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Short Report

Long-term Effects of a 30% Hepatectomy on Serum Biochemistry and Longevity in Male Adult Rats

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Abstract

The long-term effects of a 30 % hepatectomy on age-related changes in serum biochemistry and longevity were studied in rats. Adult Sprague-Dawley rats were divided into a 30 % partial hepatectomy (30%H, n=7) and a sham-operated control (N, n=9). Blood was collected at 12 weeks, 24 weeks and 48 weeks after partial hepatectomy, and changes in serum biochemical parameters and effects on longevity were studied. By 12 weeks, the serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had usually returned to within normal limits. Hepatic function maintained normal serum protein, albumin, glucose and cholesterol levels, but serum triglyceride concentration increased in the 30%H group. Forty eight weeks after surgery, the majority of vital liver functions had returned to normal, but average longevity of the 30%H group was lower than that of the normal group.

Introduction

Liver transplantation is now accepted as a useful treatment for children with end-stage liver disease [1]. An essential prerequisite for partial liver transplantation is to perform donor hepatectomy with minimal risk [1].

The study of liver regeneration in mammalian species has been a major focus for many years. Remarkable regeneration of the partially hepatectomized liver has been well demonstrated in animal [2-4] and human studies [5-6]. Generally, parenchymal regeneration begins almost immediately provided the hepatic remnant is composed of relatively normal tissue [7]. Within two to three weeks after surgery, hepatic function will have returned to pre-resection levels, although a total of three or four months is required for the liver mass to return to preoperative size [8].

On the other hand, the effects of aging on the mammalian liver have not been clearly resolved [9-10]. Senescent changes have important clinical implications with regard to surgical interventions for liver disease, e.g., resection or transplantation [11-18]. Although the liver's regenerative potential appears to remain intact in aged rats, the rate of regeneration declines with increasing age [19]. This statement is based on the observation that it takes considerably longer for the partially resected livers of older animals to regain their original volume compared to younger animals. However, hepatic regeneration is poorly understood regardless of the age of the animal.

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It is also very important to understand the long-term effects of hepatectomy on longevity. There have been many reports on the effects of hepatectomy in short-term studies, but very few from long-term studies. For these reasons, the long-term effects of hepatectomy were studied in rats.

Material and Methods

Animals

Male Sprague-Dawley rats weighing about 500 ± 5g were used in this experiment. In all the experiments, animals were housed in a climatized room with a 12h light/dark cycle.

Experiment 1: Average longevity

These animals were divided into two groups: a 30% partial hepatectomy group (30%H, n=7) and a sham-operated control group (N, n=9). After an overnight fast, the rats were anesthetized with an intraperitoneal injection of sodium pentobarbital, Nembutal, and the abdomen was opened with an upper midline incision. Normals were closed immediately. In the 30%H group, the left lateral lobes (30 % of the total liver volume) were resected according to the methods of Higgins and Anderson [20]. After two days fasting, water and a standard pellet diet were made available *ad libitum*. Daily changes in body weight were measured during the experimental period. The average longevity for the 30 %H group was compared with that of the normal group.

Experiment 2: Chemical analysis

Blood was collected from the tail vein under light ether anesthesia at 12 weeks, 24 weeks and 48 weeks. The serum parameters were assayed with an automatic analyzer (Hitachi, Model 7170). The serum biochemical parameters measured were aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, blood urea nitrogen, serum creatinine, glucose, triglycerides, free fatty acids, total cholesterol, esterified cholesterol and free cholesterol.

Statistics: Differences were analyzed by the Student's t-test, and $p<0.05$ was taken to indicate significance.

Result

Changes in body weight are shown in Fig.1. The 30%H groups decreased during the first week post hepatectomy, subsequently recovered gradually, then increased steadily. The body weights remained roughly unchanged in both groups throughout the post-operative period, and no significant difference was observed between the experimental groups. Hepatic resection did not influence body weight changes.

