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New Approaches to Studying Prevalence Gallstone Disease

Abstract

The aim — predicting the growth of gallstone disease based on the study of the dynamics of the incidence of the liver. **Materials and methods.** In clinical conditions, 98 patients (62 women and 36 men, average age 43.4 ± 3.3 years (21-60)) with various chronic liver diseases were examined. Anamnesis, clinical and laboratory data were used to verify the diagnosis. In portions "B" and "C" of bile obtained by multifractional duodenal sounding, the total concentration of bile acids, cholesterol and phospholipids was determined, and lithogenicity indices of bile were calculated: cholate-cholesterol and phospholipid-cholesterol coefficients. The results were analyzed using Microsoft Excel 2010 and PSPP statistical processing programs. The next stage of the work was the analysis of statistical indicators of the general and primary liver morbidity in the Udmurt Republic over the past 10 years (2008-2018). The study applied statistical forecasting methods. Models were built in the Microsoft Excel 2010 program in a polynomial trend. **Results.** In 52 (53,1%) examined patients, ultrasound examination of the gallbladder were signs of biliary sludge. Microscopic examination of bile 71 (72,6%) patients had crystals of cholesterol and calcium bilirubinate, which is evidence of stage I gallstone disease. In all patients with biliary sludge, a violation of the biochemical composition of bile was noted — a decrease in the concentration of bile acids and phospholipids, an increase in the concentration of cholesterol, a decrease in cholesterol and phospholipid-cholesterol coefficients. When studying statistical indicators over the past 10 years, a higher general and primary incidence of liver diseases in the Udmurt Republic was noted than in the Russian Federation as a whole. Based on the results of trend modeling, a significant increase in the total and primary liver morbidity is predicted both in the Udmurt Republic and in the Russian Federation. **Conclusion.** Summarizing the data obtained, it can be noted that over the past 10 years (from 2008 to 2018) among the adult population of Udmurt Republic, a clear tendency has been revealed for an increase in the general and primary incidence of the liver. As the results of trend forecasting showed, an increase in the incidence of the liver will continue in the coming years. With liver pathology, bile secretory function suffers, as a result of metabolic processes, bile produces supersaturated cholesterol, which is the basis for stone formation in the gall bladder. A study of the dynamics of liver disease allows predicting an increase in cholelithiasis in the coming years. Despite the fact that the asymptomatic course of cholelithiasis is often quite observed, if this disease is not diagnosed and the preventive treatment of stone formation is not carried out in a timely manner, this leads to the development of serious complications.

Key words: *gallstone disease, chronic liver disease, prognosis, trend modeling*

Conflict of interests

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BA — bile acids, BS — biliary sludge, CCC — cholate-cholesterol coefficient, CL — cholelithiasis, CS — cholesterol, PCR — phospholipid-cholesterol ratio, PL — phospholipids, UR — the Udmurt Republic, US — ultrasound

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In recent years, there has been a steady increase in the incidence of cholelithiasis (CL) — approximately twofold every ten years in all countries. More than 10% of the world population already has CL [1, 2]. It should also be noted that the incidence of CL varies greatly and depends on a number of contributing factors (place of residence, ethnic and national peculiarities, etc.) [3, 4].

The incidence of CL among residents of the Udmurt Republic (UR) from 2010 to 2015 was as follows: in men — on average 97.3 per 100 thousand of the adult population, in women — 333.8 per 100 thousand of the adult population. Thus, CL occurs in one in every 13–15 men and one in every 3–4 women. The ratio by gender in UR is 5:1, predominantly in women [2, 4]. Mortality from CL stands at 1.9 per 100 thousand adults.

CL can be considered a socially significant disease due to its high prevalence, steadily rising incidence in all developed countries of the world, and its effect on the working-age population [5]. Nevertheless, it is difficult to identify actual parameters of CL prevalence for several reasons. First of all, CL is often asymptomatic: 15–20% of the adult population have gallstones, while only 4 to 20% of them exhibit clinical signs of the disease [3, 6–9]. Also, cholelithiasis is diagnosed as a nosological form only at stages II and III (stage of lithogenesis and stage of recurrent episodes of chronic calculous cholecystitis).

