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An increased frequency of gallbladder stones in rheumatoid arthritis patients. Factors related to gallbladder stone formation

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ABSTRACT

Objective. *In this study, we determined the frequency of gallbladder stone (GBS) in rheumatoid arthritis (RA) patients and evaluated factors which could affect the formation of GBS – such as lipids and the GB motilities of the patients.*

Methods. *One hundred and thirteen RA patients (92F, 21M, mean disease duration: 8.9 years) and 117 healthy controls (94F, 23M) were included. In all RA patients, the clinical findings were recorded down; biochemical parameters and body mass index (BMI) were determined; and, abdominal ultrasonography was performed. In addition, 16 RA patients and 20 controls who were age-matched were randomly chosen for GB emptying monitored by ultrasound at 30-minute intervals for 2 hours after a mixed meal. Fasting volume (FV), residual volume (RV) and ejection fraction (EF) for all GBs were assessed.*

Results. *There was a tendency towards a higher frequency of GBS including cholecystectomy (11 GBS, 11 cholecystectomy, 19.5%) in RA patients when compared to controls (8 GBS, 5 cholecystectomy, 11.1%) ($p = 0.08$). The frequency of GBS plus cholecyctectomy in female RA patients (22.8%) was significantly higher than the control group (11.7%, $p = 0.044$). Logistic regression analysis showed that only older age was significantly associated with the presence of GBS in RA (OR:1.05, $p = 0.048$). There was no difference between the 2 groups in FV ($p > 0.05$). RV, PRV and EF were significantly higher in RA patients than in the control group ($p < 0.05$).*

Conclusions. *We diagnosed a higher frequency of GBS in female RA patients when compared to controls. Impaired GB motility in RA patients might contribute to an increased incidence of GBS development.*

Introduction

The prevalance of GBS varies in different countries and in different ethnic populations (1, 2). The main component of GBS in western countries is cholesterol (3). Advanced age, obesity, rapid weight loss, estrogen treatment and multiparity are the main factors leading to increased GBS formation (3, 4). In addition, the relationships of GBS formation with many diseases - such as diabetes and liver cirrhosis - and with drugs - such as cyclosporine, oral contraceptives - have been reported (5, 6).

Involvement of many extraarticular organs and side effects due to drugs are common in rheumatoid arthritis (RA) patients. Until now, only one study has reported an increased incidence of GBS in female RA patients (7). Data on whether non-steroidal anti-inflammatory drugs (NSAID) affect GBS formation are contradictory (3, 8).

In our case-control study, we determined the frequency of GBS and factors contributing to GBS formation in RA patients. In addition, we evaluated GB motility in a group of RA patients.

Materials and methods

One hundred and thirteen RA patients (92 females, 21 males) and 117 healthy controls (94 females, 23 males) were included into the study. Consecutive RA patients with longer than 6-month disease duration and who were hospitalized at the time of the study underwent upper abdominal ultrasonography to investigate for the presence of GBS. GBS were defined according to standard criteria (9). RA patients were diagnosed using ACR 1987 criteria (10). Apparently healthy subjects who were admitted to our hospital's general internal medicine outpatient clinic for check-up and who were age-and-sex-matched with our RA patients were taken as the control group. The control subjects had no history of rheumatologic disease, NSAID or corticosteroid usage. RA patients and controls who were heavy alcohol-users, on oral contraceptive or hormone replacement therapy and those using lipid-lowering drugs were excluded. All patients and controls have been residing in the same city, namely Edirne, in northwestern Turkey.

Data about medical history and clinical findings of RA patients were recorded down from hospital files. All patients and controls were questionned for history of typical biliary colic, previous GBS disease, cholecyctectomy, abdo-

minal surgery, and for the presence of other diseases (diabetes mellitus, liver disease, hemolytic conditions). They were also asked whether their first degree relatives had history of GBS disease.

For all RA patients, a disease activity score (DAS28) was calculated. Serum ALT, AST levels, lipid profiles (total cholesterol, triglyceride, HDL and LDL) and body mass index (BMI) were determined in each subject. Individuals with a BMI ± 30 kg/m^2 were considered to have obesity.

