

CLINICAL INVESTIGATION ON GLUCOSE TOLERANCE IN LIVER CIRRHOSIS

KATSUMOTO KATO, SABURO KIKUCHI, MADOKA ITO, SHIGERU HIDANO,
TAKAHIKO OYA, HIROSHI BANNO, AKIO TOMURA,
TOMITSUGU KOYAMA, TAKEHIKO KOMATSU, TAKESHI TAKEI,
KOICHI TOMIMURA, AND MASAHIRO YAMAUCHI

*2nd Department of Internal Medicine, Nagoya University School of Medicine
(Director: Associate Prof. Saburo Kikuchi)*

ABSTRACT

Forty-six patients with liver cirrhosis were classified into three groups according to glucose tolerance test and the presence or absence of diabetic state. The results of xylitol tolerance test, galactose tolerance test, BSP retention, ICG disappearance rate and other routine liver function tests were compared between these three groups.

The results show that liver cirrhosis in patients with overt diabetes was less severe than that in non-diabetics. It is conceivable, therefore, that the glucose intolerance in most of the cirrhotic patients with overt diabetes is not due to the so called hepatogenous diabetes, but to essential diabetes with concomitant cirrhosis.

Intravenous xylitol tolerance test may be available for the differential diagnosis of hepatogenous diabetes from essential diabetes with concomitant cirrhosis, since the change in serum glucose level after the administration of xylitol was characteristic in each group. Further studies must be done to substantiate this possibility.

INTRODUCTION

It has been reported by many authors¹⁾²⁾³⁾ that most patients with liver cirrhosis show abnormal carbohydrate tolerance. The mechanism of this carbohydrate intolerance is, however, far from clear, and many speculations as to its mechanism have been made by various authors. It is hard to differentiate the diabetic state resulting from liver cirrhosis itself from the essential diabetes with concomitant cirrhosis.

In our clinical investigation⁴⁾⁵⁾, using xylitol and galactose tolerance tests, it was demonstrated that xylitol and galactose metabolism are disturbed in hepatic disorders and that the change of serum glucose level after the administration of xylitol and galactose has a close relation to glucose intolerance.

加藤活大, 菊地三郎, 伊藤 円, 肥田野 滋, 大屋敬彦, 坂野 紘, 戸村明夫, 小山富嗣,
小松健彦, 武井 毅, 富村公一, 山内雅弘

Received for publication September 20, 1972.

The present study was undertaken to investigate the abnormalities of monosaccharide metabolism in liver cirrhosis and the possibility to differentiate diabetic state due to liver cirrhosis from essential diabetes.

MATERIALS

Forty-six patients with liver cirrhosis were classified into three groups, A, B and C as follows;

- A: patients showing normal or borderline type in 50 g glucose tolerance test (GTT)
- B: patients showing diabetic type in GTT, without fasting hyperglycemia (higher than 120 mg/dl) and glucosuria 2 hours after meals
- C: patients showing diabetic type in GTT with fasting hyperglycemia and glucosuria 2 hours after meals

Glucose tolerance test was evaluated according to the report⁶⁾ of the committee (Japan) on the diagnostic criteria of the oral glucose tolerance test for diabetes mellitus. Forty of the forty-six patients were males and six were females. Their average age was fifty years (range 26-69). Liver cirrhosis was histologically confirmed by needle liver biopsy under laparoscopy in thirty-eight patients and eight patients were diagnosed clinically without histology.

Only five of the forty-six patients showed normal type in GTT and sixteen patients showed borderline type. Twenty-one cases of the forty-six patients with cirrhosis were classed as group A, ten as group B and fifteen as group C. Table 1 shows that diabetic type in glucose tolerance test was more common in men than in women and that there were no significant differences in age among each group. Only one of fifteen cases (6.7%) had ascites in group C, while five of twenty-one cases (23.8%) had ascites in group A and six of ten cases (60%) had ascites in group B.

TABLE 1. Sex Ratio, Age-Structure, and Proportion of Ascites or the Treatment with Diabetogenic Drugs in Each Group

	Whole group	A	B	C
M : F	40 : 6	16 : 5	9 : 1	15 : 0
Mean age (range)	50 (26~69)	48 (26~68)	51 (42~62)	52 (36~69)
No. with ascites	12	5	6	1
No. receiving glucocorticoids	2	2	0	0
No. receiving thiazide etc.	8	4	3	1
Total	46	21	10	15

Although two of the forty-six patients had been treated with glucocorticoid before this classification, these two patients were both classed as group A. In eight of the forty-six patients, oral diuretics of the thiazide or furosemide had been used. Four of the eight were classed as group A, three as group B and only one as group C.

