Author's response to reviews

Title: Quality of life and health care consumption in primary care patients with elevated serum calcium concentrations in - a prospective, case control, study

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Author's response to reviews: see over
Answer to reviewers

MS: 7491079161114933 - Quality of life and health care consumption in primary care patients with elevated serum calcium concentrations in - a prospective, case control, study

Referee 1

Question/Comment: This is a very interesting study of an important topic that can be very useful in primary care setting. Just to find a hypocalcaemia independently of its cause must alert the general practitioner to take special measures.

Answer: We are delighted that the reviewer thinks this article is important and can be clinically useful in primary care.

Major comments

Question/Comment: However there is an important study limitation that authors must try to solve or at least to include in the study as the main study limitation. An elevated calcium concentration was defined as ≥2.56 mmol/l. It is well known that physiologic calcium is ionised calcium not total calcium, and hence hypocalcaemia can never be defined through the use of total calcium. As referred in table I ionised calcium was measured in the second investigation. Why was not measured in the first investigation? Probably the authors did not have ionised calcium technology availability. However, in a previous study the authors refer that albumin was also measured. Why hypercalcemia was not defined through the use of calcium corrected per albumin? I’m pretty sure that some of the patients included in the study as hypercalcemic in fact they were normocalcemic. It could explain why in some occasions and parameters there were not significant dereferences between normo and hypercalcemics patients. If authors have at its disposal serum albumin results in the first investigation, it would be necessary to reclassify patients and recalculate study results in view of the new classification of hypercalcemic patients. If not, at least, it must be stated as the main study limitation that has to be taken into consideration in future author studies. Ionised calcium requires a special technology and sample manipulation and that must be the reason.
Answer: The reviewer addressed an important question. In the first study, we unfortunately did not have ionised calcium as it was a retrospective study. Further, ionised calcium was an unusual (and expensive) test in Swedish primary health care in the 1990s. Only 38 ionised calcium were found in the medical records at Tibro health care center between 1992 and 2000. On the other hand, the number of analyses of serum calcium was 7,779. Calcium was corrected for albumin in the 75% of subjects who had that analysis performed simultaneously. Due to this, of course some misclassification was possible. To clarify this we added in the Method, (1st paragraph, line 5) “Calcium was corrected for albumin in the 75% of patients who had albumin analysed simultaneously”. In the Discussion, (9th paragraph, line 1) we have added the sentences “One limitation of this study was that the inclusion of the patients with elevated calcium concentration was based on a single measurement which was corrected for calcium in 75% of cases. This may have led to that some individuals with erroneously high calcium concentrations were included in the study.”

Question/Comment: PTH is not showed in the first investigation. Was not measured in the first investigation? But PTH is surely been measured in every patient. It would be interesting to be included in table I.

Answer: Analysis of intact PTH was introduced in 1994 at the clinical chemistry laboratory at Skövde hospital. This laboratory analysis was therefore unusual in the late 1990s in primary care. In the first investigation parathyroid hormone was measured in 23% of the patients with elevated calcium concentration (Dalemo S, Hjerpe P, Boström Bengtsson K. Diagnosis of patients with raised serum calcium level in primary care, Sweden. Scand J Prim Health Care. 2006; 24:160-5). We found in the first study that 10% of the patients had elevated PTH concentrations (≥65ng/l). The PTH concentration was analysed for all individuals in the re-examination, and these values are reported in Table 1.

Minor comments

Question/Comment: Abstract: Include in brackets n=127, n=254
**Answer:** We have changed the manuscript according to the reviewer’s recommendation.

**Question/Comment:** Figure 2 can be redundant to table 3.

**Answer:** Both reviewer have aspect on Figure 2, one of the has suggested us to change it to a histogram. We have also deleted the Table as recommended by reviewer.

**Question/Comment:** Bibliography must follow guidelines.

**Answer:** We have now changed the references according the BMC Family Practice instructions.

**Referee 2**

**Question/Comment:** Interesting case-controlled prospective study on the quality of life and health care consumption in patients with hypercalcemia detected in 1995 and followed for 10 years. Although, methodology is reasonable, I have several concerns the way it is described and a few other comments about the interpretation of the data for the authors to consider.