For GB emptying, age-matched 16 female RA patients and 20 female controls were taken. Their ages were also similar to those of the whole RA and control groups. The mean disease duration in RA patients who underwent GB emptying was 8.6 years, and this was not different from disease duration of whole RA group. All subjects fasted for 12 hours and real-time ultrasonographic studies were performed in the fasting state. Every subject was examined in either supine or decubitus position, and ultrasonographic images were obtained with 3.5-MHz transducer (Siemens, Sonoline Sienna GM-6600 Erlenger, Germany). GB volume was calculated by the sum of cylinders as described by Everson *et al.* (11). Then, GB volume was determined at 30-min intervals for 120 min after ingestion of a standard mixed meal consisting of two slices of bread (60 g), butter (10 g), two boiled eggs, and tea (300 ml) with sucrose (25 g). The test meal was equal to 500 cal and it was eaten in about 10 min. The immediate premeal GB volume was called as fasting volume (FV) and the smallest postprandial volume was called the residual volume (RV). Percent residual volume (PRV) was also calculated ((RV/FV)x100). The ejection fraction (EF) was calculated by using the following formula: ((FV-RV)/FVx100).

Results were expressed as mean ± SD. Data were compared with student's t test and chi-square test. The p value was considered significant when it was < 0.05. The relationship between GBS and factors effective on GBS formation were calculated by logistic regression analysis.

Table I. Baseline characteristics of RA patients and controls are shown.

	RA	Controls	p
n (F/M)	113 (92/21)	117 (94/23)	NS
Mean age (yrs)	53.6 ± 12.3	52.8 ± 9	NS
Birth number (n)	1.87± 0.9	1.91± 1.7	NS
Familial GBS disease, (%)	14.2	12.8	NS
D. mellitus, (%)	10.2	8.8	NS
BMI, (kg/m^2)	26.9 ± 3.8	26.4 ± 4.2	NS
Obesity (BMI30) (%)	40.5	37	NS
Triglyceride, (mg/dl)	115.8 ± 73.4	130 ± 76	NS
Total cholesterol, (mg/dl)	194 ± 46	197.4 ± 43	NS
LDL (mg/dl)	118 ± 52.3	118.5 ± 37.5	NS
HDL (mg/dl)	52.9 ± 16.8	50.3 ± 12.1	NS
ALT (mg/dl)	19.2 ± 13.7	22.7 ± 12.9	NS

The results are expressed as mean SD, NS: not significant.

Table II. The frequencies of GBS in female and male RA and control subjects.

	Female			Male		
	RA	Controls	p	RA	Controls	P
N	92	94		21	23	
Mean age (yrs)	52.9 ± 12	51.6 ± 9	NS	57.1 ± 14	58.1 ± 7	NS
GBS, n (%)	11 (12)	6 (6.4)	NS	0	2 (8.7)	NS
CC, n (%)	10 (10.9)	5 (5.3)	NS	1 (4.8)	0	NS
GBS+CC, n (%)	21 (22.8)	11 (11.7)	0.044	1 (4.8)	2 (8.7)	NS

NS: not significant, CC: cholecyctectomy.

Results

There were no significant differences between the RA and the control groups in age, sex, BMI, lipid profiles, and number of pregnancies. The demographic and clinical features of both groups are seen in Table I. The mean disease duration in RA patients after diagnosis was 8.9 years.

The frequency of GBS including cholecystectomy (11 GBS, 11 cholecystectomy, 19.5%) tended to be higher in RA patients when compared to the control group (8 GBS, 5 cholecystectomy, 11.1%); however, the difference was not significant (p = 0.08). The frequency of GBS plus cholecyctectomy in female RA patients (21 patients, 22.8%) was significantly higher than the control group (11.7%, p = 0.044). There was no significant difference among males (p > 0.05). The frequencies of GBS and cholecyctectomy in RA and control subjects according to sex are seen in Table II.