METHODS

After an overnight fast, the following tolerance tests and various liver function tests including ICG or BSP test were performed.

(1) Oral xylitol tolerance test (O-XTT); 30 g of xylitol in warm water were given orally. Blood was then drawn every 30 min. for two hours.

(2) Intravenous xylitol tolerance test (IV-XTT): 20 ml of 50% xylitol solution were given intravenously. Blood was then drawn every 10 min. for 40 minutes.

(3) Galactose tolerance test (GaTT); 30 g of galactose in 300 ml of warm water were given orally. Blood was drawn every 30 min. for two hours.

Each serum was analyzed by gas-liquid chromatography for xylitol, galactose and glucose according to the method of Sweely⁷. The results of these tolerance tests and other liver function tests in group A, B and C were compared with each other, or compared with the results in patients with chronic hepatitis, diabetics and healthy controls.

RESULTS

O-XTT

Fig. 1-1 shows the means of serum xylitol concentration at each interval. In the healthy control group the serum xylitol level increased slightly (3.5 mg/dl) at 30 min. after the administration and then decreased gradually. The level was not zero even at 120 min. In the cirrhotic groups, as well as in chronic hepatitis, it rose to remarkably high levels at 30 min. and 60 min. The xylitol concentration course in diabetics was between that in healthy controls and that in liver disease patients. In order to estimate the xylitol concentration course with one figure, the sum of serum xylitol levels of each 30 min. for 2 hours was denoted as ΣX_{yli} . As shown in Fig. 2-1 and Table 2, ΣX_{yli} was quite high in the liver disease group compared with that in the diabetics and healthy controls. It was higher in group B than in group A and C, but the differences between each group were not statistically significant.

Fig. 1-2 shows the change of serum glucose level after the oral administration of xylitol. While there was almost no change in serum glucose level in groups A and B as well as in healthy control, there was a striking increase in diabetes and a moderate increase in group C. As shown in Fig. 2-2, $\Sigma \Delta Glu$. (the sum of the differences between fasting serum glucose level and glucose

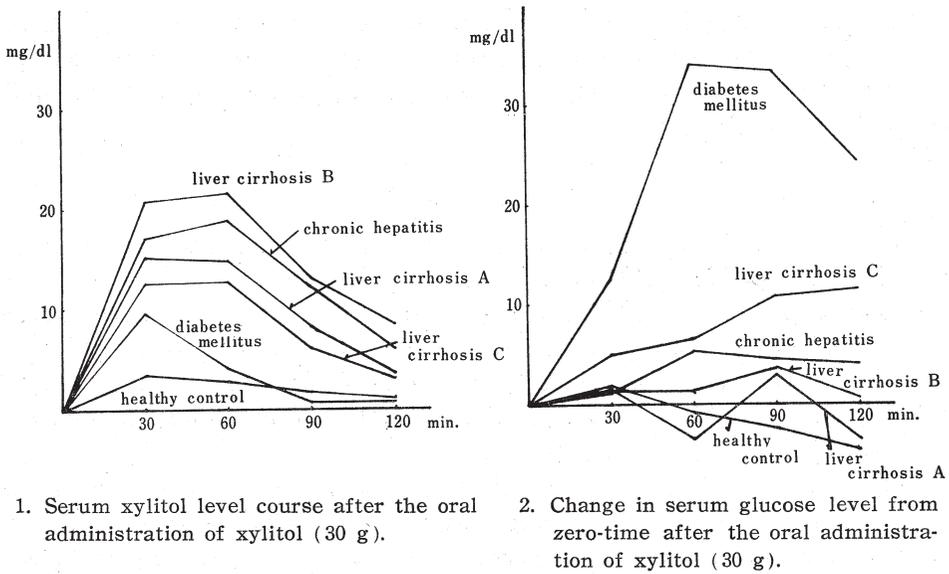


FIG. 1. Oral xylitol tolerance test (O-XTT).

