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The Possible Role of Gallbladder Motor Dysfunction in Patients with Idiopathic Bile Acid Diarrhoea

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Abstract

Purpose: *The idiopathic bile acid diarrhoea(BAD) is a rather frequent finding in diarrhoea-predominant irritable bowel syndrome(IBS-D) patients and is responsive to cholestiramine.The purpose is to investigate a possible pathophysiological role of gallbladder motor activity in patients with idiopathic BAD.*

Methods: *We examined the gallbladder volume before and 15',30',45' and 60' after a 300 Kcal meal with a D3 sonographic technique in 52 IBS-D patients with postprandial diarrhoea responsive to cholestyramine(group R).The ejection fraction at various times was calculated and compared by means of Student t test with the corresponding values of 32 healthy subjects(group C)and of 14 IBS-D patients not responsive to cholestiramine(group NR).The ejection fraction at various times of each patient of group R was examined whether fell in the 99% confidence interval(CI) of the corresponding means of group C.*

Results: *The gallbladder ejection fractions of the group R were significantly higher than those of the group C,at 30',45' and 60', and than those of group NR, at 15', 30' and 60'.During all time periods nearly 50% of group R patients were above the CI upper limit and about 10% below the lower limit,whereas at 15' about 44% was above the upper CI limit and at 60'about 17% remained below the CI lower limit.*

Conclusions: *The study showed that almost half of IBS-D patients responsive to cholestyramine had a"hyperkinetic gallbladder",that quickly ejects an increased amount of bile in the intestine, and nearly one-fifth had a "hypokinetic gallbladder",with slow and scarcer than normal emptying,suggesting that a dyskinetic gallbladder could play a role in the pathophysiology of BAD.*

Keywords: *Bile acid diarrhoea; cholestiramine; gallbladder dysmotility; gallbladder ejection fraction; irritable bowel syndrome.*

Introduction

Chronic diarrhoea is a common clinical problem with a prevalence in Western populations estimated to be in the order of 4–5% [1] . Bile acid malabsorption (BAM) was considered to be the cause of diarrhoea in 25 % to 50% of patients with chronic diarrhoea previously diagnosed as having irritable bowel syndrome with predominant diarrhoea [IBS-D) and functional diarrhoea [2-9] . Bile acid diarrhoea (BAD) is due to bile acids reaching the colon in excessive quantity that exert a laxative effect. BAD may be secondary to diseases of the terminal ileum such as ileal Crohn disease, ileal resection, radiation enteritis etc. that cause bile acid malabsorption (type I or secondary). On the other hand there are also BAMs with normal ileal histology (type II or idiopathic or primary), due to a deficiency of the ileal hormone fibroplast growth factor (FGF-19) produced in the ileum that leads to a defective inhibition of liver bile acid biosynthesis with consequent excessive bile acid secretion that exceeds the normal capacity for ileal reabsorption [10]. In addition, there is also a BAM secondary to cholecystectomy, celiac disease and other gastrointestinal non-ileal diseases (type III). In the colon bile acids enhance mucosal permeability, induce water and electrolyte secretion, and accelerate colonic transit with high amplitude colonic contractions causing diarrhoea. This kind of

diarrhoea is typically responsive to the assumption of bile acids sequestering agents, such as cholestyramine, cholestipol and cholesevelam, that prevent the contact of bile acids with the colonic mucosa.

Among the idiopathic BADs a new condition has been described by Habba some years ago [11] as caused by a gallbladder malfunction with a low ejection fraction after CCK intravenous injection at cholescintigraphy. However, the major criticism to this conjectural syndrome was advanced by Yarze [12], who outlined the contradiction between the suggestive hypothesis that the postprandial episodes of diarrhoea in these patients are due to an excess of bile acids discharged by gallbladder in the intestine after meal and a low bile ejection after a gallbladder stimulation with CCK. We would expect an increase in bile ejection causing an excess of bile acids in the intestine, that, exceeding the absorptive capacity of distal ileum, reaches the colon causing diarrhoea.

