Serum calcium is an independent predictor of quality of life in multiple myeloma

Wisløff F, Kvam AK, Hjorth M, Lenhoff S. Serum calcium is an independent predictor of quality of life in multiple myeloma.

Abstract: Bone disease is an important feature of multiple myeloma, and hypercalcaemia is a frequent complication of this disease. We examined the association between serum calcium and quality of life (QOL) scores of 686 multiple myeloma patients at the time of diagnosis. Data from two Nordic studies using the EORTC QLQ-C30 questionnaire were analysed by means of linear regression analysis and a curve fitting program. Serum calcium was independently related to appetite loss, nausea/vomiting and physical functioning (P < 0.001) and to cognitive functioning (P = 0.001), i.e. scores reflecting symptoms that are well known in non-malignant hypercalcaemia. In addition, we found a highly significant independent relationship between serum calcium and the scores for fatigue and pain (P < 0.001). Serum calcium appeared to be as strong a predictor for fatigue as the concentration of haemoglobin. A cubic model (y = a + bx^3) fitted the data slightly better than the simple linear model (y = a + bx) and suggested worsening QOL scores at levels of serum calcium above 2.5–3.0 mmol/L. Hypercalcaemia in patients with multiple myeloma seems to be associated with the same symptoms as in non-malignant hypercalcaemia. In addition, an increased level of serum calcium may aggravate the pain and fatigue caused by the skeletal disease itself.

Bone disease is an important feature of multiple myeloma. Interaction of malignant plasma cells with bone marrow stromal cells causes increased osteoclast activity mediated by a variety of osteoclast-activating factors including interleukin 1-β, interleukin-6, interleukin-11 and tumour necrosis factors (1). For this reason, multiple myeloma is often associated with osteolytic bone destruction, spontaneous fractures and skeletal pain. Hypercalcaemia is a frequent problem. From clinical experience and from textbooks in haematology, hypercalcaemia is known to be associated with appetite loss, nausea, fatigue, constipation, polyuria, confusion and impaired consciousness (2). However, these symptoms are non-specific and common in patients with malignant disease and may be caused by a variety of factors in addition to hypercalcaemia.

In primary hyperparathyroidism, the most frequent symptoms compared with a control group with non-toxic thyroid disorders were fatigue, weakness, polydipsia, polyuria, joint and bone pain, constipation, depression, anorexia and nausea (3). In another study, more than 50% of the patients reported fatigue, bone pain and muscle weakness (4).

At diagnosis, myeloma patients report a pronounced impairment of health-related quality of life (QOL) (5). We wanted to examine whether serum calcium, measured at diagnosis, was an independent predictor for QOL scores on domains in the EORTC QLQ-C30 questionnaire that correspond to the symptoms of non-malignant hypercalcaemia. Thus, we hypothesised that there was an association between serum calcium and the scores for appetite loss, nausea and vomiting, pain, fatigue, constipation, physical functioning and cognitive functioning. Thirst and polyuria are not measured by this instrument, and for obvious reasons, confusion and impaired consciousness cannot be reported by the patients themselves.

To examine our hypotheses, we used linear regression to analyse data from the time of diagnosis of 686 patients enrolled in population-based prospective trials in the Nordic Myeloma Study Group (NMSG) with integrated QOL studies. In
these analyses, we adjusted for other objective disease parameters registered at diagnosis. In the event that serum calcium turned out to be an independent predictor of one or more of these QOL domains, we wanted to estimate at what level(s) of serum calcium QOL scores deteriorated.

Materials and methods

Patients

Data from two prospective NMSG trials were pooled. In NMSG # 4/90, carried out in the years 1990–1994, melphalan/prednisone was compared with melphalan/prednisone + interferon α-2b in 583 newly diagnosed patients (6). A total of 521 (89%) of these patients took part in a QOL study, completing the EORTC QLQ-C30 questionnaire prior to the start of therapy and during follow-up (7). In the NMSG # 5/94 (1994–1998), 224 (79%) of 284 newly diagnosed patients <60 yr of age who received high dose chemotherapy with autologous blood stem cell support completed this questionnaire at diagnosis and during follow-up (8, 9). These studies were approved by ethics committees in Denmark, Norway and Sweden. Albumin-corrected serum calcium was measured at diagnosis in 686 of these 745 patients (Fig. 1). The characteristics of these 686 patients are shown in Table 1.