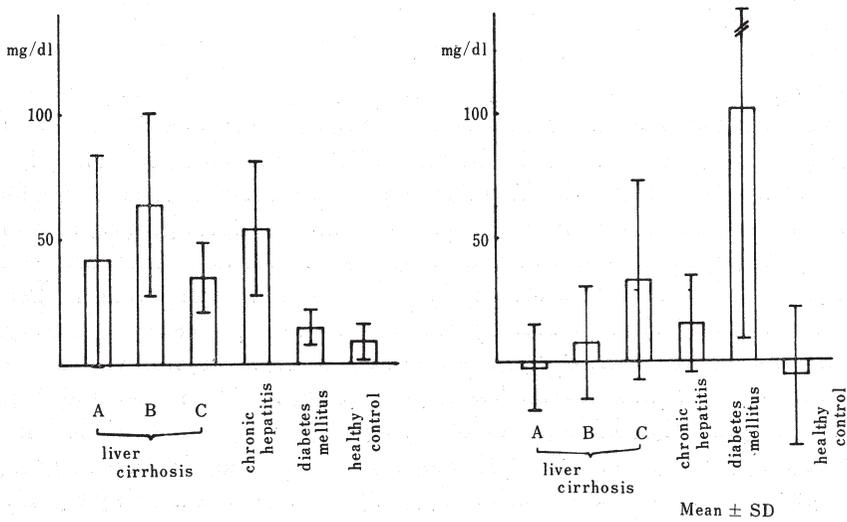


FIG. 2. ΣX_{yli} and $\Sigma \Delta Glu$. (O-XTT).

TABLE 2. Results of the Tolerance Tests Using Xylitol, Galactose, BSP and ICG in Each Group

		O-XTT		IV-XTT		GaTT		BSP ₄₅	ICG _K
		Σ Xyli.	Σ_{Δ} Glu.	T 1/2	Σ_{Δ} Glu.	Σ Gala.	Σ_{Δ} Glu.		
A (21)	Mean SD	41.6 42.0 (15)*	- 2.5 17.5	17.7 6.3 (15)	-19.6 18.2	415.8 157.5 (12)	29.3 47.9	22.9 10.9(15)	0.091 0.048(17)
B (10)	Mean SD	64.1 36.4 (6)	7.5 22.9	23.9 6.4 (6)	1.9 21.6	230.7 96.5 (0)	51.5 14.4	23.0 11.2 (7)	0.111 0.063(8)
C (15)	Mean SD	34.5 14.2 (5)	32.7 40.1	14.8 3.5 (9)	46.3 24.3	212.4 128.8 (8)	149.4 61.5	15.4 7.2 (9)	0.114 0.050(8)
chronic hepatitis	Mean SD	54.2 26.9 (6)	14.9 19.5	13.1 2.9 (9)	-16.4 50.1	184.9 107.4 (26)	42.7 33.3		
diabetes mellitus	Mean SD	14.5 7.1 (11)	101.9 92.7	11.2 1.7 (7)	99.7 21.7	83.1 66.4 (31)	131.5 128.8		
healthy controls	Mean SD	9.1 7.5 (10)	- 5.9 27.5	11.1 1.6 (8)	15.3 20.3	23.1 24.0 (17)	- 1.8 44.1		

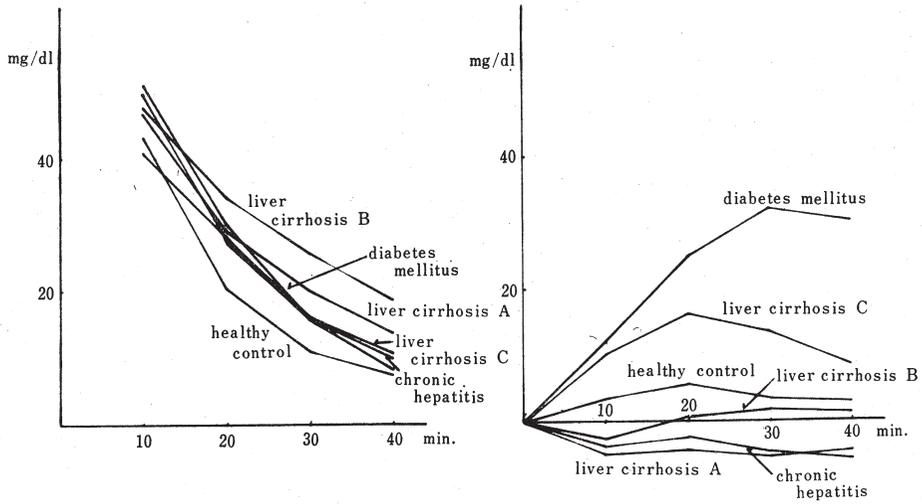
*: number of cases

level at each interval) was significantly higher in group C than in healthy controls, and Σ_{Δ} Glu. in groups A and B was also higher than in healthy controls, but the difference was not significant. There were no significant differences in Σ_{Δ} Glu. among the cirrhotic groups.