To clarify this apparent incongruence and the contradictory findings of the literature indicating after stimulation a normal [13,14] or a delayed [15] gallbladder contraction in patients with IBS, we performed a study in patients previously diagnosed with IBS-D following Rome III criteria, who were responsive to cholestyramine, by using a 3D ultrasonographic (US) technique on the gallbladder postprandial contractility and giving a standardized bromatologically equilibrated meal that is a more physiological stimulus than CCK.

Materials and Methods

Participant Characteristics

The study was carried out on patients with chronic postprandial diarrhoea that improved with cholestyramine, previously diagnosed with IBS-D on the basis of Rome III criteria, excluding inflammatory, infective, endocrine, neuroendocrine causes, as well as microscopic colitis, SIBO, lactose intolerance, celiachia, intestinal maldigestion and malabsorption, including bile acid malabsorption type I and III, by means of the following examinations: abdominal sonographic evaluation with measurement of the intestinal wall thickness, ileo-colonic endoscopy with biopsy in cases with increased intestinal wall thickness or increased calprotectin or positivity of faecal occult blood, gastrointestinal X-ray barium studies in the other cases, thyroid function tests, serum calcitonin, gastrin and chromogranin A dosage, serologic tests for celiac disease with duodenal biopsy in patients with positivity of celiac disease genetic test, glucose and lactose breath tests, stool analysis for parasites and ova, research of *Clostridium difficile* toxin and *Giardia lamblia* stool antigens, cultures for common faecal pathogens, occult blood test on 3 specimens, faecal calprotectin and faecal elastase. Age below 18 and above 80 years, pregnancy and nursing, drug addiction, smoking more than10 cigarettes a day, alcoholic and psychic diseases were also excluded, as well as patients with gallstones and dysmorphic gallbladder, body overweight, gut operations, excluding appendectomy, and severe general diseases.

The whole number of patients with chronic diarrhoea examined from year 2011 to 2017, excluding those with IBD, who were examined by the Centre for Inflammatory Bowel Disease, was 193, whose 148 received the diagnosis of IBS-D. Of the 123 IBS-D patients who took a dose of 4 g of cholestyramine 15-30 min before each meal for 10 days, 52 responders with a decrease to one or two BM/day and 14 not responders accepted to be included in the study.

The response to cholestiramine cannot be considered a side effect of the drug in all patients, because only 11% of patients taking the drug for other reasons have been reported to experience constipation [16]. Unfortunately we did not perform the ^{75}Selenium-homocholic acid taurine (75SeHCAT) test for lack of availability of the test in the Hospital. With these criteria we selected 52 patients, (18 male and 34 female, mean age ± SD, 36.6 ± 11.1 years). (group R). Some patients had lactose intolerance, but the lactose free diet did not significantly improved diarrhoea, while the gluten free diet in absence of celiac disease and the low FODMAPs diet for carbohydrate intolerance gave only slight and temporary improvements.

The study was conducted in accordance with the criteria for clinical studies of the Declaration of Helsinki and its subsequent modifications. Informed consent was obtained from each patient.

Sonographic Examinations

We used a sonographic 3D technique described in a previous publication [17], with the equipment iU22 system and QLAB software for three-dimensional reconstruction of the gallbladder shape (Philips Healthcare, Bothell, WA) and with the volumetric matrix probe with a frequency range of 6.0 to 1.0 MHz (x6-1; Philips Healthcare, Bothell, WA). Because

the volume acquisition time of this probe is very fast compared to mechanical ones, motion artifacts due to patient respiration or movements can be avoided. The possibility of checking the orthogonal planes with xPlane without moving the probe helps obtain a better data set and more accurate volumes for quantification. Other technical detail are available in the previous publication [17]. This sonographic technique furnishes the better requisites for gallbladder dynamics studies than conventional 2D sonography. The examiners were unaware of the positive response to cholestiramine of patients examined.

Experimental Design

The study was made after fasting and abstinence from smoking for at least 8 hours. We evaluated the gallbladder volume at time 0 and every 15 minutes after a standard meal for at least 60 minutes.

