Mechanical parameters and chemical composition of gallstones in Egyptian population: an approach to assess amenability to nonsurgical treatment

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Background
This study aimed to describe the mechanical parameters and chemical composition of gallstones in Egyptian patients having gallstone disease to determine amenability to nonsurgical treatment. These parameters are related to environment, and to date, it is not available for patients living in the Middle East.
Materials and methods
Three hundred gallstone samples from 39 patients living in Egypt and presented for surgical treatment at Cairo University Hospitals and to the private practice of the first author were included in the study. They were indexed into soft, intermediate, and hard. Each was cut, polished, preserved, and stored in saline. Mechanical parameters were studied and then chemically analyzed to determine cholesterol, calcium, and bilirubin content. Trace metals and elements were determined by particle-induced radiographic emission.
Results
Except four, all cases were females (mean age: 45.9 years), having a single stone in 64.1%, and multiple in 35.9%. Stones were hard in 13 patients and soft in 26, with mean specific gravity of 0.86 (0.69–1.67). The percentage share for the three major components was as follows: cholesterol 70.8% (43–88), bilirubin 29.5% (10–66), and calcium 2.27% (0.02–7.5). The mean percentage for other elements was as follows: carbon 76.2, hydrogen 10.49, nitrogen 0.51 and sulphur 1.33. Trace metals – in micrograms – were copper (0.0019), iron (0.0108), potassium (0.015), magnesium (0.023), sodium (0.146), and zinc (0.012).
Conclusion
The patients are good candidates for nonsurgical treatment. In the light of the unique chemical composition of their stones, extracorporeal shockwave lithotripsy is the best. Oral dissolution needs a long time, whereas contact dissolution has no place. Apart from calcium, the concentration of basic elements and metals is of no value for planning treatment.

Keywords:
extracorporeal shockwave lithotripsy, gallstone dissolution therapy, non-surgical treatment

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Introduction

The rate of cholecystectomy has notably increased in Egypt, probably owing to increased awareness and improved governmental health services. Little is known about the composition of gallstones of our patients who live in a region different in environment and diet from western countries. Knowing the composition is essential for successful nonoperative therapies, such as lithotripsy and oral dissolution [1]. The major three constituents of gallstones are cholesterol, bilirubin, and calcium. Cholesterol is the most important and may amount to more than 70%, whereas calcium content will decide the hardness and radio-opacity of the stone. Other elements like iron, copper, phosphorus, magnesium, cobalt, and zinc and organic materials like carbohydrates, mucus, and cellular debris are uncommonly present. Accurate structural classification of gallstones could be made by gross inspection [2] as different compositions display various colors. There are three major types of stones: white, black, and brown. Mixed stones have different proportions of cholesterol and bilirubin. Black-colored and brown-colored stones contain bilirubin in large amounts in addition to small quantities of cholesterol. Pigmented stones are usually related to infection [3] and can be further subcategorized on the basis of minor variations in chemical composition into black and brown stones in a proportion of 28–31. After chemical analysis, stones may be re-classified according to their cholesterol content into cholesterol poor (<10% by weight), intermediate (10–75%), and

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rich (>75%). Overall, 30% of them contain calcium as a central matrix [4]. Pure cholesterol or pigment stones are uncommon. The latter are composed of calcium bilirubinate in a concentration of 40–50%, with a small amount of cholesterol in concentration of 3–26%. Some of these stones, the black type, are composed purely of calcium bilirubinate and usually associate increased concentrations of biliary calcium in hemolytic disease or liver cirrhosis [4]. In addition to standard chemical analysis, determination of stone composition is also possible by ultrasound, which is currently in use, sufficiently correlating with their compressive strength and microstructure pattern [5]. Mixed types with high ultrasonic velocity, less attenuation, and higher crushing strength were difficult to break in comparison with other types. In another study, gallstone composition was determined by infrared stereoscopic analysis with similar results [6]. Other methods can also be used but are not common, like energy-dispersive radiographic fluorescence and others. Crystallography or computed tomography is used also to sort stone cholesterol content into monohydrate, phosphates or palmitate, and to detect amorphous material. The latter may also provide discrimination between cholesterol and non-cholesterol stones *in vivo* and is recommended for measuring radiodensity of gallstones before litholytic therapy. Some authors compared magnetic resonance imaging with classical chemical analysis in 32 patients and obtained identical results, with the advantage of visualizing the structure of gallstones with accuracy and in detail [7]. Energy-dispersive radiographic fluorescence spectrometry is used to determine trace element concentration, particularly calcium and iodine [8].