IV-XTT

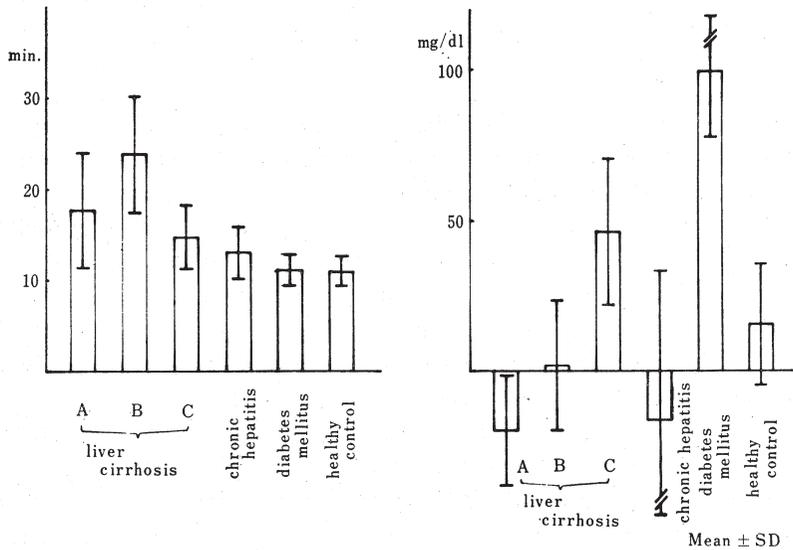
As shown in Fig. 3-1, serum xylitol level decreased, showing exponential curve in every group. In liver disease groups, the decrease in serum xylitol level was remarkably delayed compared with that in healthy controls. Since the logarithm of the serum xylitol concentration decreased linearly with time in almost all cases, we estimated T 1/2 (time in minutes required for 50% decrease in serum xylitol level) as a suitable in IV-XTT. Fig. 4-1 shows that T 1/2 was significantly longer in cirrhotic groups than in diabetics or healthy controls and it was the longest in group B. There was a significant difference in T 1/2 between groups B and C.

Fig. 3-2 shows the change of serum glucose level after the intravenous administration of xylitol. The serum glucose level increased remarkably in diabetes and moderately in group C, while it remained almost constant in group B and decreased slightly in group A. Σ_{Δ} Glu. in diabetes was significantly higher than in any other group. Characteristically, Σ_{Δ} Glu. was positive in group C, negative in group A and almost zero in group B. There were significant differences in Σ_{Δ} Glu. among the cirrhotic groups. (Fig. 4-2)



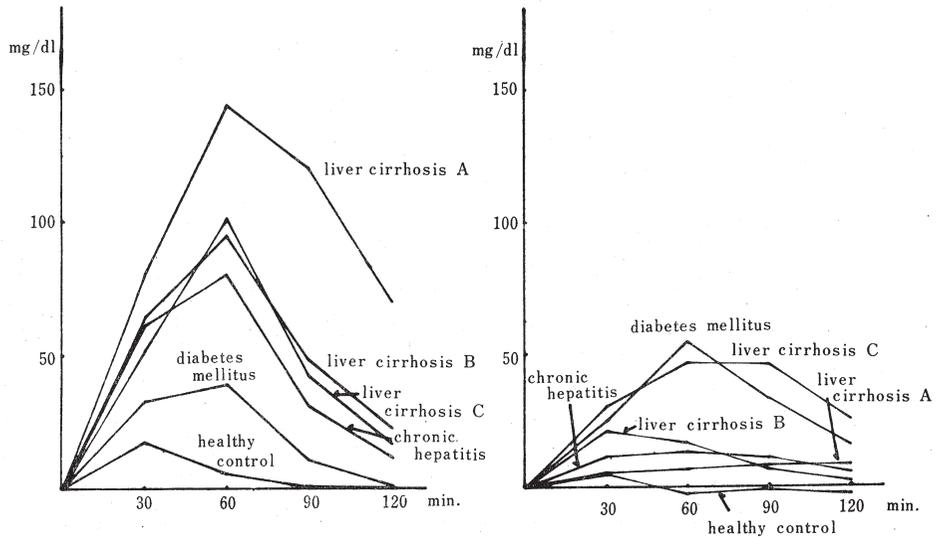
1. Serum xylitol level course after the intravenous administration of xylitol (10 g)
2. Change in serum glucose level from zero-time after the intravenous administration of xylitol (10 g)

FIG. 3. Intravenous xylitol tolerance test (IV-XTT).



