Author's response to reviews

Title: Predictors of gallstone composition in 1025 symptomatic gallstones from Northern Germany

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Author's response to reviews: see over
Dear Editors,

thank you very much for the thorough and constructive reviewer comments. We have addressed the criticisms and enclose the revised version. We hope that the manuscript is now suitable for publication in BMC Gastroenterology.

With kind regards,

Jochen Hampe
Point-by-point response to reviewers

Reviewer 1 (Karel van Erpecum)

1. We agree, that stone classifications that facilitate comparison to previous studies are important and have thus included this additional information: The two suggested references were included. The classification in the two suggested studies was done by using a threshold of >50% cholesterol content as a definition of cholesterol stones and a cholesterol content <20% as a definition for a pigment stone in the report by van Erpecum et al (Scan J Gastroenterology). The other reference (Trotman et al, Am J Dig Dis) utilized visual inspection of stones for classification in classifying yellow stones as cholesterol stones and dark stones as pigment stones. We deemed the former classification using the quantitative measures to be more easily transferable to our study and have thus adapted the criteria by van Erpecum et al and have included the appropriate numbers in the results. The respective text in the results section reads as follows:

The most common category is the dominant cholesterol stone (N=1847) in 86% of analysed specimens. These stones would contain 70% or more cholesterol as no other “main” substance was detected.

The comparison to the van Erpecum classification given in more detail in the discussion:

Previous studies from Western countries have also shown a predominance of cholesterol stones with 100% of patients under the age of 50 and 60% for older patients [35] in a Dutch study and 58% of cholesterol stones in a U.S. study using visual inspection of stones [18]. If the definition of a cholesterol stone from van Erpecum et al. is adapted to our data, 91.1% of stones contain 70% or more cholesterol (row 1 of Table 2). Some 2.2% of stones contain between 30 and 70% cholesterol and cannot be clearly put into the 50% categorisation (rows 2-3 of Table 2). Although no correlation of age of operation and stone composition was found, this might be due to the exclusion of old patients with gallstones. Thus, the high proportion of cholesterol gallstones in this investigation may be due to this age selection and also related to the same altered nutritional patterns that also lead to an increase in gallstone prevalence in susceptible populations.
2. We agree with the reviewer that the simultaneous application of both FTIR and chemical
determination of stone composition would be superior to the use of FTIR alone as in the
present study. In view of the large body of evidence that has compared chemical analysis to
FTIR, we have chosen to use FTIR in this study. This decision is described in the manuscript
as follows:
Fourier Transform Infrared (FTIR) spectroscopy has been established as a means to the rapid
assessment of the composition of gallstones [17] [18]. Only this methodology enabled the
analysis of the over 1000 stone samples and was thus used to investigate this large sample of
gallstones.
3. The reviewer required more information on the response data in percent. This was one
major point of criticism of Reviewer 2, please see the detailed response there.
4. We are very happy to move selected tables to an online supplement at the reviewers of
editorial discretion.

**Reviewer 2 (Ulf Gustavson)**

1. The reviewer requests more information on the recruitment process and on the response
rates. We agree that this information was indeed missing and have included this information
into the methods section. The respective new paragraph in the Methods section reads now:
In total, 9992 patients with operation records fulfilling the recruitment criteria were identified
and contacted by mail. Out of these, 1539 patients could not be contacted, because they had
either changed address or had died since the operation. Out of the remaining 8453 patients,
3174 patients participated in the overall study, i.e. provided questionnaires and a venous
blood sample. Out of these, 1074 patients were able to provide a gallstone. Part of this are 87
consecutive patients, who were directly recruited in the surgical department of the Kiel
university during 2005. Therefore, compared to the total operated population under or at the
age of 65, 10.3% provided a gallstone sample and complete clinical information (N=1025).
This corresponds to 32.3% of the participating patients.

2. Clearly, the samples are population-representative – we had contemplated possible
correction approaches with our epidemiologists and they confirmed that this could not be
achieved. We have stated this now also more explicitly in the discussion section. In response
to the second concern of the reviewer (stability of the stones as a confounding factor), we have looked at the 87 consecutive patients from 2005 from the Kiel university surgical department, where all patients operated were personally recruited by one of the investigators (C. Schafmayer). The stone composition (cholesterol versus pigment stones) did not significantly differ from the overall population (p>0.2). It is somewhat reassuring that the overall pattern of stone composition is correct, although these numbers are small and the university department clearly has a referral bias. We have also specifically mentioned the age restriction in the discussion now on request from reviewer 1, too.

One sentence has been inserted in the Results section:
The composition of the gallstones from the 87 directly recruited consecutive patients from the Kiel surgical department did not differ significantly from the overall population (p>0.2).

The respective paragraph in the discussion reads as follows:
The study has addressed a selected patient population and is thus not population-representative: This applies to the focus on younger patients who were operated at an age under 65, the overall response rate as compared to the total operated population of (10.3%) and to potential bias introduced through storage of gallstone samples by the patients. Here, the personality traits of the patients (orderliness etc.) and the stability of stones may have played a role. Stones that tend to disintegrate are more likely to be of rarer composition types (polysaccharide, certain calcium stones) and may have been thus underrepresented in this investigation. The overall pattern of stone composition was similar in the 87 consecutive patients directly recruited at the Kiel university hospital in 2005 thus indicating, that main findings may robust against these potential selection bias factors.

3. All typographical corrections were performed as requested.

4. A reference for the frequency of symptoms in gallstone disease was requested. Two references were included. Based on the published epidemiological study by Völzke et al., there is always about the same number of operated patients and silent gallstone carriers in their cross-sectional study.