QOL questionnaire

The EORTC QLQ-C30 is a cancer-specific questionnaire with 30 items (10). It incorporates five functional scales (physical, role, social, emotional and cognitive), three symptom scales (fatigue, pain and nausea/vomiting), a global health and QOL scale and a number of single items (dyspnoea, appetite loss, sleep disturbance, diarrhoea and constipation) as well as a scale on the financial impact of the disease and its treatment. Version 1.0 was used in these two studies. The scores of the scales used as outcome variables in the present study are shown in Table 2, along with the corresponding symptoms commonly ascribed to hypercalcaemia.
Statistical analysis

Scores for each scale were calculated and linearly transformed so that the results ranged from 0 to 100 (11). For the functional scales and the single global QOL scale, higher scores represent higher levels of functioning whereas for the symptom scales and the single items, higher scores represent higher levels of symptoms or toxicity. For calculation of scale scores where items were missing, imputation of mean values of non-missing items was used.

The association between objective disease parameters and QOL scores was examined using linear regression. The following variables recorded at diagnosis were used as independent (predictor) variables: age (continuous), gender (dichotomous), haemoglobin concentration (g/L, continuous), serum creatinine (μmol/L, continuous), serum albumin (g/L, continuous), corrected serum calcium (mmol/L, continuous), serum β-2 microglobulin (mg/L, continuous), disease stage according to Durie and Salmon (1–3) and the extent of skeletal disease [scored on the basis of X-ray examinations as 1 (normal), 2 (limited disease) or 3 (extensive osteolytic lesions)]. Dependent (outcome) variables were the EORTC-C30 scores for appetite loss, nausea and vomiting, pain, fatigue, constipation, physical functioning and cognitive functioning.

A backward elimination variable selection procedure was used. The assumptions of the model were examined by analysis of residuals. As a large number of hypotheses were tested, a $P$ value less than 0.01 was required for statistical significance. For cases with missing values for independent variables (Table 1), listwise deletion was used, i.e. all cases with missing values for any of the variables in the regression were excluded from analysis. The tolerance was ≥0.80 for the independent variables in all the models, indicating that each independent variable had little of its variability explained by the other independent variables. Thus, multicollinearity was deemed not to be a problem. SPSS version 14.0 was used throughout (SPSS Inc., Chicago, IL, USA).

As age and gender are known to have a significant impact on haemoglobin levels as well as on QOL scores, these variables were included in all regression models (12). Attempts to fit the association between serum calcium and QOL scores to non-linear equations was performed with the table curve 2d version 5.01 program (SYSTAT Software Inc., Point Richmond, CA, USA). The function 'simple equations' was selected. This option fits non-linear power and exponential equations. To evaluate the fit, plots of residuals were inspected and the coefficient of determination ($r^2$) was calculated.

Results

Linear relationship of serum calcium to QOL scores, adjusted for age, gender and additional disease variables

There was a highly significant relationship between serum calcium and appetite loss at diagnosis (Table 3). In fact, serum calcium was the only disease parameter that was associated with appetite loss. Serum calcium was also related to nausea and vomiting; so was serum creatinine. Serum calcium was a predictor of pain; this effect was independent of the covariate extent of skeletal disease and serum creatinine (weaker). Furthermore, serum calcium, in addition to the extent of skeletal disease and serum albumin, was related to the fatigue score. Serum calcium also had an independent effect on physical functioning; so did the extent of skeletal disease and serum albumin. In addition, we found an effect of serum calcium on cognitive functioning. However, the extent of skeletal disease was the only independent variable that significantly predicted constipation.

Although these linear relationships were statistically highly significant, the $R^2$ of the models were low, ranging from 0.04 to 0.19, indicating that the ability of the models to predict an individual's QOL score from the values of the independent variables was low.