1. Time in minutes required for decrease of serum xylitol level to half. (T1/2)
2. Sum of increases of each 10 minutes in serum glucose level from zero time for 40 minutes. (ΣΔGlu)

FIG. 4. T1/2 and ΣΔGlu. (IV-XTT).



1. Serum galactose level course after the oral administration of galactose (30 g)
2. Change in serum glucose level from zero-time after the oral administration of galactose (30 g)

FIG. 5. Galactose tolerance test (GaTT).

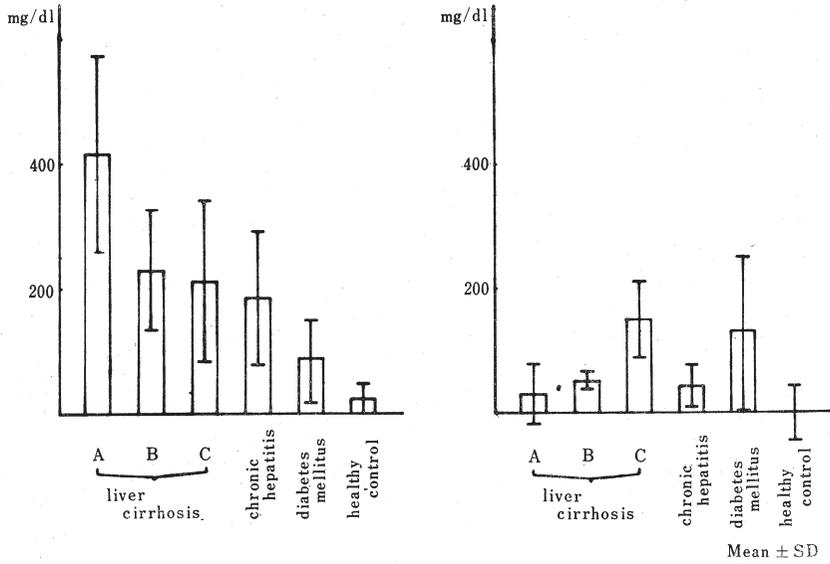
GaTT

Fig. 5-1 shows the alteration of serum galactose level. In the healthy controls serum galactose level increased slightly at 30 min. after the administration and almost zero at 90 min. In the cirrhotic groups it increased remarkably reaching the peak level at 60 min. The highest concentration was obtained in group A. As shown in Fig. 6-1, Σ Gala. (the sum of serum galactose levels at every 30 min. for 2 hours) in cirrhotic groups was significantly higher than in diabetes or healthy control. Σ Gala. in group A was significantly higher than in groups B and C.

Fig. 5-2 shows the change in serum glucose level after the administration of galactose. While serum glucose level remained constant in healthy controls, it increased remarkably in group C as well as in diabetic group and increased moderately in groups A and B. As shown in Fig. 6-2, Σ Glu. in group C was significantly higher than in groups A and B.

Other routine liver function tests

BSP retention values (% at 45 min.) in group C were lower than in groups A and B, but the differences among the cirrhotic groups were not significant. ICG disappearance rate in group A was lower than in groups B and C. However, there were no significant differences among the cirrhotic group. (Fig. 7) As shown in Table 3, choline-esterase activity in group C was not



1. Sum of serum galactose levels of each 30 minutes for 2 hours. (Σ Gala.)
2. Sum of increases of each 30 minutes in serum glucose level from zero-time for 2 hours. ($\Sigma\Delta$ Glu.)

FIG. 6. Σ Gala. and $\Sigma\Delta$ Glu. (GaTT).