It is known that bile does not become lithogenic in the gallbladder. It is excreted like that from the liver. Liver diseases often lead to the abnormal composition of bile and to the development of biliary sludge (BS), which is a sign of the early (pre-stone) stage of cholelithiasis [1]. In connection with the abovementioned facts, studying the prevalence of liver diseases will help to determine the prognosis for CL incidence.

The objective of our work was to predict the rise in the incidence of CL based on studying changes in the incidence of liver disease.

Materials and Methods

Ninety-eight patients (62 women and 36 men, average age 43.4 ± 3.3 years (21–60)) with different chronic liver diseases were examined in a clinical setting.

This study was performed at the Department of Internal Medicine of the Federal State Budgetary Educational Institution of Higher Education "Izhevsk State Medical Academy" (ISMA) of the Ministry of Health of the Russian Federation at the Budgetary Educational Institution of the Udmurt Republic "I. B. Odnopozov City Clinical Hospital No. 8 of the Ministry of Health of the Udmurt Republic" and the Budgetary Educational Institution of the Udmurt Republic "City Clinic No. 1 of the Ministry of Health of the Udmurt Republic" from 2016 to 2020. The patients were examined after obtaining voluntary informed consent and approval by the Committee on Biomedical Ethics of the Federal State Budgetary Educational Institution of Higher Education ISMA of the Ministry of Health of Russia (minutes of the Meeting No. 529 of January 24, 2017).

Inclusion criteria:

1. Male and female patients aged 20 to 60 years with liver disease.
2. Signed informed consent.

Exclusion criteria:

1. Pregnancy and lactation.
2. Chronic diseases in decompensation stage.
3. Oncological diseases.
4. Mental disorders.

Clinical and instrumental examinations and laboratory tests were used to verify liver diseases. All patients underwent tests for bilirubin and blood transaminases (Cormay Livia ACCENT 300 analyzer, Poland), markers of viral and autoimmune hepatitis (enzyme-linked immunosorbent assay); ultrasound of the hepatobiliary system was performed using the Mindray DC-60 Exp device (China). Seventy-six (77.6%) patients underwent liver elastography using the AIXPLORER analyzer (Supersonic Imaging SA, Aixen-Provence, France), 58 (59.2%) patients underwent the FibroMax test to exclude liver fibrosis and cirrhosis. Abdomen CT for 43 (43.9%) patients was performed using General Electric LightSpeed VCT XT 64 (China) device. Multifractional duodenal sounding with subsequent macroscopic and microscopic examination of bile, determination of its physical and colloidal properties and biochemical composition was performed for all of the examined patients.

Cystic and hepatic portions of bile obtained by multifractional duodenal sounding were analyzed for total content of bile acids (BA), cholesterol (CS) and phospholipids (PL); bile lithogenicity factors were calculated: cholate-cholesterol coefficient (CCC) and phospholipid-cholesterol coefficient (FCC) [10].

Verification of chronic hepatitis was carried out using ultrasound of the hepatobiliary system, increase in blood transaminase activity, positive markers of viral and autoimmune hepatitis, and alcohol consumption in hepatotoxic doses (in history). Diagnosis of liver cirrhosis was established based on cirrhotic changes in the liver according to the results of ultrasound, grade 4 fibrosis (F4) based on elastography results according to the Metavir scoring scale, typical changes in blood biochemistry.

All of the results were compared with those of the control group; the latter included 52 healthy individuals aged 21 to 60 years (36 women and 16 men, average age 40.1 ± 4.6 years).

The results were analyzed using statistical software Microsoft Excel 2010 and 2010 and Pspp 1.0.1. Distribution normality was checked using Kolmogorov—Smirnov and Shapiro—Wilk tests. The study used parametric statistical methods since the distribution was close to normal. The results are presented as M ± SD. Student's test (T) was used for assessing the statistical significance of differences (p) and comparing quantitative parameters in the two groups. Differences between the groups were deemed statistically significant at $p < 0.05$.

Clinical examination of patients was followed by studying statistical parameters of general and primary liver disease incidence in the UR over the past 10 years (2008–2018). To this end, the analysis of official statistical data was carried out, including parameters taken from the informational and analytical collection "Basic parameters of public health in the Udmurt Republic" prepared by the Budgetary Educational Institution of the UR "Republican Medical Information and Analytical Center of the Ministry of Health of the Udmurt Republic" [11].