According to other studies [18], we used a liquid test meal (Ensure Plus, 200 mL; Abbott Nutrition, Rome, Italy), which contained 16.7% protein, 29.5% fats, and 53.8% carbohydrates, for a total of 1.5 kcal/mL. This test meal has the advantage of providing a balanced composition of protein, lipids, and carbohydrates similar to that of a light meal usually eaten in Western countries. Then the gallbladder ejection fraction at various times was calculated. This gallbladder stimulation is more physiological than that of the fatty meal and than that with CCK intravenous administration, because unlike CCK activates a complex of neuro-humoral and hormonal mechanisms, is devoid of undesirable and sometimes serious side effect of CCK, and, lastly, is simple and inexpensive.

Statistics

After having verified that the distribution of the data was normal, we compared with the Student t test the gallbladder ejection fractions obtained in the group of 52 IBS-D patients with postprandial diarrhoea responsive to cholestyramine (group R) with the group of 14 IBS-D patients (9 male and 5 female; mean age ± SD, 36.3 ± 10.9 years) with postprandial diarrhoea not responsive to cholestyramine (group NR) and those obtained in a group of 32 healthy subjects (8 male and 24 female; mean age ± SD, 28.6 ± 3.1 years) (group C), all examined with the same sonographic technique and study design. In addition, as the gallbladder dyskinesia may manifest itself with an abnormal increase or decrease of contractile activity, the statistical significance tests for the whole patients group may not single out the cases with excessive or scarce bile ejection. So, we calculated the 99% confidence interval (CI) [19] for the mean of each postprandial period in the group C and then controlled whether the values of each patient of group R fell in the 99% CI range or outside for each period of time after meal.

Results

The gallbladder ejection fraction at 30',45' and 60' of the group R was significantly ($p<0.05$) higher than that of the group C and at 15', 30' and 60' it was also significantly ($p<0.05$) higher than that of group NR. None of the values of group NR was significantly different from those of the group C (Table 1), whereas the basal gallbladder volume of the 3 groups did not differ significantly among themselves: group R=23.54±12.55 (mean ± SD) , group NR= 23.79±10.35 and group C = 22.31±9.70. If the basal gallbladder volume was similar in all groups, the course of ejection fractions of each group is superimposable to that of ejected volumes and can be statistically compared to that of other groups, without being biased by percentages calculated from too much different values of basal volumes.

Table 1

Time	Group R	Group C	Group NR
15'	46.22±19.15 [B]	42.19±15.12	33.81±14.73
30'	57.23±18.18 [AB]	48.75±16.87	44.42±12.75
45'	57.33±18.25 [A]	47.61±18.34	51.16±14.96
60'	57.06±17.69 [AB]	46.98±14.43	46.65±10.00

Means ± SD of ejection fractions of group R, C and NR for each time period after meal.

[A] = significantly different ($p< 0.05$) from the group C.

[B] = significantly different ($p<0.05$) from the group NR

In addition, the numbers of patients of group R who showed a value of ejection fraction for each time period after meal above the upper limits or below the lower limits of the 99% CI of the healthy subjects group C, are summarized in Table 2. It is interesting to note that the gallbladder of 23 patients at 15' after meal have already ejected a significantly ($p<0.01$) higher than normal percent amount of bile and may be called "hyperkinetic gallbladder", whereas the gallbladder of 9 patients at 60' after meal did not.

Table 2

	Group C	Group R	
Time	99% CI	above the CI upper limit	below the CI lower limit
15'	34.74 – 49.64	23	14
30'	40.45 -57.05	25	10
45'	38.57 – 56.65	25	6
60'	39.86 – 54.10	32	9

Number of patients of group R who showed a value of ejection fraction above the upper limits of the 99% CI (confidence interval) or below the lower limits, for each time period after meal.

Discussion

The study revealed that patients labeled with the diagnosis of IBS-D and responsive to cholestyramine showed a "hyperkinetic gallbladder" and about 17% a "hypokinetic gallbladder", while the remaining patients showed a "normokinetic gallbladder". In addition, about 44% of patients labeled with the diagnosis of IBS-D and responsive to cholestyramine showed a "hyperkinetic gallbladder" and about 17% a "hypokinetic gallbladder", while the remaining patients showed a "normokinetic gallbladder".