RA patients with GBS plus cholecyctectomy were older and more obese –although the differences were not significant- than others; and steroid usage was less common in this group (p > 0.05) (Table III). Disease duration, NSAID, DMARD intake, RF positivity and other laboratory parameters were similar between the groups (p > 0.05). In RA patients, aging was independently the only factor which was significantly associated with the presence of GBS by logistic regression analysis (OR: 1.05, 95%CI: 1.01-1.1, p = 0.048). The results of GB emptying studies revealed that there was no difference in FV between RA patients and controls (p > 0.05). Nevertheless, RV, PRV and EF were significantly higher in the RA group than in the control group (p < 0.05). The results of GB emptying are seen in Table IV.

Discussion

We found a higher frequency of GBS in our female RA patients when compared to controls. We did not analyze the constituents of GBS in our patients; nevertheless, Ito *et al.* (7) who diagnosed an increased frequency of GBS in their female RA patients reported that - based on ultrasonographic appearances

- all of the stones were cholesterol stones. Three factors are important in the pathophysiology of cholesterol GBS formation: the supersaturation of bile with cholesterol, mucin hypersecretion from GB mucosa and crystal nucleation, and GB hypomotility (3).

Many studies stated that GBS were more prevalent in females (2, 12, 13); and, this was claimed to be mediated by the effects of estrogens and/or progesterone on bile saturation (14). In addition, it was reported that progesterone caused relaxation of smooth muscle thereby leading to GB emptying (13). Similar to the results of a study reported by Ito *et al.* (7), we detected an increased frequency of GBS in female RA patients. However, the number of male RA patients was not high enough; and this might have led to a type 2 error. Pregnancy is one of the factors held responsible for increased GBS formation in females (4). In our study, the mean numbers of pregnancies in RA and control groups were similar; and none of the subjects were using oral contraceptives or hormone replacement therapy.

Studies about the prevalence of GBS in the normal population demonstrated that age was an important risk factor for the development of GBS (1, 2). There was a trend towards a higher mean age in our RA patients with GBS; in the meanwhile, logistic regression analysis revealed that aging was an independent risk factor for GBS formation. The associations of diabetes and liver cirrhosis with GBS are known; however, we did not observe any significant contribution of diabetes on GBS formation.

High serum triglyceride and low serum HDL levels are risk factors for GBS formation (15). Another well-known risk factor is obesity (4). Although the differences were non significant, our RA patients with GBS were more obese and had higher serum triglyceride levels than those without GBS. Ito *et al*. (7) reported that older age and hypercholesterolemia were more frequent among RA patients with GBS than in others. As a result, obesity and hyperlipidemia might have partially contributed to the higher frequency of GBS in female RA patients.

Table III. Comparison of clinical and laboratory variables between RA patients with GBS plus cholecyctectomy and RA patients without GBS.

	RA with GBS plus CC	RA without GBS plus CC	P
F/M	21/1	71/20	0.07
Mean age (yrs)	57.6 ± 10.8	52.7 ± 12.5	0.09
Disease duration (yrs)	8.8 ± 8.9	8.9 ± 10	NS
Familial GBS disease, n (%)	4 (18.2)	12 (12.1)	NS
D.mellitus, n (%)	13.6	8.8	NS
Sjögren's syndrome, n (%)	27.3	18.7	NS
NSAID usage, n (%)	18 (81.8)	75 (82.4)	NS
MTX usage, n (%)	9 (40.9)	44 (48.4)	NS
Sulphasalazine usage, n (%)	7 (31.8)	27 (29.7)	NS
HCQ usage, n (%)	3 (13.6)	18 (19.8)	NS
Steroid usage, n (%)	8 (36.4)	52 (57.1)	0.08
Erosive disease, n (%)	9 (40.9)	52 (57.1)	NS
Obesity, n (%)	13 (59.1)	35 (38.5)	0.07
RF positivity, n (%)	11 (50)	42 (46.2)	NS
CRP (mg/dl)	2.6 ± 3.7	3.4 ± 5.6	NS
Mean DAS28 score	4.09 ± 0.8	4.24 ± 1.1	NS
Tryglyceride, (mg/dl)	142.1 ± 118	104.7 ± 51.5	0.15
Total cholesterol (mg/dl)	197.6 ± 39	191.4 ± 47.4	NS
LDL (mg/dl)	111.9 ± 38.3	119.4 ± 57.2	NS
HDL (mg/dl)	57 ± 21.4	52.3 ± 15.7	NS

NS: not significant, CC: cholecyctectomy, MTX: methotrexate, HCQ: hydroxychloroquine

Table IV. The clinical features of RA and control subjects who underwent GB motility evaluation and values for GB motility.

