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Effect of Weight Control on Hepatic Abnormalities in Obese Patients with Fatty Liver

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This study was aimed at finding out whether weight reduction alone can improve liver function in obese patients with fatty liver. We did a longitudinal, clinical intervention study on weight reduction by behavior modification, diet and exercise. The study subjects were 25 patients referred to an obesity clinic in whom obesity is the sole factor causing abnormal liver function and fatty liver. Patients were weighed about one year later. We compared the degree of improvement in hepatic function between Group I that showed weight reduction and Group II that showed no-weight reduction. Group I (13) showed dramatic improvement in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, nearly all down to within normal levels. AST showed statistically significant improvement from 74±36 IU/l to 25±7 IU/l. ALT also showed statistically significant improvement from 109±67 IU/l to 30±14 IU/l. Group II (12) showed higher AST and ALT levels on follow-up visit than initial visit. AST showed statistically significant elevation from 43±11 IU/l to 59±23 IU/l. ALT also showed statistically significant elevation from 64±21 IU/l to 97±33 IU/l. If we can rule the other causes of hepatic abnormalities in obese patients with fatty liver, we suggest these patients would benefit by weight reduction.

Key Words : *Hepatic abnormality, Fatty liver, Weight control*

INTRODUCTION

Abnormal liver function tests are often found in obese patients with fatty liver (Alder and Shaffner, 1979; Nomura et al., 1980; Anderson and Gluud, 1984). This may cause some distress and confusion to patients as to whether medical therapeutic intervention is necessary for such conditions.

Fatty liver related to obesity was first described a long time ago. Beginning just before World War II, a spectrum of liver diseases from fatty liver to cirrhosis was found in obese patients, and "fatty liver hepatitis" identical to alcoholic hepatitis was recognized (Thaler, 1975). As testing has become more widespread and the standard of living higher all over the world, liver disease from overnutrition and the abnormal nutrient metabolism related to it has become increasingly frequent. The number of obese persons with abnormal liver structure and function must be relatively large, although precise data about prevalence in any

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population are lacking. In large biopsy series, frequency rates of fatty liver have ranged from 60 % to 90 % among obese persons (Kern et al., 1973 ; Nasrallah et al., 1981).

The finding of hepatomegaly in an obese person has long been attributed to fat. However, only after the widespread utilization of screening and biopsy procedures beginning around 1950 (Zelman, 1952) was it realized that these fatty livers may not function normally.

Fatty liver may present as diffuse, smooth hepatomegaly defined as fat, largely triglyceride, exceeding 5 % of liver weight. Fatty liver could thus be due to increased delivery of fatty acids to the liver, decreased oxidation of fatty acids or a defect in the removal of triglyceride as very low density lipoproteins (Sherlock, 1989).

Liver biopsy is the best method for diagnosing fatty liver. But ultrasonography is commonly used to diagnose fatty liver, and ultrasound is a sensitive and reasonably accurate diagnostic tool in assessing fatty infiltration of the liver (Scatarige et al., 1984). It has been reported that weight reduction by dietary therapy alone may improve liver function and decrease fatty infiltration of the liver (Berkowitz, 1964 ; Moran et al., 1983 ; Enksson et al., 1986 ;).

In this study, we tried to compare the degree of improvement in hepatic function between the weight reduction group and the non-weight reduction group of obese patients with fatty liver.

MATERIALS AND METHODS

Subjects

All obese patients referred to the obesity clinic with fatty liver who showed abnormal liver function from Sep. 1993 through Jun. 1994 were included. The patients were diagnosed as have fatty liver by ultrasonography. Although liver biopsy is essential for the diagnosis of fatty liver disease, it is an invasive method and is not commonly used in the outpatient clinic. Since the overall accuracy of ultrasonography in detecting fatty infiltration of the liver is 85 percent, with 100 percent sensitivity and 56 percent specificity (Scatarige et al., 1984), we diagnosed fatty liver by ultrasound and several clinical findings.

Subjects were screened to exclude those with any other possible factors that might affect liver function other than obesity. Thus a selection of patients in whom obesity is the sole factor causing abnormal liver function and fatty liver was made. We conducted thorough medical histories including alcohol, medication and other metabolic diseases, and physical examinations. All subjects underwent tests for viral hepatitis markers including HBsAg, anti-HBs and anti-HCV to exclude other factors that could result in abnormal liver function.

