

The Incidence of Cholelithiasis, Cholesterosis, and Liver Disease in Diabetes Mellitus

An Autopsy Study

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It has long been known that in diabetes mellitus there is a disturbance of fat metabolism. This, and the hypercholesterolemia are held responsible for the increased tendency to cholelithiasis and gallbladder disease. On this basis there may be some relationship between diabetes and cholesterosis of the gallbladder, since in both conditions there is a disturbance of fat metabolism. To investigate this relationship we undertook the study of the findings in 1319 autopsies of adults: first to determine the incidence of diabetes, second to see how often it was associated with cholesterosis, with gallstones, and with liver disease.

In the 1319 autopsies there were 137 cases of diabetes mellitus (10.4 per cent), of which 34 were associated with gallstones and 14 with cholesterosis. In only 3 cases were both cholesterosis and gallstones present.

CHOLELITHIASIS

A review of the literature gives the impression that gallstones are more frequent in diabetic patients than in nondiabetics (table 1). The incidence in diabetics ranges from 6.0 to 33.5 per cent (average 25.1 per cent). Warren⁵ reported an incidence of 31 per cent in 453 diabetic patients over thirty years, compared with 21 per cent in 500 nondiabetics. In our series of autopsies, gallstones were found in 22.7 per cent of all cases, compared with 24.8 per cent in the diabetic cases and the average incidence of 25.2 per cent recorded in the literature. There thus appears, contrary to the prevailing opinion, to be no significant difference in the incidence of gallstones among diabetic and nondiabetic patients.

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We are indebted to Dr. Tobias Weinberg, Head of the Department of Laboratories of the Sinai Hospital, for the privilege of using the autopsy material.

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CHOLESTEROSIS

So far as can be ascertained there have been no studies on the relationship between cholesterosis of the gallbladder and diabetes mellitus. In the present series, there were 165 cases of cholesterosis (12.5 per cent), including 15 cases of diabetes (9 per cent). In the 137 cases of diabetes, cholesterosis occurred in 10.2 per cent. Thus the incidence of cholesterosis of the gallbladder in the diabetic patient parallels that in the nondiabetic. Although there is a disturbance of fat metabolism in both conditions, it seems that cholesterosis is a localized condition unrelated to the fat imbalance of diabetes.

LIVER DISEASE

There has been comparatively little statistical evaluation of gross liver disease associated with diabetes. In the literature, the incidence of Laennec's cirrhosis of the liver in the general population varies from 2.4 to 18.6 per cent, depending on the source of material. According to Ratnoff and Patek⁸ the incidence based on autopsy material ranges from 0.43 to 6.3 per cent. In our series there were 49 cases with Laennec's cirrhosis, and in only 3 of these was diabetes present. In the same series there were 12 cases of biliary cirrhosis, 2 of which were diabetic. Thus in the 61 cases of cirrhosis the incidence of diabetes was 8.2 per cent. Herbut and Tamaki⁹ reported 12 cases of diabetes in 115 cases of cirrhosis of the liver. Comparing these percentages, one sees clearly that there is no statistical difference in the incidence of diabetes among cirrhotic and noncirrhotic patients.

In our 137 autopsied cases of diabetes there were 4 cases of cirrhosis of the liver (2.9 per cent). In the literature the incidence of cirrhosis of the liver in autopsied diabetics ranged from 2.5 to 12.7 per cent (average 7.0 per cent). From these data, it appears that cirrhosis of the liver is not commonly associated with diabetes mellitus, being merely an incidental finding.

TABLE 1
Incidence of gallstones in diabetes

	Cases of Diabetes	Cases with Gallstones	Per cent
Lieber ¹	1259	381	30.2
Seckel ²	430	26	6.0
Jones and others ³	68	15	22.0
Wilder ⁴	197	66	33.5
Warren ⁵	453	139	31.0
Joslin et al ⁶	319	59	18.5
Feldman ⁷	137	34	24.8
Totals	2863	720	25.1