Table 1 shows the postoperative changes in AST, ALT, total protein (TP), albumin (Alb), blood urea nitrogen (BUN), creatinine (Cr) and glucose (Glc) values in the experimental groups. TP, Alb, BUN, Cr and Glc remained roughly unchanged in both groups during the post-operative and no significant difference was noted between the experimental groups. 30% hepatectomy did not influence serum protein and albumin levels. The liver plays an important role in the lipid metabolism of the body. Any effect of hepatic regeneration must also be related to lipid metabolism. The total cholesterol (TC), free cholesterol (FC), esterified cholesterol (EC), free fatty acids (FFA) and triglyceride (TG) data are shown in Fig.2. By 24 weeks, the TC, EC, FC and TG levels of the partially hepatectomized animals were similar to the serum levels observed in the normal rats. In contrast, triglyceride showed an increase at 48 weeks after surgery.

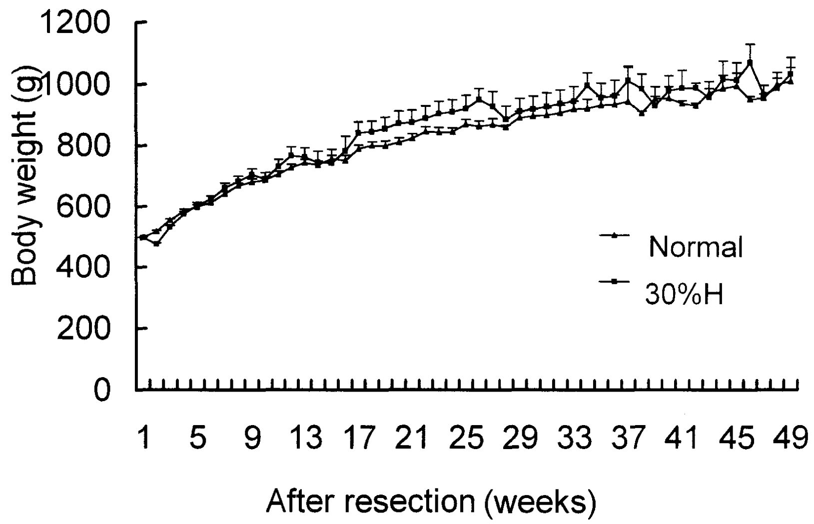

Fig. 1 Changes in body weight in normal and 30% hepatectomy (30%H) rats. All values are expressed as means ± SEM.

Table 1 Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein (TP), albumin (Alb), blood urea nitrogen (BUN), creatinine (Cr) and glucose (Glc) in 30% partially hepatectomized rats (30%H).

Serum	Weeks after operation	Normal (n=9)	30%H (n=7)
AST (IU/l)	12w	147.10 ± 13.69	139.00 ± 9.19
	24w	231.50 ± 65.72	162.00 ± 38.52
	48w	164.11 ± 24.33	151.73 ± 25.17
ALT (IU/l)	12w	60.20 ± 14.00	53.08 ± 12.21
	24w	156.60 ± 58.84	104.50 ± 50.10
	48w	126.40 ± 42.10	99.82 ± 37.80
TP (g/100ml)	12w	6.55 ± 0.04	6.43 ± 0.06
	24w	6.58 ± 0.06	6.64 ± 0.11
	48w	6.49 ± 0.07	6.52 ± 0.06
Alb (g/100ml)	12w	4.54 ± 0.05	4.37 ± 0.08
	24w	4.60 ± 0.07	4.57 ± 0.09
	48w	4.36 ± 0.09	4.27 ± 0.08
BUN (mg/100ml)	12w	14.61 ± 0.61	15.41 ± 0.32
	24w	14.03 ± 0.55	15.09 ± 0.38
	48w	14.98 ± 0.76	15.42 ± 0.71
Cr (mg/100ml)	12w	0.28 ± 0.01	0.28 ± 0.01
	24w	0.32 ± 0.02	0.33 ± 0.01
	48w	0.37 ± 0.02	0.40 ± 0.01
Glc (mg/100ml)	12w	156.80 ± 4.57	146.83 ± 4.56
	24w	172.30 ± 4.27	175.25 ± 4.47
	48w	173.78 ± 0.20	171.55 ± 0.17

Values are expressed as means ± SEM.
n=number of rats.

