Diabetic Cholecystopathy

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Summary. In a group of patients with juvenile-onset diabetes of over 10 years duration without known liver and bile duct diseases the following examinations were performed: 1. cholecystography; 2. measurement of the time of contraction of the Lütken's and Oddi's sphincters; 3. measurement of the time of gall-bladder contraction; 4. measurement of the time of BSP appearing in the bile. Compared with the control group, there was a markedly more frequent impairment of gall-bladder contraction (in 47 percent of cases), as well as prolongation of the time of Lütken's sphincter contraction (82.5 percent), prolongation of the time of the efflux of bile from the gall-bladder (70.6 percent) and prolongation of the bile BSP time (58.8 percent). The calculated means have shown in diabetic patients a significant prolongation of the Lütken's sphincter contraction (8 min : 4 min), of the time of the efflux of bile from the gall-bladder (28 : 18) and of the bile-BSP time (24 : 19).

The results obtained prove a greater incidence of gall-bladder hypotony in patients with long-lasting diabetes. That dysfunction of the gall-bladder seems to be a specific complication of diabetes, similar to others found in the gastrointestinal tract of diabetic patients.

Cholécystopathie diabétique

Résumé. Dans un groupe de malades atteints de diabète juvénile, évoluant depuis plus de 10 ans, sans affections manifestes du foie ou des voies biliaires, on a effectué les recherches suivantes: 1. cholécystographie, 2. détermination du temps de contraction du sphincter de Lütken et du sphincter d'Oddi, 3. détermination du temps de contraction de la vésicule biliaire, 4. détermination du temps d'apparition de BSP dans la bile C. En comparaison avec le groupe témoin (groupe de contrôle), on a constaté: un défaut beaucoup plus fréquent de la contraction de la vésicule biliaire (47% des cas), l'allongement du temps de la contraction du sphincter de LÜTKENS (82.5%), l'allongement du temps d'écoulement de la bile vésiculaire (70.6%), ainsi que l'allongement de l'apparition de BSP dans la bile C (58.8%). La confrontation des valeurs moyennes montre chez les malades

atteints de diabète, un allongement marqué: du temps de contraction du sphincter de LÜTKENS (8 min : 4 min), du temps d'écoulement de la bile vésiculaire (28 : 18), ainsi que du temps de l'apparition de BSP dans la bile C (24 : 19). Les résultats obtenus permettent de constater l'apparition plus fréquente de l'hypotonie de la vésicule biliaire chez les malades avec un diabète de longue durée. Cette perturbation du fonctionnement de la vésicule biliaire semble être une complication spécifique du diabète, semblable à d'autres troubles fonctionnels du tube digestif, constatés au cours du diabète.

Diabetische Cholecystopathie

Zusammenfassung. Bei einer Gruppe von Patienten mit juvenilem Diabetes mellitus, der mehr als 10 Jahre andauerte und ohne manifeste Erkrankungen der Leber bzw. der Gallenwege verlief, wurden folgende Untersuchungen durchgeführt: — 1. Cholezystographie, 2. Bestimmung der Kontraktionszeit des Lütken- und des Oddi-Sphinkters, 3. Bestimmung der Kontraktionszeit der Gallenblase, 4. Bestimmung der Erscheinungszeit des Bromsulphalein in der C-Galle. Der Vergleich mit der Kontrollgruppe ergab: eine bedeutend häufigere Verlängerung der Kontraktionszeit der Gallenblase bei 47% der Fälle, eine Verlängerung der Ausflußzeit der B-Galle bei 70.6%, eine Verlängerung der Kontraktionszeit des Lütken-Sphinkters bei 82.5%, sowie eine Verlängerung der Erscheinungszeit von BSP in der C-Galle bei 58.8%. Die Zusammenstellung der Mittelwerte weist bei Diabetikern eine signifikante Verlängerung auf: der Kontraktionszeit des Lütken-Sphinkters auf 8 Min. zu 4 Min., der Ausflußzeit der B-Galle auf 28 zu 18, sowie der Erscheinungszeit von BSP in der C-Galle auf 24 zu 19. — Die erhaltenen Resultate gestatten die Feststellung, daß bei Kranken mit langdauerndem Diabetes mellitus eine Hypotonie der Gallenblase auftritt. Diese Funktionsstörung der Gallenblase scheint eine ähnliche spezifische Komplikation des Diabetes zu sein, wie es auch andere Funktionsstörungen der Verdauungsorgane sind, die im Gefolge der Zuckerkrankheit beobachtet werden.

The possibility of diabetes being specifically complicated by disorders of abdominal organs whose function is regulated by the autonomic nervous system, was frequently drawn attention to in the recent past. At present the notions of diabetic cystopathy and enteropathy are accepted as included in the pathologic picture of the later stage of diabetes (JORDAN and CRABTREE, 1935; BARGEN et al., 1936 quoted by CHLEBOWSKI, 1966; KARWOWSKA-STAUER and KRZESKI, 1959; BERGE et al., 1956; BARTLEY et al., 1966; PIRART, 1967).