We further explored the effect of serum calcium, haemoglobin and the extent of skeletal disease on

<p>| Table 3. Multiple regression of objective disease parameters on quality of life (QOL) scores at diagnosis. Only statistically significant effects ($P &lt; 0.01$) are included |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>OQL scale</th>
<th>S-calcium</th>
<th>Skeletal disease</th>
<th>Haemoglobin</th>
<th>S-creatinine</th>
<th>S-albumin</th>
<th>$R^2$ of model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite loss</td>
<td>19.44</td>
<td>3.00</td>
<td>&lt; 0.001</td>
<td>11.46</td>
<td>1.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>7.18</td>
<td>2.00</td>
<td>&lt; 0.001</td>
<td>5.22</td>
<td>1.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>14.19</td>
<td>3.42</td>
<td>&lt; 0.001</td>
<td>11.46</td>
<td>1.75</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13.45</td>
<td>2.68</td>
<td>&lt; 0.001</td>
<td>5.22</td>
<td>1.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.31</td>
<td>2.50</td>
<td>0.001</td>
<td>5.22</td>
<td>1.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>12.49</td>
<td>2.93</td>
<td>&lt; 0.001</td>
<td>5.22</td>
<td>1.42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>−8.31</td>
<td>2.50</td>
<td>0.001</td>
<td>5.22</td>
<td>1.42</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
fatigue. We calculated from the beta coefficients of Table 3 that the estimated corrected difference in fatigue score between the group with normal skeletal X-rays and the group with extensive skeletal disease was $5.2 \times 2 = 10.4$ on the 0–100 scale. Because the groups with normal X-rays, limited skeletal disease or extensive skeletal lesions contained 18%, 45% and 38% of the entire patient population (Table 1), the medians of the two groups with normal X-rays and extensive skeletal disease corresponded to the 9th and 81st percentiles of the patient population, respectively. These percentiles corresponded to haemoglobin values of 82 and 123 g/L and serum calcium concentrations of 2.26 and 2.78 mmol/L. With a beta coefficient for haemoglobin of $-0.18$ (Table 3), the difference between these two percentiles amounts to 7.4 on the fatigue scale. Similarly, with a beta coefficient for serum calcium of 13.45, the expected difference in fatigue score between patients at these percentiles was 7.0. These differences are within a range (5–10% of the scale) that are usually considered clinically significant (13). As judged from the remaining beta coefficients in Table 3, the effect of serum calcium on appetite loss, pain and physical functioning was of a similar magnitude to the impact on fatigue, while the effect on nausea/vomiting and cognitive functioning seemed to be somewhat weaker.

Fitting of data to non-linear equations

We expected that the relationship between serum calcium and QOL scores might not be entirely linear. Based on clinical experience, increasing impact on QOL with values of serum calcium above the upper reference limit of approximately 2.60 mmol/L was anticipated. We attempted to fit the data to a number of non-linear equations, using the curve fitting program. The exponential function $y = a + bx^3$ gave a slightly higher $r^2$ than the simple linear function $y = a + bx$ (see legend to Fig. 2). The corresponding curves are shown for fatigue (Fig. 2) and physical functioning (Fig. 3). Very similar curves were obtained for the remaining QOL scores. The shape of these curves suggests increasing symptoms and decreasing functioning at serum calcium levels above 2.5–3.0 mmol/L.

Transformation of the serum calcium variable

Based on these findings, the multivariate regression was re-run after logarithmic or square root transformation of the serum calcium variable. The $R^2$ of the resulting regression models were almost identical to the values obtained with the untransformed variable (data not shown), suggesting that they did not explain an appreciably larger proportion of the variability of the dependent variables.

Discussion

As expected from clinical experience, we found statistically highly significant relationships between serum calcium and appetite loss, nausea and vomiting, that were independent of other disease variables. In fact, serum calcium was the only disease variable that was related to appetite loss. In addition to calcium, serum creatinine had an impact on nausea and vomiting, confirming the well-known association between renal failure and
Calcium and quality of life in myeloma

necessity. Rising serum calcium was related to impaired cognitive functioning. Somewhat surprisingly, there was no significant association between serum calcium and constipation, which is supposed to be a typical symptom of hypercalcaemia. Unfortunately, we do not have any data on the use of analgesics and laxatives, which may have had a bearing on this symptom.