TABLE 2
Incidence of cirrhosis of the liver in diabetes

	Autopsied Diabetics	Cirrhosis of Liver	
		No.	Per cent
Schleusner ¹⁰	355	45	12.7
Joslin and associates ⁶	319	8	2.5
Pollack and associates ¹¹	113	8	7.0
Feldman ⁷	137	4	2.9
Totals	924	65	7.0
	Clinical Diabetics		
Joslin and associates ¹²	10,235	51	0.5
Barach ¹³	1,300	2	0.15
Frankel and others ¹⁴	3,543	36	1.0
Totals	15,078	89	0.6

TABLE 3
Incidence of liver disease in diabetes

	No. of Cases
Cirrhosis	4
Hepatomegaly	4
Simple cyst (single 1, multiple 1)	2
Hemangioma	7
Adenoma (bile duct)	2
Necrosis	2
Hepatitis	1
Total	22

Other investigators have expressed similar views.

While there is little if any liver disease noted grossly in treated diabetics, there are presumed to be some physiologic or functional changes that are not obvious in gross and histological studies. Although fatty livers of varying degrees are found in untreated diabetics, this condition is uncommon in treated adult diabetics. In our 137 cases

of diabetes, gross liver disease was present in 22. There appeared to be no difference in incidence between the diabetic and nondiabetic cases. It is worthy of mention that the lesions seen in the liver are for the most part unrelated to the diabetic condition. Table 3 presents the various lesions found in the 22 autopsied diabetics. These included 4 cases of cirrhosis of the liver (2 Laennec's cirrhosis, 1 biliary cirrhosis and 1 toxic cirrhosis). There were two cases with simple cysts of the liver, one single, the other multiple.

There is no unanimity of opinion regarding some of the liver abnormalities associated with diabetes mellitus. According to Duncan¹⁵ fatty infiltration of the liver with moderate enlargement is a fairly common finding in diabetes, especially in children. According to Frankel¹⁴ and others, most adult diabetics have little or no enlargement of the liver. According to Marble and co-workers¹⁶ this condition in the diabetic is attributed to an excessive amount of fat and glycogen. This may be true of juvenile and untreated cases, but in the treated adult the picture differs. In our 137 cases, the majority of which had received diabetic therapy, there was gross enlargement in 4 cases indicated by the appearance and weights of 5250, 2880, 2440 and 2050 gm. respectively. In 231 diabetics Hanssen¹⁷ found only one case of enlarged liver in patients over twenty years of age. According to Goodman^{18, 19} enlargement is frequent in diabetic patients. In his clinical study it occurred in 44.5 per cent of cases. This incidence seems extremely high and is open to question because the measurements were made by percussion and palpation of the abdomen. It is not comparable to the incidence in autopsied cases.

Numerous studies have been made in diabetic patients to determine whether the liver presents any functional abnormality. Pomeranze²⁰ reports that 93 of 162 diabetic patients (57.2 per cent) retained over 5 per cent of bromsulphalein sodium 45 minutes after receiving a test dose of 5 mg. of bromsulphalein per kg. according to the method recommended by Mateer and associates.²¹ Frankel¹⁴ studied 319 diabetics, 46 of whom had abnormal retention; in 28 of these cases the abnormality could be attributed to causes other than diabetes, but in the other 18 the diabetes alone accounted for the abnormal retention.

SUMMARY

An autopsy study was made to determine the association of cholelithiasis, cholesterosis, and liver disease with diabetes mellitus. In 1319 adult autopsies, there were 137 cases of diabetes (10.4 per cent). The incidence of gallstones in the 127 cases was 24.8 per cent, compared

with 22.7 per cent in the whole series and an average of 25.2 per cent in the literature. It is concluded that gallstones are no more prevalent in diabetics than in nondiabetics.

Cholesterosis of the gallbladder was present in 14 of the 137 diabetics (10.2 per cent). The incidence of cholesterosis in the 1319 autopsies was 12.5 per cent, and that in the diabetics was 10.2 per cent.

Laennec's cirrhosis of the liver occurred in only 4 of the 137 diabetic cases (2.9 per cent). The autopsy study revealed no gross liver disease in the diabetics, although others have reported abnormal liver function in diabetic patients.