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The problem of gall-bladder pathology in diabetes has also been repeatedly discussed in the literature. Initially, diseases of biliary ducts have been incriminated as the primary cause of pancreatic disorders giving rise to diabetes (TWISS and CARTER, 1952; FELDMAN and FELDMAN, 1954; JOSLIN et al., 1959; TWAILL and MCCARRON, 1961; MUNDTH, 1962). Only recently GITELSON et al. (1963) have suggested that the disturbances in the neuro-regulation of gall-bladder function could represent a specific complication of diabetes, by analogy with some disorders of the same type observed in other parts of the gastrointestinal tract, and referred to as diabetic enteropathy.

The present study was designed to investigate gall-bladder contractility, as determined by means of

X-ray examination and functional tests in patients with long-standing diabetes. The presence of other gall-bladder diseases, e.g. cholelithiasis, cholecystitis, and neoplasms was excluded beforehand in these patients.

Experimental

The material was composed of 34 subjects including 17 diabetic patients. Age distribution is recorded in Table 1.

Diabetic patients comprised 11 males and 6 females, whereas controls included 7 males and 10 females.

Subjects exhibiting primary pathology of the gall-bladder, according to anamnesis, objective examination and X-ray pictures were not included in the study.

Table 1. Age of subjects examined

Group of examined persons	Diabetics	Healthy
Group of Age		
14—20 years	8	2
21—30 years	5	5
31—40 years	3	6
41—50 years	1	4

Table 2. Planimetric evaluation of the gall-bladder contraction

Group of examined persons	Diabetics N = 17	Nondiabetics with no signs of gall-bladder disease N = 17
Gall-bladder surface		
1. mm ² before contraction	1.529 ± 142	1.795 ± 150
after	1.035 ± 168 <i>p</i> < 0.05	959 ± 75 <i>p</i> < 0.01
2. Degree of gall- bladder's contrac- tion in %	30 ± 5.3	45 ± 3.8
	<i>p</i> < 0.05	

Table 3. Mean duration of individual fraction collecting periods (Duodenal fractional probe)

Group of examined persons	Periods (minutes)					
	1	2	3	4	5	6
Diabetics	11 ± 0.9	5 ± 0.7	8 ± 0.8	28 ± 2.2	2.1 ± 0.2 [ml/min]	24 ± 2.1
Healthy	12 ± 1.2	5 ± 1.3	4 ± 0.5	18 ± 0.4	2.5 ± 0.2 [ml/min]	18 ± 1.1
Standard values	10	5	4	20	3 [ml/min]	20

In diabetics the duration of disease remained within 10—23 years (mean 12 years), the age was from 14 to 50 years (mean 24 years). Accordingly, the present study involved patients with the juvenile type of diabetes suffering from the disease for over 10 years, and for the most part less than 40 years of age. Insulin was administered to all diabetics in a dose of 50—90 U. The examination of the fundus of the eye

disclosed in six cases evidence of disturbances of the retinopathia diabetica type. Neurological complications occurred in three cases. Persistent albuminuria was recorded in four cases.

X-ray examination of the gall-bladder was carried out by the typical procedure, with oral administration of a double dose of the contrast medium ("Iodopanoic acid", Winthrop Products Ltd). Boyden's breakfast (two yolks) was administered for inducing gall-bladder contraction.

Duodenal fractional probe was carried out after VALERA et al. (1950), as modified by CAROLI et al. (1952) with reference to the time of bromsulphthalein appearance in C-bile. The following periods were distinguished: 1st corresponding to the distention of the sphincter of Oddi; 2nd corresponding to the contraction of this sphincter; 3rd corresponding to the contraction of the sphincter of Lütken's; 4th determining the outflow of B-bile/gall-bladder bile; 5th determining the rate of the outflow of C-bile. In the 5th period BSP was injected intravenously into all subjects in a dose of 5 mg/kg of body weight, whereupon the time of appearance of the dye in C-bile was determined after Caroli et al. (6th period).

Results

I. X-ray examination. There was no significant difference between the two groups as regards the surface of the gall-bladder prior to ingestion of Boyden's breakfast. The mean surface of the gall-bladder in diabetics was even slightly (and not significantly) smaller than in controls. On the other hand, average contractility of the gall-bladder was definitely lower in diabetics compared with controls. This finding followed from the comparison of the mean values of gall-bladder surface calculated in mm², prior to and

after the administration of Boyden's breakfast in both groups. In diabetics the decrease in the surface due to the contraction-inducing stimulus was slightly significant (*p* < 0.05), whereas in controls it showed a very marked level of significance (*p* < 0.01). This fact was also confirmed by percentile calculation of the decrease in the surface of the gall-bladder in both groups: *p* < 0.05 (see Table 2).

In individual cases the disturbances in the contractility of the gall-bladder were particularly pronounced, as shown for example in Fig. 1.

Fig. 1a.

Fig. 1b.