**Major:**

**General:**

**Question/Comment:** Since it is unclear how many of the original hypercalcemic cohort had primary hyperparathyroidism (PHPT) and of those, how many had parathyroidectomy (PTX), it is difficult to know if it is the high calcium or the disease causing it is responsible for the observation. If my calculations from the information in the discussion are correct, 46 patients had PHPT in the original cohort, half of whom had PTX. Thus 81 patients (127-46=81), had hypercalcemia due to causes other than PHPT (presumably cancer). If so, the entire premise that hypercalcemia is the cause of the abnormalities sounds too simplistic.
**Answer:** The reviewer address a very interesting issue. We think that it was difficult to know what caused the lower quality of life. There is a debate whether it is the elevated calcium concentration per se, the elevated parathyroid hormone in pHPT, other diseases connected with high calcium concentrations or other factors that affect patients' quality of life. Our conclusion from this study, however, was that physicians should be alerted when elevated calcium concentrations are found in patients to be able to take appropriate measures.

Our material was from primary care. In a previous study (Dalemo S, Eggertsen R, Hjerpe P, Jansson S, Almqvist EG, Bengtsson Boström K: Long-term follow-up of patients with elevated serum calcium concentrations in Swedish primary care. Scand J Prim Health Care 2013, 31:248-254) we have described that pHPT was the most common diagnosis, followed by seven different diagnoses, please see below the table from the article:

**Table.** Diagnoses of patients with elevated calcium concentrations found after second clinical examination and register investigation in 2009-2010.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hyperparathyroidism</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>Cancer</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Vitamin D medication</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Lithium treatment</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Transient thyroiditis</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Skeletal disease</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Unresolved elevated calcium</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>127</td>
<td>100</td>
</tr>
</tbody>
</table>

**Question/Comment:** Another way to analyse the data would be to explore any differences in QoL and other outcome variables between the 46 PHPT patients and the other 81 presumably non-PHPT patients.

**Answer:** In our study from primary care, there were many different underlying diagnoses to the elevated calcium concentration. The material is unfortunately too small for it to be meaningful to study the different diagnoses separately.
Cancer also causes impaired QoL. But in the follow-up study only 15 of the 127 patients had an underlying cancer disease.

**Question/Comment:** The separate analyses for men & women are interesting at best and uninformative at worst. As evident, at least to me, the majority had PTH-independent hypercalcemia (81 of 127), and thus used more hospitalisations and medications, died more frequently, and had low QoL scores than the normocalcemic patient cohort or the Swedish norms.

**Answer:** We do not agree with the reviewer in this case. There was a clear difference between men and women in morbidity and mortality described in the earlier publication (Dalemo S, Eggertsen R, Hjerpe P, Jansson S, Almqvist EG, Bengtsson Boström K: Long-term follow-up of patients with elevated serum calcium concentrations in Swedish primary care. Scand J Prim Health Care 2013, 31:248-254) so we do not think that it is without interest to study the sexes separately. pHPT is for instance a more common disease among women.

Specific:

**Question/Comment:** Abstract (Methods): it was mentioned that the participation rate was 86%. This should also be explicitly stated in the Methods section as well on page 5, para-1, line 1.

**Answer:** Following the recommendations of the reviewer we have added a sentence about the participation rate in the Method, (4th paragraph, line 1)

**Question/Comment:** Pg-4, para-3, Methods: it is unclear how the specific dates were selected (01/01/1998 to 12/08/2010, and 11/04/2003 to 12/27/2010). For inpatient calculations, data from 1967, approximately 18 years prior to the index cohort was started in 1995, was included. Please rewrite for clarity and provide rationale for going back to 1967.

**Answer:** The different time intervals were due to variation of registration in the registries. Our intention was to investigate morbidity as far back as we have records,
because we didn’t know how long the patients have had the elevated calcium concentrations. We additionally report hospitalisations from both 1967 and 1995 in Table 2. We have clarified this in the Method section (3rd paragraph, line 4).

**Question/Comment:** On page 6, para-2, Results last line: what does the two groups having similar values of PTH mean?

**Answer:** The group of patients with elevated calcium concentration had a mean PTH value of 68 ng/L and the group of patients with normal calcium concentrations had a mean value of 58 ng/L. This difference was not significant. We believe that the 20 patients with PTX contribute the PTH levels in the group with elevated calcium concentrations. We have clarified this in the discussion (5th paragraph, line 1).