For nonsurgical stone management, fragmentation by extracorporeal shockwave lithotripsy (ESWL) may be appropriate for patients having solitary stones less than two centimeters in diameter. This may be combined with oral bile acid treatment or followed by surgery. The mortality rate for lithotripsy is essentially zero, but pain and pancreatitis were sometimes reported. Moreover, some of the fragments may not clear off the bile duct and can cause problems later on. In contradistinction to surgery, which has 21–47% incidence of postcholecystectomy symptoms, abdominal complaints disappear after ESWL although anatomical structures are left intact [9]. The symptomatic success rate in both is equal and ranges between 72 and 95%. Oral dissolution therapy uses bile acids in pill form to dissolve gallstones and may be used in conjunction with lithotripsy. Ursodeoxycholic acid, and chenodiol are the standard oral bile acids used for dissolution, but the first is preferred because of its safety and insignificant adverse effects. As a long-term treatment for patients having small cholesterol stones (<1.5 cm in diameter), oral dissolution appears to reduce the risk of biliary pain and acute cholecystitis, but recurrence is common. Pigment stones are not suitable for such therapy [10]. Contact dissolution therapy entails the injection of the organic solvent methyl tertbutyl ether into the gallbladder through a percutaneous catheter [11]. The stones begin to dissolve within 5–12 h and completely disappear within 1–3 days. Serious adverse effects are reported, and the commonest is severe burning pain. However, such therapy is very successful and in the future may provide a safe and cost-effective means of treating gallstones without surgery. Laser fragmentation of gallstones needs higher energy pulses than that required for diagnostic purposes. With infrared laser, fragmentation is possible and depends on the pulse duration and duty cycle of the laser operation. The process is mechanical and not ablative acting by acoustic shock waves [12].

Materials and methods

Materials

Three hundred stones delivered from 39 patients living in Egypt and treated at Cairo University Hospital as well as the private practice of the first author were enrolled in the study. The study was conducted from July 2016 through December 2018. The patients presenting for elective cholecystectomy were randomly chosen, and their ages ranged from 31 to 66 years. All were nonobese, normolipidemic, and nondiabetic and had no evidence of parenchymatous kidney or liver disease. They were indexed according to their external appearance and then classified into three categories: soft (cholesterol), intermediate (bilirubinate), and hard (mixed).

Methods

After taking the approval of the Ethical Committee, gallstones were extracted during surgery, 25 laparoscopic and 14 open, and preserved under sterile conditions. The gallstone samples (>1 cm in diameter to facilitate manipulation, cutting and grinding) were stored in saline solution to maintain their biological conditions stable and to avoid structural alteration owing to drying. Using a hardness tester, the mechanical parameters of the stones were studied, and after desiccation, they were chemically analyzed to determine cholesterol, calcium, and bilirubin content. Metal content was studied using particle-induced radiographic emission.

Results

The study group included 39 patients [four (10.3%) males and 35 (89.7%) females], whose ages ranged

Table 1 Present study group: patients' and gallstone features

Study features			SG	Gallstone major components		
Age	Number patients	Number stones		Cholesterol	Bilirubin	Calcium
45.9	39	300	0.86	70.8	29.5	1.096
31–66			0.69–1.67	43–88	10–66	0.02–7.50

SG, specific gravity.

Table 2 Trace element concentration in micrograms (radiographic Emission)

C	H	N	S	
76.2	10.49	0.5	1.33	
14.77–83.92	0.66–12.47	0–3.05	0.08–1.6	
Cu	Fe	K	Mg	Na	Zn
0.0019	0.0108	0.015	0.023	0.146	0.012
0.002–0.014	0.005–0.097	0.002–0.095	0.002–0.222	0.035–0.439	0.001–0.170

Table 3 Stone composition in different geographic zones [22]

References	Location	Geographic Z	Number of patients	Number of stone	Cholesterol[#]	% composition mixed	Pigt*
Stewart *et al*. (1997)	S. Francisco	N. America		183	27	–	44
Angwafo *et al*. (1998) [16]	Yaoundé (Cameroon)	W. Africa	26				
Liu *et al*. (2002)	Taiwan	SE. Asia		100	35	–	33
Darko *et al*. (2000) [17]	Ghana	W. Africa				34	
Kim *et al*. (1999) [18]	Korea	SE. Asia			58.1	–	37.3
Kotwal *et al*. (1998) [6]	Himalayas (India)	S. Asia	487		*100*		
Kaufman *et al*. (1989)	W. Europe	W. Europe	65		71	–	29
Rambow *et al*. (1989)	W. Europe	W. Europe	28	29[(')]	62	–	38
Ravnborg *et al*. (1990)	Scandinavia	W. Europe	80		81[(w)]		–
Jayanthi *et al*. (2004)	Tamil	S. India	39	300	6.9	6.9	80
This study	Egypt	M. East			61.5	23.1	15.4

Include brown and black stones. M, Middle; N, North; Pigt, Pigment; S, South; SE, South East; W, West; Z, Zone. [#]Contains 70% cholesterol or more. [&]Children are not included. [(')]12 CBD stones are included. [(w)]For women only.

between 31 and 66 (mean age 45.9), years with ultrasound-proven gallstones. The majority (97.4%) was in the age range 31–60 years. Thus, most of the cases were middle-aged females (Table 1).