REFERENCES

- ¹ Lieber, M. M.: The incidence of gallstones and their correlation with other diseases. *Ann. Surg.* 135:394-405, March 1952.
- ² Seckel, H.: Observations on hereditary and constitutional diseases of metabolism in diabetes mellitus. *Zeitschr. f. klin. Med.* 102:195-228, 1925.
- ³ Jones, C. M., Castle, W. B., and Mulholland, H. B.: Pancreatic and hepatic activity in diabetes mellitus; alterations, with some observations on etiology of the disease. *Arch. Int. Med.* 35:315-36, March 1925.
- ⁴ Wilder, R. M.: *Clinical Diabetes Mellitus and Hyperinsulinism*. Philadelphia, W. B. Saunders Co., 1940, p. 311.
- ⁵ Warren, S.: *The Pathology of Diabetes Mellitus*. Philadelphia, Lea & Febiger, 1938, 2nd ed., pp. 106, 246.
- ⁶ Joslin, E. P., Root, H. F., White, P., and Marble, A.: *Treatment of Diabetes Mellitus*. Philadelphia, Lea & Febiger, 1940, 7th ed.
- ⁷ Feldman, M.: Cirrhosis of the liver: its relationship to cholesterosis of the gallbladder and gallstones; an autopsy study. To be read before the National Gastroenterological Association 19th annual meeting, Washington, Oct. 25, 1954. To be published in *The American Journal of Gastroenterology*.
- ⁸ Ratnoff, O. D., and Patek, A. J., Jr.: Natural history of Laennec's cirrhosis of the liver: analysis of 386 cases. *Medicine* 21:207-68, Sept. 1942.
- ⁹ Herbut, P. A., and Tamaki, H. T.: Cirrhosis of the liver and diabetes as related to hemochromatosis. *Am. J. Clin. Path.* 16: 640-50, Oct. 1946.
- ¹⁰ Schleusner: Über die Zusammenhänge zwischen Diabetes Mellitus und Erkrankungen der Leber und der Gallenwege. Herman Bauer, Marburg-Lahn, 1938.
- ¹¹ Pollack, H., Dolger, H., and Ellenberg, M.: An analysis of the diabetic morbidity and mortality in a general hospital. *Am. J. Med. Sci.* 202: 246-51, Aug. 1941.
- ¹² Joslin, E. P., Root, H. F., White, P., Marble, A., and Bailey, C.: *Treatment of Diabetes Mellitus*. Philadelphia, Lea & Febiger, 1946, 8th ed., p. 544.
- ¹³ Barach, J. H.: *Diabetes and Its Treatment*. London, Oxford University Press, 1949.
- ¹⁴ Frankel, J. J., Ashbury, C. E., Jr., and Baker, L. A.: Heart insufficiency and cirrhosis in diabetes mellitus. *Arch. Int. Med.* 86:376-90, Sept. 1950.
- ¹⁵ Duncan, G. G.: Objective Pathologic Changes in Fat Metabolism in Diabetes Diseases of Metabolism. 1947, 2nd ed., pp. 731, 918.
- ¹⁶ Marble, A., White, P., Bogan, I. K., and Smith, R. M.: Enlargement of the liver in diabetic children. *Arch. Int. Med.* 62: 740-50, Nov. 1938.
- ¹⁷ Hanssen, P.: Enlargement of the liver in diabetes mellitus. *J.A.M.A.* 106:914-16, March 1936.
- ¹⁸ Goodman, J. I.: The enlarged liver in diabetes mellitus: its determination by percussion. *Am. J. Digest. Dis.* 18:181-85, June 1951.
- ¹⁹ Goodman, J. I.: Hepatomegaly and diabetes mellitus. *Ann. Int. Med.* 39:1077-87, Nov. 1953.
- ²⁰ Pomeranze, J.: Bromsulphthalein sodium retention evaluation of hepatic function in diabetes mellitus. *Metabolism* 1:540-43, Nov. 1952.
- ²¹ Mateer, J. G., Balts, J. I., Commanduras, P. D., Steele, H. H., and Brouwer, S. W.: Further advances in liver function tests in facilitating the earlier diagnosis and treatment of liver impairment. *Gastroenterol.* 8:52-70, Jan. 1947.