In addition to these symptoms, patients with malignant skeletal disease and hypercalcaemia often report fatigue, pain and reduced physical functioning. One might suspect that these symptoms were due to the underlying malignant disease causing the skeletal disease and the hypercalcaemia. However, our findings suggest that in multiple myeloma, the impact of serum calcium on fatigue, pain and reduced physical functioning were independent of the extent of skeletal disease as evaluated by skeletal X-rays, and of other objective disease parameters. These observations are in accordance with results reported with the use of the SF-36 questionnaire in patients with primary hyperparathyroidism. Compared with a normal population, these patients had reduced scores for all QOL domains, most pronounced for physical functioning, bodily pain, physical and emotional role limitations and vitality (4). Most symptoms and QOL scores were improved after parathyroidectomy, particularly those related to pain, and physical functioning and vitality (4, 14).

In the present study, the independent effect of serum calcium on fatigue was of a similar magnitude as the concentration of haemoglobin. This finding suggests that hypercalcaemia substantially contributes to the fatigue in multiple myeloma and potentiates the effect of disease extent and anaemia (15). In contrast to haemoglobin, serum calcium was shown to have an association with several other QOL domains. The independent impact of hypercalcaemia on pain, seen also in patients with primary hyperthyroidism, indicates that in multiple myeloma, hypercalcaemia may increase the pain due to the skeletal disease itself.

In a study with 12 patients with squamous cell carcinoma complicated by hypercalcaemia, Iwase et al. (16) administered the EORTC QLQ-C30 questionnaire before and after the administration of calcium-lowering drugs. Six of the 10 subscales (appetite loss, nausea/vomiting, cognitive functioning, emotional functioning, fatigue and dyspnoea) improved after the anti-hypercalcaemic therapy, confirming that these QOL subscales may reflect symptoms of hypercalcaemia.

The results of the multivariate regression analysis show that it is quite likely that there is a linear component to the relationship between serum calcium and the scores for appetite loss, nausea and vomiting, fatigue, pain and physical functioning. However, clinical experience would lead us to expect that serum calcium levels within the reference range do not influence QOL scores, while values above the upper reference limit would have an increasing impact. To explore these relationships, we fitted the data to a large number of functions and also repeated the multivariate regression analysis after logarithmic and square root transformation of the serum calcium variable. The $R^2$ obtained in multivariate analysis after transformation of the serum calcium variable was virtually unchanged. The coefficient of determination ($r^2$) of the cubic curves fitted to the same data ($y = a + bx^3$) was only marginally higher than for the simple linear equation ($y = a + bx$). Thus, we cannot exclude the possibility that serum calcium concentrations within the reference range may have an impact on QOL. However, the shape of the cubic curves was more consistent with clinical experience, suggesting impaired QOL scores (lower functioning scores and higher symptom scores) with serum calcium rising above 2.5–3.0 mmol/L. As the coefficient of determination was low for all these curves, their shapes have to be interpreted with caution. In general, the small $R^2$ obtained in our regression models indicate that although the models were highly significant statistically, < 20% of the variability of the QOL scores was explained by the variability of the predictor variables. A large proportion of the variability of QOL scores is likely to be due to individual psychological factors.

One recent study suggests that the hypercalcaemia of malignancy may be often be undiagnosed and undertreated (17). Our findings highlight the important contribution of hypercalcaemia to the symptoms of malignant disease. Knowledge of the impact of serum calcium on the patients’ QOL adds to our understanding of the symptoms of multiple myeloma. However, it does not alter our management of the disease, as the diagnosis of hypercalcaemia always warrants vigorous treatment of the hypercalcaemia itself as well as of the underlying malignant disease.

Conflict of interest
There are no conflicts of interest.

References

Wisloff et al.