The criteria required for entrance into this study were (1) obese patients whose BMI exceeded 25 kg/m^2 (2) diagnosis of fatty liver by ultrasonography by experienced radiologists (3) abnormal liver function, verified by elevated aspartate aminotransferase (AST >40 IU/l) or alanine aminotransferase (ALT>40 IU/l) (4) negative viral hepatitis markers (5) normal routine blood screen results and renal function.

The criteria for exclusion were (1) any viral hepatitis of hepatitis A, B or C (2) habitual alcohol drinking (3) history of taking any medications that affect liver function (4) transfusion history (5) metabolic diseases such as diabetes mellitus (6) normal liver function even though fatty liver was diagnosed by ultrasonography.

Methods of study

There were 25 patients (19 men and 6 women) in whom all of above the criteria were satisfied. The patients were educated for weight reduction including individualized behavior modification, diet and exercise by a physician, dietitian and exercise physiologist.

Behavioral modifications was focused on changing life styles using stimulus control, reinforcement and cognitive change. Diet therapy of low calorie diet (25-30 calories X ideal body weight[kg] per day) was done by individual interview after diet survey, but severely imbalanced diets were avoided. Exercise therapy was given as low intensity, low impact aerobic exercise on an individualized basis after fitness tests.

We made no alterations in medical therapy from the time of the initial visit to the follow-up visit. All patients were prohibited from drinking alcohol and taking any other medications. The patients were followed up for about one year on the average. After one year, the body weights of patients were rechecked on the same standard balance-beam scale and liver function tests were redone including aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and total bilirubin.

Table 1. Basic characteristics of all study subjects (n=25)

Variables	Group I (Mean ± S.D.)	Group II (Mean ± S.D.)	Total (Mean ± S.D.)
Age(years)	38.1 ± 16.1	37.9 ± 7.7	38.0 ± 12.5
Body Weight(kg)	83.5 ± 15.4	73.7 ± 7.9	78.6 ± 11.6
BMI(kg/m^2)[1]	31.1 ± 3.7	25.7 ± 2.2	28.5 ± 4.0
AST(IU/l)[2]	74 ± 36	43 ± 11	59 ± 31
ALT(IU/l)[3]	109 ± 67	64 ± 21	87 ± 55
Protein(g/dl)	7.7 ± 0.4	7.7 ± 0.4	7.7 ± 0.4
Albumin(g/dl)	4.8 ± 0.3	4.9 ± 0.3	4.9 ± 0.3
Total Cholesterol(mg/dl)	203 ± 36	211 ± 38	207 ± 36
Total bilirubin(mg/dl)	0.7 ± 0.3	0.7 ± 0.2	0.7 ± 0.3

1) Body mass index, 2) Aspartate aminotransferase, 3) Alanine aminotransferase

Statistical analysis

The Wilcoxon-signed rank test was used for comparison of data between the initial and the follow up visits. The Wilcoxon-rank sum test was also applied for comparison of data between the weight reduction group and the non-weight reduction group. The Spearman correlation coefficient was applied to compare the changes of AST or ALT between the changes of body weight or BMI. The statistical significance level used in this study was $P<0.01$.

RESULTS

There were 25 patients (19 men, 6 women) included in this study. Ages ranged from 13 to 61 years with a mean of 38.0±12.5 years. Body weights ranged from 57.7 to 118.1 kg with a mean of 78.6± 11.6 kg. Mean body mass index was 28.5±4.0 kg/m^2. Mean aspartate aminotransferase value was 59± 31 IU/l (Reference value : below 40 IU/l). Mean alanine aminotransferase value was 87±55 IU/l (Reference value : below 40 IU/l). Mean protein level was 7.7±0.4 g/dl, albumin 4.9±0.3 g/dl, total cholesterol 207±36 mg/dl, and total bilirubin 0.7±0.3 mg/dl.