Fig. 1. Cholecystography. Gall-bladder's surface before (a) and after (b) Boyden's breakfast: 2.770 mm² and 2.700 mm²

The degree of gall-bladder contraction after Boyden's breakfast was lower than 25% in eight diabetics, but in only two controls. This corresponded to 47% and 12% respectively, in relationship to the number of subjects in the two groups studied.

II. Duodenal fractional probe. The results obtained by duodenal fractional probing are in good agreement with those derived from X-ray examination. There was no significant difference between the two groups as regards the 1st and 2nd period, corresponding to the

distention and contraction of the sphincter of Oddi. On the other hand, a highly significant increase in the 3rd period ($p < 0.01$) corresponding to the contraction of the sphincter of Lütken's, and the 4th one ($p < 0.01$) corresponding to gall-bladder contraction was observed in diabetics compared with controls. Moreover, the time of the appearance of BSP in C-bile was markedly prolonged in diabetics ($p < 0.02$) — Table 3.

When analyzing individual cases it was found that abnormal values of one or more periods of the fractional probe were exhibited by all diabetics, and by only six controls. In conformity with the results recorded in Table 4, in the great majority of cases these abnormalities involved the 3rd, 4th and 5th period.

Table 4. Occurrence of abnormal duration of duodenal fraction collecting periods

Duodenal fractional probe	Group of examined persons		Diabetics		Healthy	
	number	per- cent	number	per- cent	number	per- cent
Normal	0	—	11	64.7	6	35.3
Abnormal	17	100	4	23.5	3	17.6
Elongation of 1st period (Oddi's sphincter dilatation)	2	11.7	0	—	1	5.8
Elongation of 2nd period (Oddi's sphincter contraction)	4	23.5	0	—	1	5.8
Elongation of 3rd period (Lütken's sphincter contractions)	14	82.5	0	—	1	5.8
Elongation of 4th period (Efflux of B-bile)	12	70.6	0	—	1	5.8
Lack of B-bile	1	5.8	0	—	1	5.8
Increased efflux rate of C-bile (5th Period)	0	—	1	5.8	1	5.8
Delayed appearance of BSP in C-bile	10	58.8	1	5.8	1	5.8

Discussion

Notwithstanding the small number of cases under study, the agreement of the results obtained on examination of the biliary ducts by two different methods supports the view of the occurrence, in later stages of diabetes, of specific disturbances in the function of the gall-bladder characteristic for this disease. The foregoing disturbances are expressed by an impairment of gall-bladder contractility and evacuation of the bile into the duodenum. The increase in the time of BSP appearance in C-bile indicates that possibly the functional disturbances concern not only the gall-bladder but also the biliary ducts.

The present results, as well as their confrontation with analogous diabetic disorders in other organs whose function is regulated by the autonomic system (e.g. the intestine or urinary bladder), suggest that in this case disturbances in gall-bladder neuroregulation are involved; the latter constitute a manifestation of the general syndrome known as neuropathia diabetica visceralis.

In the material investigated, no evidence was disclosed of "primary" atony of the gall-bladder, i.e. the increase in the planimetrically-determined surface in the diabetic prior to ingestion of Boyden's breakfast. The mean values of gall-bladder surface before contraction were approximate in both groups. The only significant difference involved the degree of gall-bladder contractility. These results are in agreement with those obtained by fractional probe of duodenal contents, and indicate that above all there is a question of functional disorders, which possibly lead to anatomical changes in the later stages of diabetes.

The reliability of the results obtained by both foregoing methods as criteria of functional evaluation of the gall-bladder (these results being interpreted independently of one another) is not too highly commended by some authors (HAFTER, 1966). However, according to the present investigation, the remarkable consistency of the results obtained by these two different diagnostic methods discloses evidence of the objectiveness of our mode of interpretation of the experimental data.

In our relatively small material, no correlation could be established between the disturbances in gall-bladder function and manifestations of the type of microangiopathy disclosed by examination of the fundus of the eye. In the entire group of 17 diabetics specific retinal changes of the retinopathia diabetica type were only moderate (microaneurysms and punctual haemorrhages). These signs were observed in six cases, including one patient out of eight in whom gall-bladder dysfunction was particularly pronounced. It is stressed however, that in electron microscopic investigations of the wall of gastrointestinal tract from the oesophagus to the rectum, ANGERVALL and SÄVE-SÖDERBERGH (1966) found some changes in the capillaries and veinlets typical of diabetes, and expressed by thickening of the wall, a decrease in the lumen, and atrophy of endothelial cells. These findings support the suggestion that the disturbances of the microangiopathia diabetica type can be the primary cause of visceral disorders in the late stages of diabetes.

It is noteworthy that, notwithstanding the unquestionable evidence of objective disturbances in gall-bladder function, none of the patients under study complained of subjective abdominal discomfort. Con-

sequently, at the discussed stage of disease, the foregoing disorders can be qualified as asymptomatic. ELLENBERG et al. (1966) made a similar observation with regard to urinary bladder dysfunction. Evidently it is hitherto unrecognized to what extent these functional disturbances support the later development of biliary duct and gall-bladder infections, as well as cholelithiasis, showing relatively high coincidence with diabetes.

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