Discussion

There have been many reports on the effects of hepatectomy in short-term studies, but very few from long-term studies. Therefore, the long-term effects of hepatectomy were studied using the rat as the animal model. The serum proteins and lipids levels remained essentially unchanged for long periods. This indicates

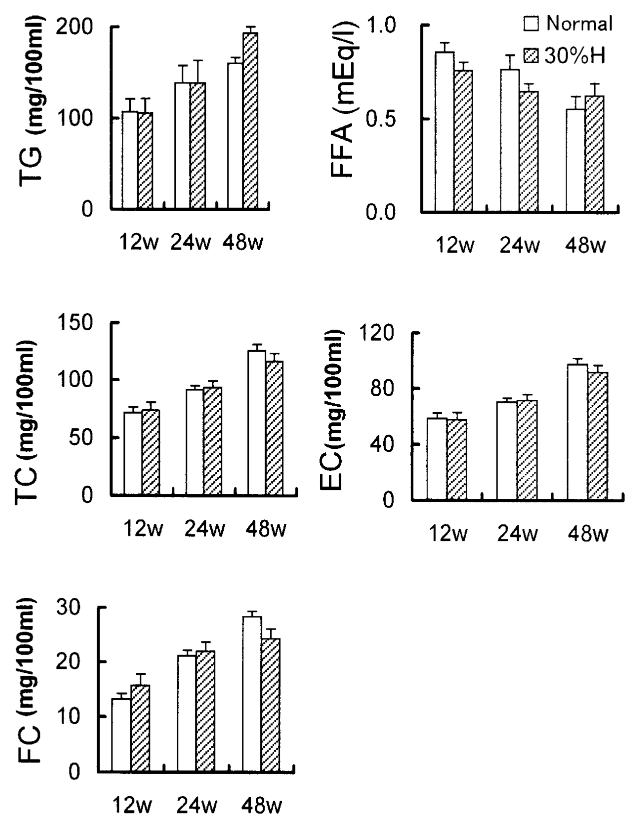

Fig. 2 Serum levels of triglycerides (TG), free fatty acids (FFA), total cholesterol (TC), esterified cholesterol (EC) and free cholesterol (FC) in 30% partial hepatectomized rats (30%H). Values are expressed as means ± SEM.

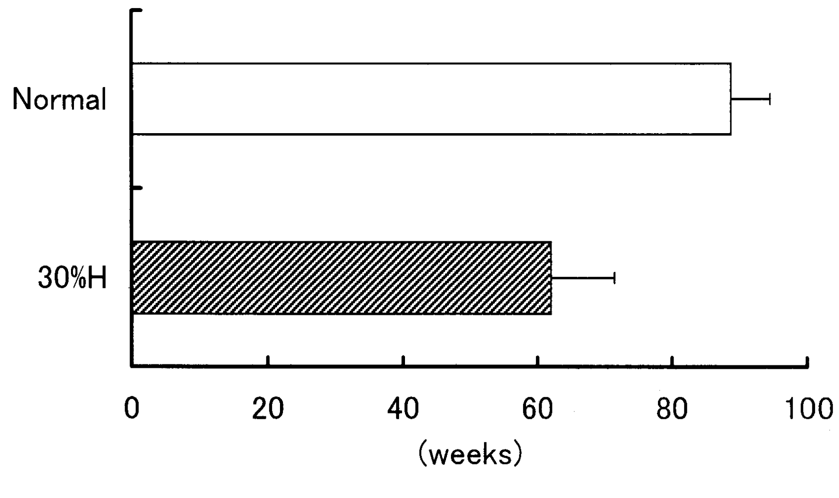

Fig. 3 Comparison of average longevity between 30% partial hepatectomy (30%H) group and normal group.

that by the end of 48 postoperative weeks, the majority of vital liver functions had returned to normal. But the serum triglyceride concentration increased in the 30% partially hepatectomized rats.

