliquots (20ml) of whole blood were obtained by peripheral venous puncture early in the a. m. otherwise indicated. Blood sampling was performed within 10 seconds to obtain accurate FFA levels. Following clot retraction, sera were stored at 4°C until analysis of lipids.

PHLA determination : Following injection of 20 units per kg body weight of heparin, aliquots (5ml) of whole blood were obtained in 10 and 30 min, after which PHLA was determined *in vitro*. PHLA was defined as the amount of FFA liberated in the reaction mixture when Intralipids® was used as substrate. Four diabetic patients were selected for PHLA determination. Postoperative PHLA (12 hours after operation) was compared with their preoperative values.

RESULTS AND DISCUSSION

Changes in the concentrations of lipids such as triglycerides (TG), cholesterol, phospholipids and free fatty acids (FFA) in the blood from diabetic and non-diabetic patients undergoing surgery as listed in Table I, were investigated. As depicted in Fig. 1, TG levels from diabetic and non-diabetic patients markedly decreased to 50 and 60%, respectively, 24 hours after surgery as compared to respective preoperative conditions. The decreased TG reached preoperative levels by the third day in diabetic group and the fifth day in the non-diabetic group. The serum TG values found in diabetic group were higher than values in non-diabetic group at significant levels throughout the experimental periods, except for a period of equality for 24 hours after operation ($p < 0.01$).

In both the diabetic and non-diabetic groups, the serum cholesterol decreased 24 hours after operation, and the decreases in cholesterol were most evident in the diabetics ($p < 0.01$). The cholesterol levels remained low for several days. Decreases in phospholipids were also observed on the first postoperative day in both groups. In contrast to the fact that TG levels in diabetic group were higher than those in non-diabetic group, cholesterol and

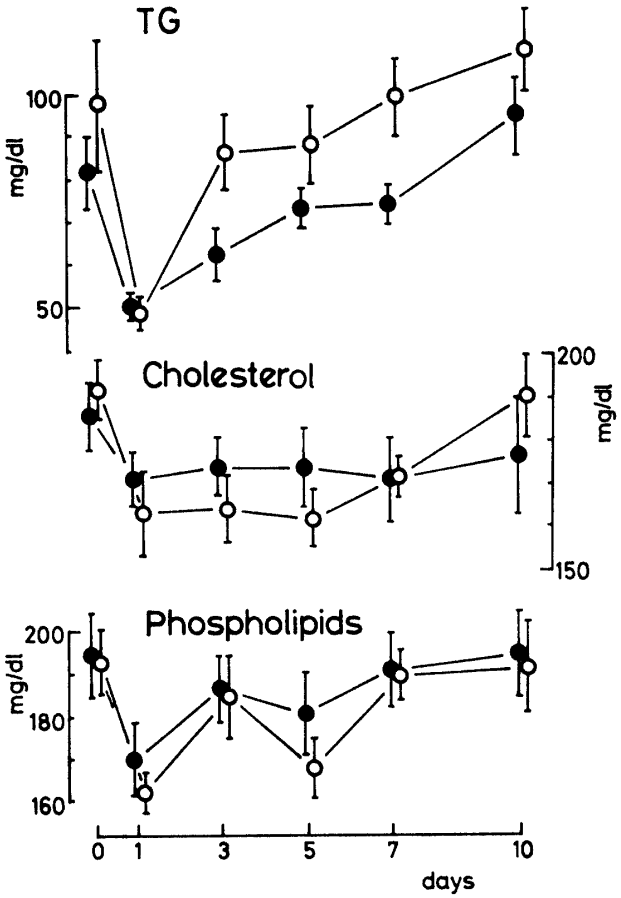

Fig. 1. Postoperative changes in serum lipids. ○——○ : diabetic group, ●——● : non-diabetic group (Mean±S. E.).

phospholipids levels in the diabetic group were not so low as in the non-diabetic group at significant levels throughout the experimental periods, except for the first and fifth postoperative days.

We investigated the changes in serum FFA levels in diabetic and non-diabetic patients undergoing surgery. As seen in other lipids, FFA also decreased after operation and was restored to preoperative levels by the fifth day (Fig. 2). Here differences in FFA between diabetic and non-diabetic groups were

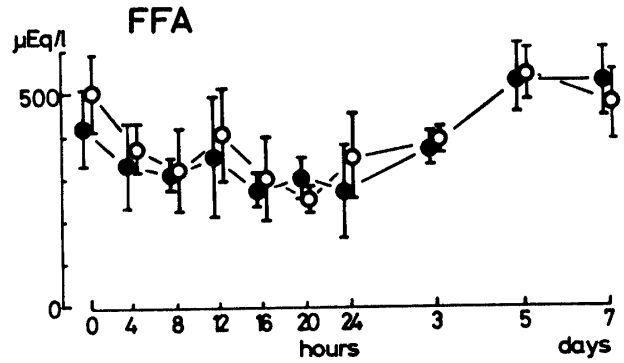

Fig. 2. Postoperative changes in serum FFA. ○——○ : diabetic group, ●——● : non-diabetic group. (Mean±S. E.)

not observed.

In general, low serum TG levels are due to a suppression of mobilization of lipoproteins, probably due to decreases in the biosynthesis of lipoproteins in certain tissues. Under the experimental conditions described herein, liver, but not intestine, participates mainly in changes in the serum TG levels. Therefore, we estimated the lipoprotein lipase activity with or without heparin injection (9). As seen in healthy subjects, no appreciable enzyme activity was observed in the serum from diabetic surgical patients.