After one year, 13 patients showed weight reduction (Group I) and 12 patients showed no weight reduction (Group II). Mean age of Group I was 38.1± 16.1 years. Mean body weights was 83.5±15.4 kg, body mass index 31.1±3.7 kg/m^2, AST 74±36 IU/l, ALT 109±67 IU/l, protein 7.7±0.4 g/dl, albumin 4.8 ±0.3 g/dl, total cholesterol 203±36 mg/dl, and total bilirubin 0.7±0.3 mg/dl. Mean age of Group II was 37.9±7.7 years. Mean body weights was 73.7±7.9 kg, body mass index 25.7± kg/m^2, AST 43±11 IU/l, ALT 64±21 IU/l, protein 7.7±0.4 g/dl, albumin 4.9 ±0.3 g/dl, total cholesterol 211±38 mg/dl, and total bilirubin 0.7±0.2 mg/dl (Table 1).

Fig. 1 shows the body weight changes on the initial and the final visits of each patient in the weight reduction group. The range of weight loss in Group I was between 2 to 20 %. Fig. 2 shows the changes of aspartate aminotransferase values on the initial and the final visits of each patient in Group I. It shows dramatic improvement, nearly all down to within normal ranges. Fig. 3 shows the changes of alanine aminotransferase values on the initial and the final visits of each patient in Group I. It also shows marked improvement.

Table 2 shows the changes in measurements of mean body weight, body mass index, aspartate aminotransferase and alanine aminotransferase levels on the initial and the final visits in those patients who

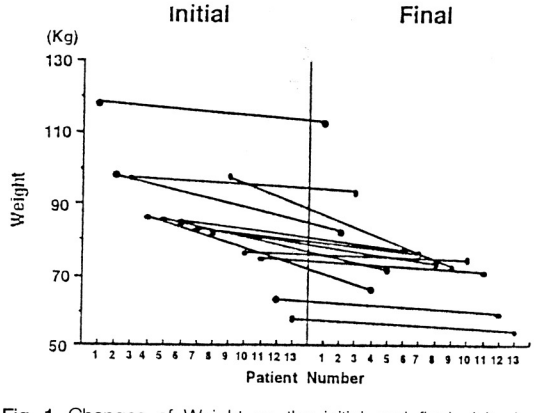

Fig. 1. Changes of Weight on the initial and final visits in Group I.

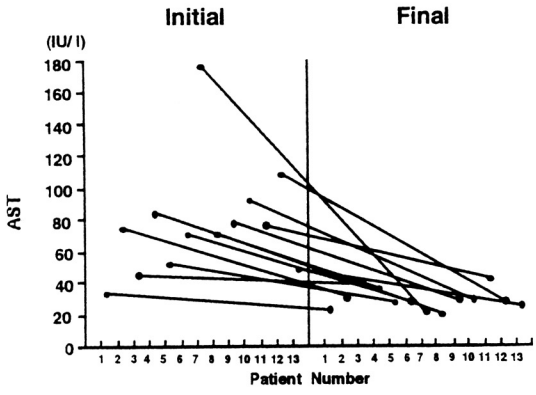

Fig. 2. Changes of AST on the initial and final visits in Group I.

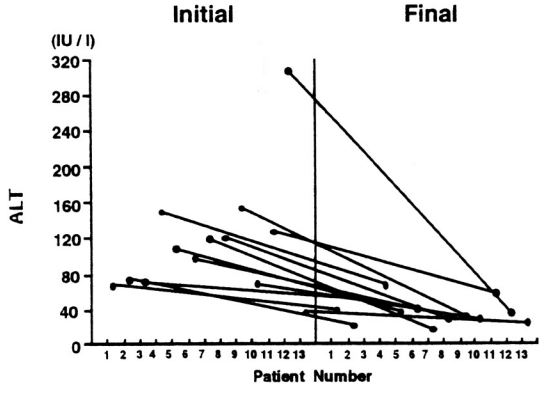

Fig. 3. Changes of ALT on the initial and final visits in Group I.

Table 2. Changes of variables on the initial and final visits in weight reduction group (n=13).