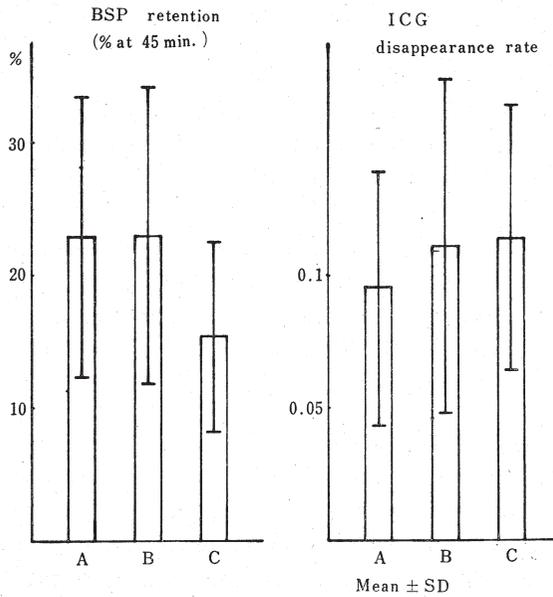


FIG. 7

TABLE 3. Results of Routine Liver Function Tests in Each Group

	A (21)	B (10)	C (15)
GPT (Unit)	78 ±65 (21)*	36 ±23 (10)	54 ±15 (15)
Al. ph (K-K Unit)	9.3 ± 5.9 (18)	10.5 ± 7.1 (9)	11.8 ± 4.1 (15)
ChE (ΔpH)	0.48± 0.20 (19)	0.37± 0.14 (8)	0.60±0.18 (11)
Albumin (g/dl)	3.5 ± 0.9 (20)	3.5 ± 0.6 (10)	3.7 ± 0.6 (12)
γ-globulin (g/dl)	2.1 ± 0.5 (18)	1.8 ± 0.6 (9)	1.9 ± 0.6 (12)
A/G	1.10± 0.37 (20)	1.02± 0.26 (10)	1.06± 0.30 (14)
TTT (Maclagan U.)	8.3 ± 3.2 (19)	6.2 ± 3.2 (9)	5.5 ± 3.6 (14)
cholesterol (mg/dl)	160 ±35 (18)	151 ±25 (8)	180 ±41 (14)

Mean±SD

*: number of cases

so low as those in groups A and B, and the difference between groups B and C was significant statistically.

DISCUSSION

The data obtained in this study confirm the high incidence of glucose intolerance in patients with cirrhosis in accord with previous reports. In the present study, fifteen of forty-six patients had not only diabetic glucose tolerance curve, but also such diabetic signs as fasting hyperglycemia and glucosuria at 2 hours after meals (group C). The cause of glucose intolerance in patients with cirrhosis is still unknown. Probably it may be due to a combination of several mechanisms. Creuzfeldt *et al.*^{8,9)} proposed the conception of "hepatogenous diabetes" that chronic parenchymal liver disease leads to impairment of glucose tolerance and eventually to clinical diabetes. Megyesi *et al.*¹⁾ proposed that glucose intolerance in chronic liver disease is directly or indirectly a consequence of insulin resistance. On the other hand, some of patients with essential diabetes may be associated with concomitant cirrhosis. However, in any individual subject we cannot differentiate clearly the diabetic state attributable to liver cirrhosis from the essential diabetes with concomitant cirrhosis. The patients in group C in this study, therefore, are composed of both the so called hepatogenic diabetes cases and the essential diabetes cases with concomitant cirrhosis.

The liver function tests and clinical signs in group C were, therefore, compared with those in groups A and group B, in order to investigate the mechanism of diabetic state in liver cirrhosis. Although some patients were treated with potentially diabetogenic drugs such as glucocorticoids, thiazide

or furosemeide, only one of these patients were classified into group C. Age distribution was not different in all three groups.

From the results of xylitol and galactose tolerance tests, it was evident that each three group showed a characteristic tolerance curve which was evaluated statistically. In GaTT, galactose was rather easily metabolized in group C compared with groups A and B. In O-XTT and IV-XTT, xylitol in the blood of group C was eliminated more quickly than in groups A and B. From the clinical and experimental investigations reported previously by us⁽⁴⁾⁵⁾, galactose and xylitol tolerance tests have been proven to reflect well the degree of liver damage and to be valuable liver function tests. So, the results of these tolerance tests show that there was not so severe liver damage in group C as in groups A and B.

As for BSP and ICG tests, the retention in groups A and B was more remarkable than in group C. Choline-esterase activity in group C was not so low as in groups A and B. Moreover, diabetic state is less common in cirrhotic patients with ascites. These results also show that there was no severe liver damage in group C.