**Question/Comment:** Page 8, the explanation for the decline in the serum calcium was due either to death or PTX is reasonable. However, looking at the figure it is unclear exactly what were the causes of death in 53 patients and how many of the remaining 63 patients with follow-up visit had PHPT; presumably 46 of the 63, and how many had PTX. Please clarify.

**Answer:** All patients with elevated calcium concentrations were studied both in the early 2000s and 10 years later in order to determine the underlying diagnoses to their elevated calcium concentrations. The diagnoses were described in an earlier study (Dalemo S, Eggertsen R, Hjerpe P, Jansson S, Almqvist EG, Bengtsson Boström K: Long-term follow-up of patients with elevated serum calcium concentrations in Swedish primary care. Scand J Prim Health Care 2013, 31:248-254). Please, also see the inserted figure below:
Figure. Diagnoses at follow-up in patients with elevated calcium concentrations, divided in subgroups Dead, Drop-out and those attended the Follow-up visit.

**Question/Comment:** Page 8, para-3: this information appears tangential. I am not aware of any relationship between hypercalcemia and menopause, parity, number of the teeth left etc. at least teleologically speaking.

**Answer:** We have deleted information about menopause, parity and number of teeth in the manuscript according the reviewers recommendations.

**Question/Comment:** Page 8, the authors acknowledged that many dropouts may be related to diseases severe enough not to participate. Please expand a bit more on exactly what condition(s) did they have?

**Answer:** Of the 11 drop-out patients six reported "do not want" as a reason for not taking part in the study. Many in this sub-group were young and the average age was 55 years. Further, in the drop-out group two patients had severe dementia, they lived in nursing homes and their families did not want them to participate in the study. Two patients stated they were too old and infirm to participate in the study, their average age was 84 years. We have changed in the manuscript to that "one third of the drop outs reported disease as a reason not to participate in the follow up" in the Discussion, (4th paragraph, line 8).

**Question/Comment:** Table-4: Could be deleted.
**Answer**: We experience Table 4 informative and has therefore chosen to retain it.

**Question/Comment**: Fig-1: Please include the proportion of patients with & without PHPT and indicate how many of the 63 at follow-up had PTX (please see my comment above).

<table>
<thead>
<tr>
<th></th>
<th>Dead 53</th>
<th>Drop-out 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pHPT 11</td>
<td>pHPT 5</td>
</tr>
<tr>
<td></td>
<td>Parathyroidectomy 5</td>
<td>Parathyroidectomy 1</td>
</tr>
<tr>
<td></td>
<td>Other diagnoses 37</td>
<td>Other diagnoses 5</td>
</tr>
</tbody>
</table>

**Follow-up visit 63**
- pHPT 30
- Parathyroidectomy 9
- Other diagnoses 24

**Answer**: We think that if you want to find reasons to lower QoL others than elevated calcium concentration you have to break it down in all the different diagnoses. In primary care, there are many underlying diagnoses to elevated calcium concentrations as opposed to what is the case of inpatient care, where pHPT and cancer dominate. We had eight different diagnoses, the groups probably become too small to demonstrate the differences.

Minor:
**Question/Comment**: Fig-2: I prefer paired histograms rather than connected symbols, which is really not correct.

**Answer**: We have replaced Figure 2 with a histogram.

**Question/Comment**: Finally, what is the incremental knowledge gained beyond what has been reported in your reference 12?
Answer: In the study referred, we examined the diagnoses in the medical records of patients with elevated calcium concentration between 1995 and 2000. In the current study we investigated QoL health care consumption in patients with elevated calcium concentration compared with patients with normal calcium concentrations regardless of their diagnoses. Patients with elevated calcium concentration had a low QoL and high health care consumption and our conclusion was that the physicians should be alerted so that these patients can be further investigated and cared for. This would probably be of benefit both for the individual and for the society. We have further emphasised this in the conclusion and now write “Elevated calcium concentration is therefore an important warning flag that should alert the physician to further investigate and care for the patient”, Conclusion (1st paragraph, line 6).

Question/Comment: Also I did not have access to your reference #2.

Answer: Please find the referred article attached to this mail.