Variables	Initial visit (mean ± S.D.)	Final visit (mean ± S.D.)	p value
Weight(kg)	83.5 ± 15.4	75.4 ± 14.8	0.0002*
BMI(kg/m^2)[1)]	31.1 ± 3.7	28.1 ± 3.4	0.0002*
AST(IU/l)[2)]	74 ± 36	25 ± 7	0.0002*
ALT(IU/l)[3)]	109 ± 67	30 ± 14	0.0002*
TC(mg/dl)[4)]	203 ± 36	198 ± 26	0.0391

*P<0.01

1) Body mass index, 2) Aspartate aminotransferase

3) Alanine aminotransferase, 4) Total cholesterol

showed weight reduction. Body weight showed a statistically significant decrease, from 83.5±15.4 kg to 75.4±14.8 kg ($p<0.0002$). Body mass index also showed a statistically significant decrease, from 31.1± 3.7 kg/m^2 to 28.1±3.4 kg/m^2 ($p<0.0002$). Aspartate aminotransferase levels showed a statistically significant improvement from 74±36 IU/l to 25±7 IU/l ($p<0.0002$). Alanine aminotransferase levels also showed a statistically significant improvement from 109±67 IU/l to 30±14 IU/l ($p<0.0002$). Total cholesterol levels showed no statistically significant change ($p<0.0391$).

Fig. 4 shows the body weight changes on the initial and the final visits of each patient in the non-weight reduction group. It appears that in nearly all patients, body weights were the same or increased on the follow-up visits. Fig. 5 shows the changes of aspartate aminotransferase values on the initial and the final visits of each patient in the non-weight reduction group. It shows that all patients had higher aspartate aminotransferase values on the follow-up visits. Fig. 6 shows the changes of alanine aminotransferase values on the initial and the final visits of each patient

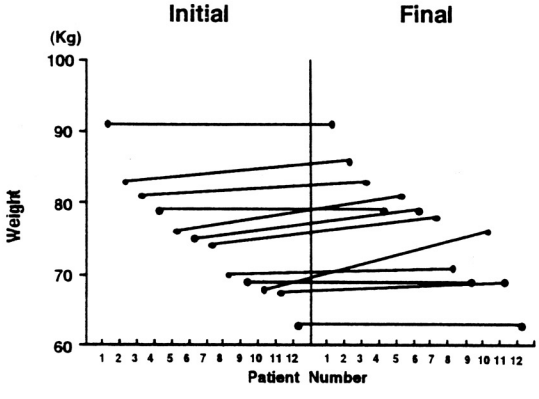

Fig. 4. Changes of Weight on the initial and final visits in Group II.

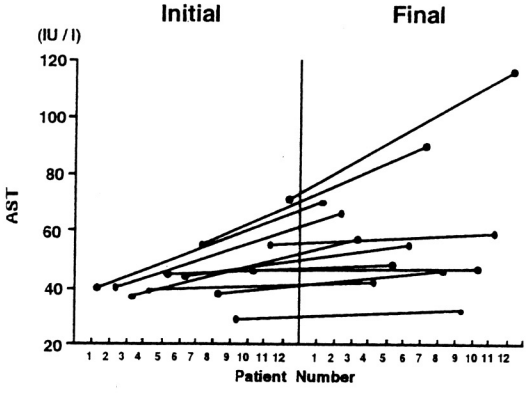

Fig. 5. Changes of AST on the initial and final visits in Group II.

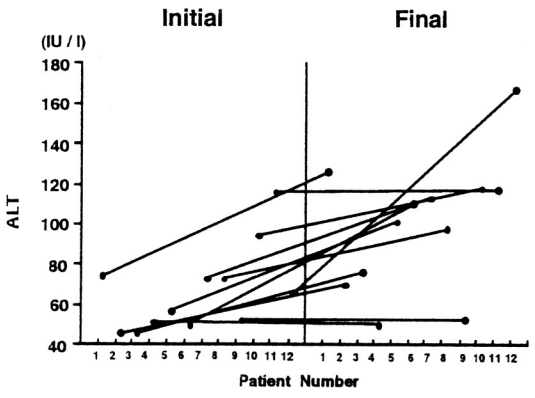

Fig. 6. Changes of ALT on the initial and final visits in Group II.

in the non-weight reduction group. It also shows that all patients had higher alanine aminotransferase values on the follow-up visits.

Table 3 shows the changes in measurements of mean body weight, body mass index, aspartate aminotransferase and alanine aminotransferase levels on the initial visits and the final visits in those patients who did not show weight reduction. Body weight showed a statistically significant increase from 73.7±7.9 kg to 76.1±8.0 kg ($p<0.0078$). Body mass index also showed a statistically significant increase from 25.7±2.2 kg/m^2 to 26.6±2.2 kg/m^2 ($p<0.0078$). Aspartate aminotransferase levels showed a statistically significant elevation from 43±11 IU/l to 59±23 IU/l ($p<0.0005$). Alanine aminotransferase levels also showed a statistically significant elevation from 64±21 IU/l to 97±33 IU/l ($p<0.0020$). Total cholesterol levels showed no statistically significant change ($p<0.2881$).