In so called hepatogenous diabetes, if it exists, it is anticipated that the occurrence of diabetic state has good correlation with hepatic disorder and also with age, but our results did not accord with this anticipation. So, it is conceivable that the diabetic state in most of the cirrhotic patients in group C is not of hepatogenous origin but due to essential diabetes with concomitant cirrhosis. All the cases where the hepatic disorder precedes the diabetic state are not hepatogenous diabetes, because it is possible that the latent diabetes advances to be overt owing to hepatic disorder in some cases.

The changes in serum glucose level in IV-XTT were characteristic in each cirrhotic group. Serum glucose level remained almost constant in group B, while it rose in group C and decreased slightly in group A. Consequently, it seems to be quite useful to apply this characteristic result for differentiating group B from group A and group C. The cases in group B did not show so remarkable glucose intolerance as those in group C. As for the results of many liver function tests including O-XTT, IV-XTT and GaTT, the former showed more severe liver disorder than the latter. Therefore, most of the cases in group B may be considered to have mild glucose intolerance due to liver cirrhosis itself and to correspond to the forstage of hepatogenous diabetes, although a few cases may show slightly abnormal glucose tolerance due to the concomitant essential latent diabetes. On the other hand, the diabetic state in most of the cases in group C is considered to be due to essential diabetes with concomitant cirrhosis. From these evidences, it may be allowed to provide a working hypothesis that hepatogenous diabetes shows almost constant or slight increase in glucose level after IV-XTT and essential diabetes with concomitant cirrhosis shows moderate or remarkable increase.

This hypothesis may be possibly available for differential diagnosis of hepatogenous diabetes and essential diabetes with concomitant cirrhosis in group C. In order to substantiate this possibility, further studies must be done, including the clinical long-term observation of many cases, especially of cases progressing from group B to group C. Serum glucose level in O-XTT and GaTT also showed as similar changes as that in IV-XTT, but these changes were not verified to be significant statistically.

CONCLUSION

In an attempt to differentiate hopatogenous diabetes from essential diabetes with concomitant cirrhosis, forty-six patients with liver cirrhosis were investigated, using xylitol and galactose tolerance tests.

1. It may be concluded that the glucose intolerance in most of the cirrhotic patients with overt diabetes is due to essential diabetes with concomitant cirrhosis and that the so called hepatogenous diabetes is not common in cirrhotic patients.

2. Intravenous xylitol tolerance test may be available for the differential diagnosis of hepatogenous diabetes from essential diabetes with concomitant cirrhosis.

REFERENCES

- 1) Megyesi, C. *et al.*, Glucose tolerance and diabetes in chronic liver disease, *Lancet*, 1051, 1967.
- 2) Carneiro de Moura *et al.*, Carbohydrate metabolism studies in cirrhosis of the liver, *Amer. J. Med.*, **13**, 891, 1968.
- 3) Conn, H. O. *et al.*, Cirrhosis and diabetes I, Increased incidence of diabetes in patients with Laennec's cirrhosis, *Amer. J. Med.*, **14**, 837, 1969.
- 4) K. Kato *et al.*, Clinical and experimental studies on xylitol metabolism, *Jap. J. Med.*, **11**, 92, 1972.
- 5) S. Kikuchi *et al.*, Studies on galactose tolerance test in patients with liver disease, *Nagoya J. med. Sci.*, **35**, 19, 1972.
- 6) N. Kuzuya *et al.*, Report of the committee on the diagnostic criteria of the oral glucose tolerance test for diabetes mellitus Recommendations on the evaluation of the oral glucose tolerance test for the diagnosis of diabetes mellitus, *J. Jap. Diab. Soc.*, **13**, 1, 1970.
- 7) Sweely, C. C. *et al.*, Gas-Liquid chromatography of trimethylsilyl derivatives of sugars and related substance, *J. Am. Chem. Soc.*, **85**, 2497, 1963.
- 8) Creutzfeldt, W. *et al.*, Intravenöse belastungen mit glucose, insulin und tolbutamide bei gesunden, diabetikern, leberzirrhotikern und insulomträgern, *Deutsch Med. Wschr.*, **87**, 2189, 1962.
- 9) Leevy, C. *et al.*, Hyperglycemia and glucosuria in the chronic alcoholic with hepatic insufficiency. Clinical obserbations in 10 patients., *Amer. J. Med. Sci.*, **223**, 88, 1961.