This study used statistical forecasting (trend modeling). Models were built using Microsoft Excel 2010 in a polynomial trend. Model adequacy was checked using the *R criterion:*

$$R^2 = 1 - \frac{SSE}{SST},$$

where

$$SSE = \sum \left(Y_i - \hat{Y}_i\right)^2$$

and

$$SST = \left(\sum Y_i^2\right) - \frac{\left(\sum Y_i\right)^2}{n}$$

where Y_i — actual value of the studied parameter, $\hat{Y}_i$ — value of a model, $i = 1 \ldots n$

Results

Thirty-six of the examined patients (36.7%) were diagnosed with hepatic steatosis, 42 (42.9%) had chronic hepatitis (of alimentary (57.1%), viral (31%) and autoimmune (11.9%) etiologies), 20 (20.4%) had cirrhosis in the compensation stage. The predominant disease of the digestive system was the pathology of the small intestines and pancreas (Table 1).

This is due to the close anatomical and morphological position of the organs in the hepatobiliary and pancreatic regions, which leads to common pathogenetic mechanisms of diseases. Among concomitant pathologies of other organs and systems, cardiovascular diseases were the most common — in 38 (39.2%) patients. This can be attributed to

Table 1. *The frequency of concomitant diseases in examined patients with cholelithiasis*

Concomitant diseases	The absolute number	%
Gastroesophageal Reflux Disease	57	14,4
Chronic gastritis (including erosive)	48	12,1
Reflux gastritis	88	22,2
Chronic duodenitis (including erosive)	67	16,9
Duodenal ulcer	108	27,3
Chronic pancreatitis	113	28,5
Irritable bowel syndrome	63	15,9
Hypertonic disease	28	28,6
Coronary heart disease	15	15,3

atherogenic dyslipidemia, one of the common pathogenetic mechanisms of cardiovascular pathology, liver diseases and CL [12].

Gallbladder ultrasound in 52 (53.1%) of the examined patients revealed signs of biliary sludge (BS) (microlithiasis, putty-like bile). Microscopic examination of bile revealed crystals of cholesterol (CS) and calcium bilirubinate in 71 (72.6%) patients, which is a sign of CL stage I (pre-stone).

Also, all patients with BS demonstrated abnormal physical and chemical properties of B and C bile portions, as shown in Table 2.

Levels of bile acids (BA) and phospholipids (PL), which are stabilizers of bile colloidal properties, were low in comparison with the control group, while the CS level was high. Low bile lithogenicity coefficients, CCC and FCC, were also observed in the examined patients compared with the control group. Therefore, 52 (53.1%) patients with liver diseases and CL stage I (pre-stone) had a very high probability of gallstone formation.

The past ten years have seen a rapid increase in the incidence of liver diseases: in the Udmurt Republic, the incidence of liver diseases increased

Table 2. *Indicators of the biochemical study of bile in examined patients with biliary sludge*

Indicators	Group of control (n=52) M±SD	Patients with liver diseases (n=98) M±SD	Generally accepted norms	
Cholesterol (mmol/l)				
Portion B	7,56±0,07	26,34±0,65	5,2-15,6	0,00082
Portion C	3,63±0,06	16,21±0,52	1,3-2,8	0,00013
Bile acids (mmol/l)				
Portion B	54,33±0,14	30,22±0,47	57,2-184,6	0,004
Portion C	20,76±0,20	15,24±0,58	17,4-52,9	0,006
Phospholipids (mmol/l)				
Portion B	3,90±0,03	1,98±0,05	3,2-4,1	0,00035
Portion C	0,39±0,003	0,23±0,02	0,35-0,4	0,00042
Cholato-cholesterol coefficient (units)				
Portion B	7,15±0,07	1,52±0,10	8,5-7,8	0,00031
Portion C	6,14±0,10	1,13±0,05	7,1-6,3	0,00063
Phospholipid-cholesterol coefficient (units)				
Portion B	0,51±0,01	0,10±0,01	0,61-0,26	0,00052
Portion C	0,11±0,001	0,04±0,003	0,26-0,14	0,00012

Note: n — number of observations; ρ — the significance of differences between the indicators in the control group and in patients with liver diseases

Table 3. *Dynamics of the general incidence rate per 100 thousand population for liver diseases*