Table 4 shows the difference of each variable between the initial and the final visits in two groups. There were significant differences of changes of body weight, body mass index, aspartate aminotransferase and alanine aminotransferase levels between the weight reduction group and the non-weight reduction group.

Table 5 shows correlation coefficients compairing the changes of AST or ALT with the changes of body weight or BMI. The degree of liver function improvement or deterioration did not correlate with the degree of weight reduction or gain.

DISCUSSION

Fatty liver disease has become one of the most common problems in recent years, as a result of more frequent use of ultrasonography or computer tomography even in health screening. The incidence of fatty liver in obese patients is known to range from 60 % to 90 % in large biopsy series (Kern et al., 1973

Table 3. Changes of variables on the initial and final visits in non-weight reduction group (n=12).

Variables	Initial visit (mean ± S.D.)	Final visit (Mean ± S.D.)	p value
Weight(kg)	73.7 ± 7.9	76.1 ± 8.0	0.0078*
BMI(kg/m^2)[1]	25.7 ± 2.2	26.6 ± 2.2	0.0078*
AST(IU/l)[2]	43 ± 11	59 ± 23	0.0005*
ALT(IU/l)[3]	64 ± 21	97 ± 33	0.0020*
TC(mg/dl)[4]	211 ± 38	218 ± 38	0.2881

*P<0.01

1) Body mass index, 2) Aspartate aminotransferase
3) Alanine aminotransferase, 4) Total cholesterol

Table 4. Comparison of changes of variables between group I (weight reduction group) and group II (non-weight reduction group).

Variables	Group I	Group II	p value
△ Weight(kg)	-8.0 ± 5.4	2.4 ± 2.5	0.0001*
△ BMI(kg/m^2)[1]	-3.0 ± 2.0	0.8 ± 0.9	0.0001*
△ AST(IU/l)[2]	-49 ± 38	16 ± 25	0.0001*
△ ALT(IU/l)[3]	-79 ± 67	33 ± 2	0.0001*

*P<0.01

△ : difference of variables between initial and final visits

1) Body mass index, 2) Aspartate aminotransferase, 3) Alanine aminotransferase

Table 5. Correlation coefficients comparing the changes of AST or ALT with the changes of body weight or BMI.

	Group I		Group II	
	△ Weight r(p value)	△ BMI[1] r(p value)	△ Weight r(p value)	△ BMI[1] r(p value)
△ AST[2]	0.08575 (0.7806)	0.19807 (0.5165)	0.23700 (0.4583)	0.25091 (0.4315)
△ ALT[3]	0.36465 (0.2206)	0.42308 (0.1497)	0.14492 (0.6532)	0.15537 (0.6297)

△ : difference of variables between the initial and final visits

1) Body mass index, 2) Aspartate aminotransferase, 3) Alanine aminotransferase

; Nasrallah et al., 1981). The biopsy abnormalities of fatty liver were lobular hepatitis, fibrosis, portal hepatitis and steatosis. Adult overweight patients have been found to develop liver damage of variable severity after long-standing steatosis. With appropriate weight reduction measures, the amount of fat in the liver cells decreases and the cells resume a normal appearance ; if there has been a considerable degree of inflammation or septal condensation, some changes may remain even after all fat has disappeared from the liver. In several subjects, repeated liver biopsy has shown fatty infiltration to be superseded by the development of cirrhosis with connective tissue septa and other appurtenances of chronic hepatic fibrosis. This is unfortunate because this evidence suggests that the condition can progress to cirrhosis (Alder and Shaffner, 1979).

Fat deposition in the liver in patients with fatty liver related to overweight is not always uniform. Since hepatic fat content is based on the dynamics of fat deposition and removal, the rate of reversal is expected to vary from patient to patient and to depend somewhat on the cause (Nomura et al., 1987). Excess fat deposition is primarily composed of triglyceride and varies from mild to extensive (Leevy, 1962). One report suggested that insulin excess in the liver may be an important factor in producing the changes in fatty liver hepatitis (Wanless et al., 1989).