	RA	Control	p
F/M	15/1	18/2	
Mean age (yrs)	52 ± 8.7	51 ± 11	NS
Disease duration (yrs)	8.6 ± 10.3	-	-
Fasting volume (ml)	21.7 ± 6.2	19.8 ± 8.6	NS
Residual volume (ml)	7.15 ± 3.6	4.45 ± 2.4	0.011
PRV (%)	35.2 ± 17.8	24.2 ± 13.3	0.042
Ejection fraction (%)	64.8 ± 17.8	75.8 ± 13.3	0.04

PRV: percent residual volume.

In some experimental animal models, NSAIDs have been shown to prevent GBS formation (16). There are also data in favour of this in human beings (17, 18). Although the mechanism is not known for certain, it was suggested to be associated with the inhibition of prostaglandin synthesis (19). It was said that NSAIDs inhibited prostaglandin-related GB mucin secretion and GBS formation (8, 20). Therefore, NSAIDs were used for GBS prophylaxis (3). Although the initial results were promising, studies performed later could not demonstrate the GBS-preventive effect of NSAIDs (7, 8, 21). In our study, NSAID usage did not differ between RA patients with and without GBS. As at least 80% of our patients were using NSAIDs, we might say that NSAIDs do not have any GBS-preventive effect. One interesting result of our study was that there was a trend towards less steroid usage in RA patients with GBS. We normally expect steroids to affect the lipid profile negatively, thereby causing a higher frequency of GBS. Our RA patients with GBS used less steroids this was probably because they had less active disease with less erosivity, lower CRP levels and DAS28 scores, and less use of MTX.

Gallbladder is mainly innervated by the autonomic nervous system; the vagus nerve provides parasympathetic innervation and the splanchnic nerves provide sympathetic innervation to the GB (22). Some studies pointed out that GB stasis and difficulty in emptying were important factors which increased GBS

formation (23). This mechanism is held responsible especially in situations like diabetes mellitus, hyperglycemia, pregnancy, progesterone usage and total parenteral nutrition (24, 25). It was reported that there was autonomic nervous dysfunction in RA, and that there were antibodies against autonomic nervous structures (26, 27). In addition, it was reported that there was elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease (28). In our study, our RA patients had impaired GB emptying and decreased RV and EF.

It was stated that NSAIDs inhibited lithogenity by preventing PG-related GB hypomotility (29, 30). It was also reported that NSAIDs had minimal effect on biliary motility in normal subjects and that they improved GB emptying in subjects with GBS (31). It was demonstrated that indomethacin increased postprandial GB emptying (29); however, contrary results were obtained in animal studies (16). In our study, most RA patients who underwent GB emptying examination were using NSAIDs regularly; and their results were not different from others. There seems to be no relationship between NSAID usage and impaired GB emptying in our RA patients. Although we are unable to explain the mechanism exactly, the tendency to impaired GB motility in our RA patients might be responsible for the higher frequency of GBS formation.

One of the limitations of our study was that all the patients were hospitalized at the time of the study, and this might have introduced a selection bias. This sample might not be representative of the whole RA population. Another drawback of our study was that we could not perform the biochemical analysis of the constituents of GBS. As the design of our study was cross-sectional, cholecyctectomy and analysis of GBS were not undertaken in RA patients with GBS.

Our study investigated the frequency of GBS in RA patients. As a result, we observed that the frequency of GBS disease including cholecyctectomy were significantly increased in our female RA patients. The impaired GB emptying in our female RA patients might have contributed to the higher frequency of GBS in this patient group.

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