Class of diseases	Observed Dates (year)										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Liver Diseases in the Udmurt Republic	461,6	444,5	429,0	464,7	480,1	479,0	623,4	641,9	774,7	821,1	783,6
Liver diseases in the Russian Federation	349,0	357,1	360,9	365,3	370,0	379,5	391,9	398,6	416,1	428,0	441,4

Table 4. *Dynamics of the primary incidence rate per 100 thousand population for liver diseases*

Class of diseases	Observed Dates (year)										
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Liver Diseases in the Udmurt Republic	57,2	46,8	44,4	48,3	38,1	43,4	78,3	149,1	113,2	144,6	125,5
Liver diseases in the Russian Federation	53,5	54,9	55,5	56,6	56,5	58,6	63,0	69,9	72,8	73,6	71,4

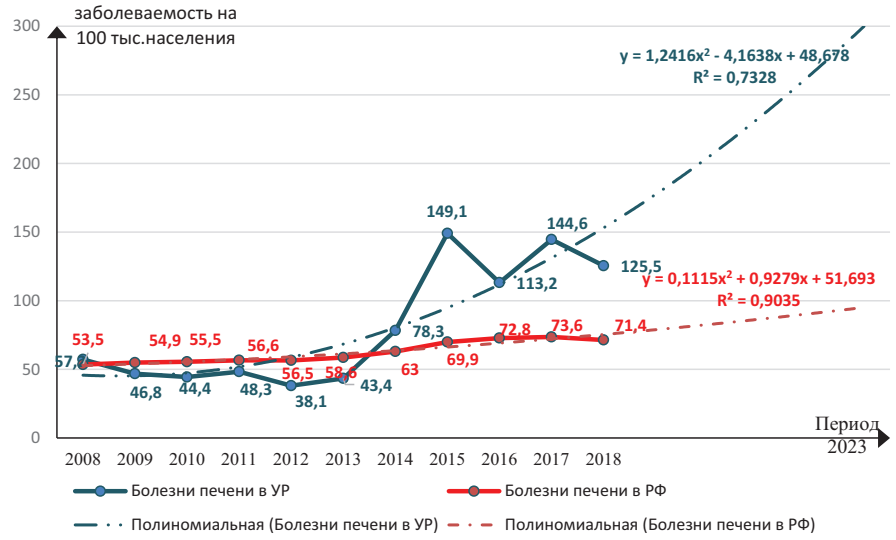

Figure 1. *Prediction for 5 years of the dynamics of the primary incidence of liver diseases in the Udmurt Republic and the Russian Federation (per 100 thousand population)*

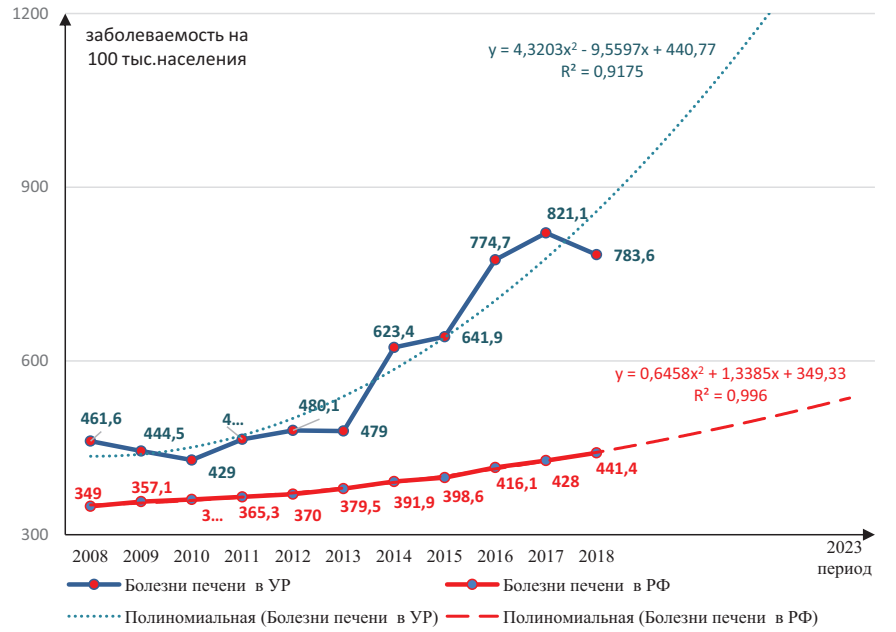

Figure 2. *Prediction for 5 years of the dynamics of the general incidence of liver diseases in the Udmurt Republic and the Russian Federation (per 100 thousand population)*