In patients with the "hyperkinetic galldladder", one may hypothesize that the arrival in the distal ileum of a marked amount of bile ejected by the gallbladder may overwhelm the absorptive capacity of the ileal mucosa and reach the colon, causing diarrhoea. In addition, bile acids in the intestine, in absence of the meal, stimulate intestinal propulsive contractions [20], that could contribute to a rapid arrival of an abnormal quantity of bile acids in the distal ileum and, if not completely absorbed, in the colon. A "gallbladder hyperkinesia" has been observed after vagotomy and in patients with Chagas disease [21-23], where the gallbladder after meal expels rapidly an increased quantity of bile which swamps the reabsorbing capacity of the distal ileum and induces diarrhoea [24]. This kind of diarrhoea is bile acid mediated, as demonstrated by the results of ^{75}SeHCAT test and by the good results obtained with cholestyramine treatment [25-28]. Nobody to date have considered a gallbladder excessively rapid emptying a patho-physiological factor in the pathogenesis of BAD. Previous researches with gallbladder stimulation by means of a high fat meal in IBS patients did not show at ultrasonography significant differences with respect to healthy subjects [13,14], whereas in another study an increase of residual volumes after 2 hours was found [15]. However, all these studies were performed on a very small number of patients. In another research [11] the author examined the gallbladder function of 19 patients with chronic postprandial diarrhoea by means of cholescintigraphy and intravenous administration of CCK, showing a "hypokinetic gallbladder" and, afterward, performed a treatment with cholestyramine with a remission of diarrhoea in all cases. We, on the contrary, firstly selected the IBS-D patients responsive to cholestyramine and then evaluated their gallbladder function. The difference in results could perhaps be due either to a different selection of patients with a greater percentage of females, a gender with a higher incidence of cholecystopaties than males, and to the use of intravenous CCK for gallbladder stimulation. This, in fact, does not activate the first phase of the gastro-colic reflex unlike our bromatologically equilibrated meal, that with its organoleptic characteristics stimulates before meal ingestion neuro-humoral and hormonal factors starting the gallbladder contraction. One may argue that the postprandial diarrhoea described in some IBS-D patients [29,30], may simply be due to an accentuation of the gastro-colic reflex [31,32], but the first phase of the gastro-colic reflex is blunted in IBS patients [33,34] and cannot explain the symptom of early postprandial diarrhoea of these patients. The latter may be due to an early gallbladder contraction of 15% following a cephalic stimulation through cholinergic mechanisms and neurogenic release of CCK [35-37].

In patients with a "hypokinetic gallbladder" it is difficult to explain the BAD. The presence of gallbladder stasis may suggest a pathophysiologic mechanism similar to that of cholecystectomy patients with BAD. Perhaps, the continuous interdigestive flow in the intestine of bile not stored in the already replete gallbladder could resemble that of cholecystectomy. However in the latter case there is also an increased bile production due to the lack of the inhibitory hormone FGF-19 produced by gallbladder [38]. Unfortunately it was not possible to measure FGF-19 in our patients, due to lack of availability of the test in our Hospital. In both cases, however, the interdigestive continuous flow of bile acids in the intestine is able to stimulate propulsive contractions [20] and could reach the distal ileum and the colon.

Conclusion

The present study showed that with a sonography technique nearly half of patients with postprandial diarrhoea previously diagnosed with IBS-D and responsive to cholestyramine had an abnormally precocious and increased gallbladder emptying after meal ("hyperkinetic or hyperactive gallbladder"), whereas in almost one-fifth gallbladder emptying was slower and scarcer than normal ("hypokinetic or hypoactive gallbladder"). The finding of an accelerated gallbladder emptying after meal does not conflict with, neither exclude, the existence of a FGF-19 deficiency, but explain the urgency that in some cases takes place during the meal ingestion, acting as a trigger. We believe that an abnormally precocious and increased or a slow and scarce bile ejection may play some role in the pathophysiology of idiopathic bile acid diarrhoea.

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