The liver plays an important role in the metabolism of the body. After partial hepatectomy in rats, the residual liver soon becomes infiltrated with fat, mainly triglycerides [21-25]. Bengmark et al. reported that rats subjected to partial hepatectomy rapidly develop a fatty liver [26-27]. This is one of the earliest and most striking changes found in the regeneration of the liver after partial hepatectomy. It is possible that an increased free fatty acid uptake by the liver is the most important factor in early steatosis [28].

The cause of this impairment could be a deficiency of the protein moiety, since observations by Walton et al. [29] and Furman et al. [30] indicate that the rate of synthesis of the protein moiety of lipoproteins is much lower than the rate of triglyceride synthesis. Therefore, the increased TG levels found in the present experiment may be related to lipid metabolism in the early phase after partial hepatectomy. In addition, since the average longevity of the 30%H group was lower than that of the normal groups, the effects of surgery should be reflected in the blood biochemical parameters. However, the increases in the levels of AST and ALT, indications of the extent of ischemic liver injury, were unremarkable in the hepatectomized rats. It appears that the hepatic parenchyma is able to maintain normal serum protein, albumin, glucose and cholesterol levels. For this reason, by the end of 48 postoperative weeks, the majority of the vital liver functions had returned to normal.

The reasons for differences in longevity between groups are not clear. But considering the results of this study, the surgical procedure did not appear to be a major factor. It is possible that serum triglycerides may play a role in longevity.

References

1. Makuuchi M, Kawasaki S, Noguchi T, Hashikura Y, Hidetoshi M, Hayashi K, Harada H, Kakazu T, Takayama T and Kawarasaki H (1993) Donor hepatectomy for living related partial liver transplantation. *Surgery*, **113**, 395–402.
2. Holness MJ, Schofield PS and Sugden MC (1989) Altered interactions between glycogenesis and lipid synthesis after liver resection: specific effects of liver regeneration, coupled with non-specific effects of surgery. *Clinical Science*, **76**, 317–322.
3. Gaub J and Iversen J (1984) Rat liver regeneration after 90% partial hepatectomy. *Hepatology*, **4**, 902–904.
4. Zieve L (1989) Regenerative enzyme activity of the liver after partial hepatectomy or toxic injury depressed by continuous NH4+ infusion. *Journal of Laboratory and Clinical Medicine*, **114**, 527–530.
5. Pack GT, Islami AH, Hubbard JC and Brasfield RD (1962) Regeneration of human liver after major hepatectomy. *Surgery*, **52**, 617–623.
6. Chen MF, Hwang TL and Hung CF (1991) Human liver regeneration after major hepatectomy: a study of liver volume by computed tomography. *Annals of Surgery*, **213**, 227–229.
7. Bucher NLR (1967) Experimental aspects of hepatic regeneration. *The New England Journal of Medicine*, **277**, 686–696.
8. Monaco AP, Hallgrimsson J and McDermott WV (1964) Multiple adenoma (hamartoma) of the liver treated by subtotal (90%) resection: morphological and functional studies of regeneration. *Annals of Surgery*, **159**, 513–519.
9. Schmucker DL (1998) Aging and the liver: an update. Journal of Gerontology: *Biological Sciences*, **53**A, B315–B320.
10. Stahlberg D, Angelin B and Einarsson K (1991) Age-related changes in the metabolism of cholesterol in rat liver microsomes. *Lipids*, **26**, 349–352.
11. Nagino M, Nimura Y and Hayakawa N (1993) Logistic regression and discriminant analysis of hepatic failure after liver resection for carcinoma of the biliary tract. *World Journal of Surgery*, **17**, 250–255.
12. Fortner JG and Lincer RM (1990) Hepatic resection in the elderly. *Annals of Surgery*, **211**, 141–145.
13. Chen MF, Hwang TL, Jeng LB, Jan YY and Wang CS (1991) Influence of age on results of resection of hepatocellular carcinoma. *European Journal of Surgery*, **157**, 591–593.
14. Nagasue N, Chang YC, Takemoto Y, Taniura H, Kohno H and Nakamura T (1993) Liver resection in the aged (seventy years or older) with hepatocellular carcinoma. *Surgery*, **113**, 148–154.