by 1.69 times, and in the Russian Federation by 1.26 times. The annual increase in the overall incidence of liver diseases in the Udmurt Republic ranged from 3.2% to 23.16%, in the Russian Federation — from 1.05% to 4.2%. During this period, the primary incidence of liver diseases in the Udmurt Republic increased at an even faster pace: by 2.19 times; in the Russian Federation, this figure was no more than 1.33 (Table. 3, 4). From 2008 to 2018, the primary incidence of liver diseases accounted for 7.9% to 23.2% of the overall incidence in the Udmurt Republic.

The trend modeling method shows that in the near future, a significant increase in the overall and primary incidence of liver diseases is expected both in the Udmurt Republic and the Russian Federation as a whole (Fig. 1, 2).

Discussion

The higher incidence of liver diseases in the Udmurt Republic in comparison with the Russian Federation as a whole can be explained by the worse economic situation compared to neighboring regions and, as a result, a greater number of risk factors for hepatic steatosis (diet dominated by flour-based food and sausages, stress-induced eating and alcohol consumption) [12]. The resulting high burden of liver diseases is accompanied by an increase in the incidence of CL since the impaired bile formation function of hepatocytes and the production of lithogenic (supersaturated cholesterol) bile are considered among the primary links involved in the pathogenesis of cholesterol cholelithiasis [13, 14]. The oversaturation of bile with cholesterol

is a consequence of abnormal complex metabolic processes in the liver; primary among said processes are the increased activation of hydroxymethyl-glutaryl-coenzyme-A reductase, which contributes to increased formation of cholesterol, or decreased activity of cholesterol-7-alpha-hydroxylase, which leads to reduced bile acid synthesis [15].

The results are consistent with published data [5]: the level of BA and PL, which are the stabilizers of bile colloidal properties, was low in the hepatic portion of bile, while the CS level was high. As a result, there was a decrease in bile lithogenicity coefficients (CCC and FCC).

Already oversaturated bile is transported to the gallbladder from the liver as a part of micelles and vesicles. The role of the gallbladder in the stone formation processes is undeniable: with a good functional state of the gallbladder and as a result of its contraction, all agglomerated vesicles and micelles enter the duodenum with bile flow; when gallbladder contractility decreases, subsequent crystal growth and BS formation begin [7]. Nevertheless, factors associated with functional disorders of hepatocytes and leading to bile oversaturation are fundamental in triggering lithogenesis [16].

Consequently, the results of studying the incidence of liver disease can be the determining parameters in predicting the incidence of CL. We think that all patients with liver disease require early detection of CL (ultrasound, multifraction duodenal sounding with subsequent macroscopic, microscopic examination of bile, determination of its physical and colloidal properties and biochemical composition), which is often neglected today.

Conclusion

In brief, the past ten years (2008–2018) have seen a clear trend of rising overall and primary incidence of liver diseases among the adult population of the Udmurt Republic. Results of trend forecasting showed that the increase in the incidence of liver diseases will continue in the coming years. Liver disorder affects the bile secretory function: bile oversaturated with cholesterol is produced as a result of disruption of metabolic processes, which is the cause of stone formation in the gallbladder.

Studying changes in the incidence of liver diseases enables to predict the increase in the incidence of cholelithiasis in the coming years. Although asymptomatic CL is very common, if stone formation is not diagnosed and preventive treatment is not carried out on time, it can lead to serious, often life-threatening, complications.

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

Khokhlacheva N.A. (ORCID ID: https://orcid.org/0000-0003-4634-2658): development of the concept and design of the study; verification of critical intellectual content; final approval of the manuscript for publication.

Kosareva T.S. (ORCID ID: https://orcid.org/0000-0003-1374-7894): collection, analysis and interpretation of data; substantiation and writing of the manuscript.

Lukashevich A.P. (ORCID ID: https://orcid.org/0000-0001-9424-6316): data collection, analysis and interpretation; substantiation and writing of the manuscript.

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