With heparin injection, however, significant enzyme activity was detected in both groups. In this case, insignificant differences in PHLA were noted between pre- and postoperative states of diabetic patients. The average age of these four patients who underwent subtotal gastrectomy was 68.5 years. It is known that postheparin lipoprotein lipase consists of lipoprotein lipase and hepatic TG lipase, and that PHLA correlates with either age or the state of atherogenesis of the subjects (10, 11, 12). Furthermore, decrease in hepatic lipase activity was reported in such atherogenic conditions as diabetes mellitus and hypothyroidism, in which the plasma levels of intermediate density lipoprotein (IDL) were increased (13). This explains why the PHLA levels found in patients in both pre- and postoperative states are less than half the levels seen in healthy subjects (average 27.5). To determine the response of FFA and TG levels to heparin injection, the following experiments were carried out in preoperative and postoperative patients with diabetes mellitus.

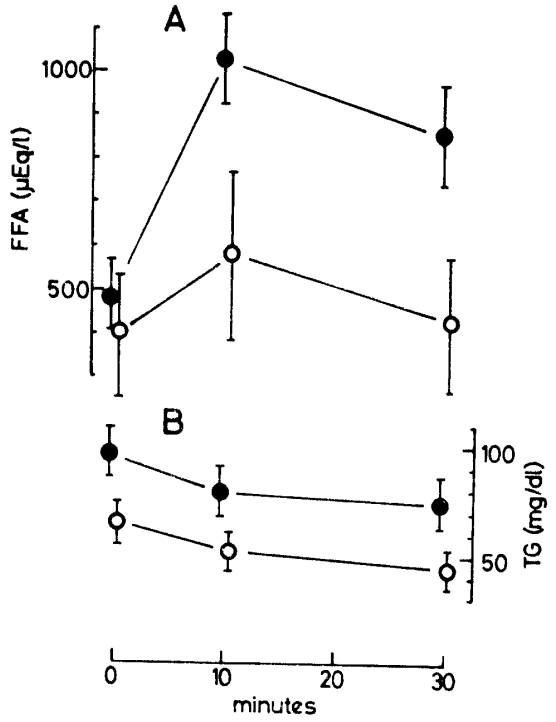

Fig. 3. Pre- and postoperative changes in plasma FFA (A) and TG (B) of diabetic patients following heparin injection. ●——● : preoperative fasting state, ○——○ : 12 hours after operation. (Mean±S. E.)

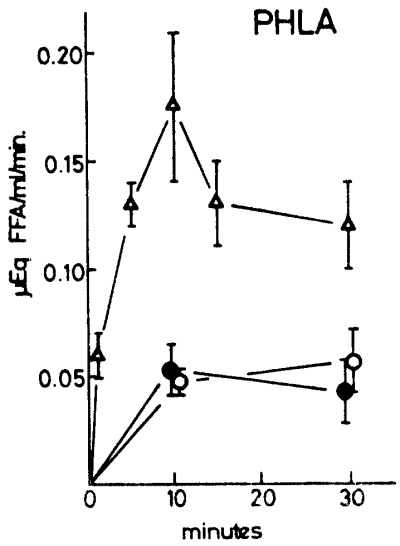

Fig. 4. Pre- and postoperative PHLA of diabetic patients. ●——● : preoperative fasting state, ○——○ : 12 hours after operation. Healthy controls in a fasting state. △——△ (Mean±S. E.)

As shown in Fig. 3, A, FFA rose to a peak 10 min after heparin injection. Furthermore, the decrease in TG was observed concomitant with increase in FFA (Fig. 3, B). The levels of TG and FFA in the blood from the preoperative group were higher than those in the postoperative group. However, no difference of PHLA was observed between the two groups (Fig. 4). These results suggest that low TG levels found 24 hours after surgery in diabetic and non-diabetic patients are due to decreases in the biosynthesis and release of lipoproteins, particularly very low density lipoprotein (VLDL).

Concerning lipoprotein lipase, it is known that this enzyme in extrahepatic tissue is activated with insulin and glucose (14). Under the conditions of such caloric intake as listed in Table II, blood glucose levels in diabetic and non-diabetic subjects reached a peak 8 hours after surgery, and then decreased gradually to the respective preoperative levels by the fifth day (data not shown). Furthermore, both glucocorticoids and catecholamines increased by surgical stress may counteract the action of insulin, thus resulting in "stress diabetes" (15). For this reason, hormone sensitive lipase must be activated and consequently serum FFA should increase, significantly (16). However, continuous infusion of glucose as much as 140g per day completely prevented the elevation of FFA in both the diabetic and non-diabetic groups. In fact, plasma FFA concentrations in the postoperative diabetic subjects were as high as in the postoperative non-diabetic subjects (Fig. 2). These results indicate that injected glucose metabolized by aerobic as well as anaerobic glycolysis in diabetic patients is not impaired.

Fatty acids which serve as an energy source, are also potentially toxic when the concentration is elevated in excess of what can be carried by the albumin. FFA uncouples oxidative phosphorylation and induces bleeding, thrombus formation, and arrhythmia. FFA, when in excess, is also incorporated into

the alveolar lining cells of the lung and interferes with the production of surfactant. These toxic effects of fatty acids may be responsible for the production of postoperative complications such as hemorrhage, thrombophlebitis, arrhythmia, and atelectasis (17).

Nitrogen loss can be reduced from 12 to 1g per day by ingestion of as much as 150g of glucose (18), which in turn could suppress the liberation of FFA. Therefore, the administration of 150g or so of glucose per day is defined to be the critical amount for maintainance of uncomplicated postoperative courses.

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