15. Mentha G, Huber O, Robert J, Klopfenstein C, Egeli R and Rohner A (1992) Elective hepatic resection in the elderly. *British Journal of Surgery*, **79**, 557–559.
16. Hoofnagle JH, Lombardero M, Zetterman RK, Lake J, Porayko M, Everhart J, Belle SH and Detre KM (1996) Donor age and outcome of liver transplantation. *Hepatology*, **24**, 89–96.
17. Bromley PN, Hilmi I, Tan KC, Williams R and Potter D (1994) Orthotopic liver transplantation in patients over 60 years old. *Transplantation*, **58**, 800–803.
18. Fong Y, Blumgart LH, Fortner JG and Brenhan MF (1995) Pancreatic or liver resection for malignancy is safe and effective for the elderly. *Annals of Surgery*, **222**, 426–437.
19. Rabes HM and Brandle H (1969) Synthesis of RNA, protein and DNA in the liver of normal and hypophysectomized rats after partial hepatectomy. *Cancer Research*, **29**, 817–822.
20. Higgins GM and Anderson RM (1931) Experimental pathology of the liver. *Arch Pathology*, **12**, 186–202.
21. Mahley RW, Hamilton RL and Lequire VS (1969) Characterization of lipoprotein particles isolated from the Golgi apparatus of rat liver. *Journal of Lipid Research*, **10**, 433–439.
22. Simek J, Husakova A, Erbenova Z and Kanta J (1968) The role of the adrenals in changes of liver triglycerides content after partial hepatectomy in rats of different ages. *Physiologia Bohemoslovaca*, **17**, 563–567.
23. Glende EA Jr and Morgan WS (1968) Alteration in liver lipid and lipid fatty acid composition after partial hepatectomy in the rat. *Experimental and Molecular Pathology*, **8**,190–200.
24. Fex G and Olivecrona T (1968) Secretion of triglyceride by the liver after partial hepatectomy. *Biochemica et Biophysica Acta*, **164**, 424–426.
25. Fex G and Olivecrona T (1968) The metabolism of (3H) oleic acid in the partially hepatectomized rat. *Biochimica et Biophysica Acta*, **152**, 237–243.
26. Almersjo O, Bengmark S, Engevik L, Kerstell J and Svanborg A (1968) Serum lipids after extensive liver resection in man. *Acta Hepato- Splenologica*, **15**, 1–12.
27. Tijburg LB, Nyathi CB, Meijer GW and Geelen MJ (1991) Biosynthesis and secretion of triacylglycerol in rat liver after partial hepatectomy. *Biochemical Journal*, **277**, 723–728.
28. S.Bengmark (1969) Liver steatosis and liver resection. *Digestion*, **2**, 304–311.
29. Walton KW, Scott PJ, Verier Jones J, Fletcher RF and Whitehead T (1963) Studies on low-density lipoprotein turnover in relation to atromid therapy. *Journal of Atherosclerosis Research*, **3**, 396–414.
30. Furman RH, Sanbar SS, Alaupovic P, Bradford RH and Howard P (1964) Studies of the metabolism of radioiodinated human serum alpha lipoprotein in normal and hyperlipidemic subjects. *Journal of Laboratory and Clinical Medicine*, **63**, 193–204.