The stones were single in 14 (64.1%) patients and multiple in the rest. They were hard in 13 patients and soft in 26. The specific gravity ranged from 0.701 to 1.666, with an average of 0.86. Chemically, the average percentage values for the three major components were as follows: cholesterol 70.8% (43–88), bilirubin 29.5% (10–66), calcium 2.27% (0.02–6.49). For the trace element composition, the mean values are in shown in Table 2.

Discussion

Unless malignancy is suspected or its risk is present, half of the patients having gallstones are asymptomatic and should be left alone [13,14]. This decision is important for Egyptians where gallstones may be associated with liver fibrosis, cirrhosis, and/or viral hepatitis, rendering cholecystectomy hazardous owing to vascular adhesions [15]. Symptomatic patients need elective cholecystectomy, but other nonsurgical treatment options are now available. Those options uniquely depend on the physical features and chemical composition of the stones. With its three subtypes (pure, combination, and mixed), cholesterol stones tend to be more frequent in urban population probably owing to dietary factors [2]. However, the incidence of cholesterol stones is not the same in different geographic zones of the world (Table 3), where the dietary habits are different according to place-ignoring ethnic and economic differences. Economic standard also has no influence [3,19].

For example, the highest incidence of gallstones in the USA occurs in people of Mexican-American and

Native American descent, whereas other Americans of both sexes have the lowest incidence of gallstones. In developing and underdeveloped countries, the proportion of cholesterol stones varies widely from 34 to 60% [20]. In the present study, 61.5% of the stones are of the cholesterol type. This applies to Egyptian patients as well as to citizens of other Arab countries living in Egypt, with no detectable differences. This projects a possible universal incidence in Middle East patients owing to similarity of diet and climate. Although gallstone dissolution with the orally taken bile acid chenodiol was in common use, it carries ~50% recurrence rate within the first 5 years [1,21]. Overall, 21% of our patients were good candidates for it. They had small cholesterol stones and a functioning gallbladder compared with 15% only in the USA [21]. The poor dissolution rate (11–13.5%) reported in some studies may require extending treatment course more than the specified 2 years, limited only by the probable appearance of the adverse effects such as diarrhea, elevation of low-density lipoprotein cholesterol, and elevation of liver enzyme levels. The latter is particularly important in our patients who may have an associated liver disease.

Changing chenodiol to its 7-ß epimer ursodiol may be then suggested as it yields superior results with fewer adverse effects [21]. Unlike the kidneys, which are unobstructed by other organs from the back, the gallbladder lies buried deep within the body. This makes shock wave lithotripsy hazardous if not done properly, as misdirected shock waves may damage lung tissue. The gallbladder also has the disadvantage of having its opening to the tiny cystic duct near its top; moreover, the shattered pieces of the stones after the shock waves settle to the bottom by gravity making their drainage at a disadvantage. As most of our patients have gallstones with more than 70% cholesterol, the technique is a good alternative to surgery in 60% of them, if need arises. Exclusion criteria include patients having more than three stones, with size less than 0.5 cm or more than 3.0 cm in diameter. Radio-opaque stones in a nonfunctioning gallbladder are a contraindication. Presumably having a rapid effect (1–3 days), contact dissolution using methyl tertbutyl ether requires percutaneous or endoscopic access to the gallbladder. It needs specialized infusion equipment and the result is not predictable. To date, it may be considered experimental, and we do not recommend it for clinical use. Careful handling of the drug is needed as it is inflammable and toxic [11].

Conclusion

Once gallstones become symptomatic, surgical removal of the gallbladder is recommended. If nonsurgical options are looked for, ESWL is the best for our patients, in the light of the unique chemical composition of their stones. Oral dissolution therapy needs a very long time with high recurrence rate, whereas contact dissolution is still at an experimental level. Apart from the calcium content which affects fragmentation ability, the concentration of other trace elements in gallstones is of no value in planning treatment.

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Conflicts of interest

There are no conflicts of interest.

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