The abnormal results found in routine laboratory testing include mild elevation of the activities of alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase. In a study of the histologic findings of the liver in HBsAg negative patients with chronic aminotransferase elevation in Korea, fatty liver disease was found in 64.7 % (Yang et al., 1992). The results of the liver fuction test however, correlate poorly with biopsy findings (Galambos and Wills, 1978).

Although values of alanine aminotransferase are rarely more than 2 or 3 times the upper limit of the normal range (Berk, 1985), alanine aminotransferase predominance rather than aspartate aminotransferase has been shown in other studies (Alder and Shaffner, 1979 ; Clain and Lefkowitch, 1987). Alanine aminotransferase concentration was used as a variable in the scoring system applied for prediction of the extent of hepatic damage in obese subjects (Charnzzi et al., 1987). In our study, the elevation of alanine aminotransferase on the initial visit and it's change was more prominent than that of aspartate aminotransferase. Overweight men were reported to have a higher incidence of hepatic dysfunction and an increased degree of hepatic involvement compared to wemen (Manes et al., 1973).

The duration of obesity was reported to correlate with the extent of damage found in liver biopsy specimens, with no comparable correlation with abnormalities in enzyme activities (Kinugasa et al., 1984).

Liver biopsy is required for the diagnosis of fatty liver, but it is very inconvenient and invasive. On the other hand, fatty liver can be easily diagnosed by ultrasonography. Sonographically, hepatic fatty infiltration appears as areas of bright echogenicity in contrast to the less echogenic normal liver parenchyme (Gosink et al., 1979). The sensitivity of detection, by recognition of a bright liver echo pattern, is related to the degree of infiltration and increases to 90 % in moderate and severe cases. The false positive rate is very low, making the ultrasound finding of a bright liver highly significant (Foster et al., 1980). So we included patients with fatty liver diagnosed by ultrasonography.

Abnormal liver function test results due to fatty liver may cause some distress and confusion to patients as to whether medical therapeutic intervention is necessary or how it is to be managed, in such conditions. Although the degree of liver function improvement or deterioration did not correlate with the degree of weight reduction or gain, there were significant differences in liver function changes with weight changes between the weight reduction group and the non-weight reduction group. Liver function in obese persons was found to improve with weight loss as in this study.

Whether the fat or the inflammation in the liver decreases proportionately to weight reduction has not been studied, but it seems unlikely. Reduction in the mean liver volume after diet therapy has been reported, indicating that the volume reduction was mainly due to disappearance of fat. However, factors other than fat deposition, such as protein or water retention, may contribute to hepatomegaly in patients with fatty liver associated with overweight (Nomura et al., 1987). Fatty infiltration of the liver is reversible and can be monitored by repeated CT examinations (Moran et al., 1983). The reversal of fatty infiltration during caloric restriction in obese patients took longer than that reported in patients with alcohol-induced fatty liver (Nomura et al., 1987).

In overweight adults, a weight reduction of above 10 % can correct abnormal liver function results (Palmer and Shaffner, 1990), but in our study even a 2 % weight reduction improved liver function. The degree of obesity before and after weight loss, age, gender, associated conditions, manner of presentation, physical findings, or degree or type of elevation of hepatic chemistries do not correlate with these improvements (Palmer and Shaffner, 1990).

In our study the degree of improvement or deterioration of liver function did not correlate with the degree of weight reduction or gain. The degree of change is expected to vary from patient to patient. The weight reduction group had higher values of initial body weight, body mass index, aspartate aminotransferase and alanine aminotransferase than the non-weight reduction group. The non-weight reduction group had a low obesity index and mild abnormalities of liver function on the initial visit, so we think that they would tend to have less motivation and compliance for weight reduction.

Although this study does not contain a large number of cases, it would be reasonable to draw the following conclusions from the obtained results. Even though, the degree of hepatic improvement or deterioration did not correlate with the degree of weight reduction or increment, there were significant differences in hepatic function changes with weight changes between the weight reduction group and the non-weight reduction group. Therefore, if we can rule out other causes of hepatic abnormalities in obese patients with fatty liver, we can assume that liver function of these patients would benefit by weight reduction.

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