Could a vitamin D deficiency cause a combined long-term FEV1 and bone mineral density deterioration in female asthmatics?

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Abstract

Objective. We already know that asthma is associated to osteoporosis/osteopenia and characterized by an accelerated lung function decline. Our study aimed at assessing whether lung function decline and bone mineral density (BMD) deterioration in time were associated in a group of female long-standing asthmatics. We also tried to understand whether these two aspects were related to ICS treatment and vitamin D levels.

Methods. 35 female asthmatics were retrospectively analysed. Results of methacholine challenge test at asthma onset, FEV1%, bone density scan at moment of recruitment and after at least 5 years later were considered.

Results. A significant positive relationship between femoral-t-scores changes and FEV1, decline was found after a median follow-up time of 7 [6-9] years (r=0.43; p=0.04). Femoral-t-score variations and vitamin D values were also significantly related (r=0.669; p=0.024). Furthermore, we found that FEV1, decline was worse in subjects with lower vitamin D levels (-57.5 [-80.4-35.9] ml/year), compared to those with normal vitamin D rates (12 [-16-23.6] ml/year; p=0.055). Femoral/vertebral t-score changes, as well as FEV1, decline were not associated to the use of medium/high ICS doses when compared to subjects treated with low ICS dosages.

Conclusion. FEV1, decline and BMD deterioration in time observed in a group of female asthmatics were associated; low vitamin D levels may be the link.
density changes in time, we considered the 23 of them that had repeated both a bone density scan (median femoral-t-score change: -0.1 [IQR: -0.5-0.2]; median vertebral t-score change: -0.2 [IQR: -0.8-0.6]) and FEV₁ measurements (median FEV₁ decline: -38.4 [IQR: -66.6-16.4] ml/year) at least 5 years later (median years 7 [IQR: 6-9]). Since some of them (15 patients) had been measured the serum 25(OH) vitamin D values (at the beginning of study), we also evaluated if there was a relationship between femoral/vertebral t-score changes, FEV₁ decline and vitamin D level. We also analyzed the FEV₁ decline level obtained in subjects with normal and pathological vitamin D values using a < or ≥30 ng/ml cut-off. All 23 patients were being continuously treated with inhaled corticosteroids (7 with low dose, 10 with medium dose and others with high dose) often associated with long-acting bronchodilators and sometimes also with montelukast.

Statistical analysis

Pearson correlation was used to evaluate a possible relationship between femoral/vertebral-t-scores, measured at baseline and at least after 5 years, and PD₂₀ and between femoral/vertebral-t-scores and FEV₁ decline (all data were normally distributed). It was also evaluated the relationship between the femoral/vertebral-t-scores changes in time and PD₂₀/FEV₁ decline. This test was also used to assess whether femoral/vertebral-t-scores changes and FEV₁ decline were related to serum 25 (OH) Vitamin D level (UI). Independent t-test was used to compare femoral/vertebral-t-scores, measured at baseline and at least after 5 years, t-score differences and FEV₁ decline in individuals with different AHR levels. Linear regression models (corrected for age, BMI and ICS doses) were applied to test if femoral/vertebral-t-score changes and FEV₁ decline were associated to vitamin D levels. Normality of residuals and heteroscedasticity were tested using Shapiro-Wilk and White test but results were not significant (p>0.05).

Independent t-test was also performed with the purpose to compare FEV₁ decline level obtained in subjects with a vitamin D values < or ≥30 ng/ml.

Results

Features of patients at baseline are reported in table 1, whereas all correlation coefficients in table 2. No significant relationships were found either between baseline femoral/vertebral-t-scores and PD₂₀ (r=0.1, p=0.54; r=0.05; p=0.75) or FEV₁ decline (r=0.08, p=0.65; r=0.13; p=0.47). No differences in T scores, measured both at baseline and at the end of the study, were found in the different levels of AHR. No significant relationships were found between PD₂₀ and T femoral (r=0.22, p=0.29) or vertebral (r=-0.1, p=0.64) changes scores measured at least 5 years later. Also when comparing both FEV₁ decline and t-score differences in hyperreactive/normoreactive subjects, no differences were detected. No significant correlation was found between vertebral-t-scores changes and FEV₁ decline (r=-0.16, p=0.46). On the contrary, we detected a significantly positive relationship between femoral-t-scores changes and FEV₁ decline (r=0.43, p=0.04) (figure A). This relationship was also confirmed when we adjusted for age, BMI and ICS doses (r=0.47, p=0.032). At this point, we wanted to see whether vitamin D insufficiency was associated to FEV₁ decline and bone mineral density changes in time. We only found a significant relationship between femoral-t-score variations and vitamin D levels (r=0.669, p=0.024; see figure B). Also the linear regression model (corrected for age, BMI and ICS doses) found a significantly positive association between change in femoral-t-score and baseline vitamin D levels (ß=0.053, p=0.024). No significant relationships were detected between vitamin D and FEV₁ decline. However, when we subdivided subjects into those with normal and low vitamin D level (< or ≥30 UI cut-off), we found that FEV₁ decline was worse in subjects with lower vitamin D level.

Table 1. Features of patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Median</th>
<th>IQR</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>51 [43-54]</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>26 [23.8-28.1]</td>
<td></td>
</tr>
<tr>
<td>FEV₁ ∼%</td>
<td>103.1 [91.4-108.7]</td>
<td></td>
</tr>
<tr>
<td>PD₂₀ (µg)</td>
<td>273 [26-551]</td>
<td></td>
</tr>
<tr>
<td>Baseline femoral T-score</td>
<td>-0.6 [-1.2-0.0]</td>
<td></td>
</tr>
<tr>
<td>Baseline vertebral T-score</td>
<td>-1.3 [-1.9-0.4]</td>
<td></td>
</tr>
<tr>
<td>FEV₁ decline (ml/year)</td>
<td>-38.4 [-66.6-16.4]</td>
<td></td>
</tr>
<tr>
<td>Vitamin D (UI)</td>
<td>21 [18-24]</td>
<td></td>
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Table 2. Correlation coefficients obtained by putting in relation various parameters listed in the table

<table>
<thead>
<tr>
<th>PD₂₀ (µg)</th>
<th>Baseline femoral t-score</th>
<th>Baseline vertebral t-score</th>
<th>Femoral t-score change in time</th>
<th>Vertebral t-score change in time</th>
<th>PD₂₀ (µg)</th>
<th>FEV₁ decline (ml/year)</th>
<th>Vitamin D (UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.103</td>
<td>0.054</td>
<td>-0.219</td>
<td>-0.099</td>
<td>-</td>
<td>0.123</td>
<td>0.178</td>
<td>0.091</td>
</tr>
<tr>
<td>FEV₁ decline (ml/year)</td>
<td>0.078</td>
<td>0.127</td>
<td>0.432*</td>
<td>-0.163*</td>
<td>-0.123</td>
<td>0.091</td>
<td>0.091</td>
</tr>
<tr>
<td>Vitamin D (UI)</td>
<td>0.202</td>
<td>0.089</td>
<td>0.669*</td>
<td>-0.061</td>
<td>0.178</td>
<td>0.091</td>
<td>-</td>
</tr>
</tbody>
</table>

Pearson correlation test was used; *p=0.040; °p=0.024. Only the statistically significant correlations are also showed in the figures); when we adjusted for BMI and age, Femoral t-score change in time was 0.468, p=0.032 and Vertebral t-score change in time was -0.277, p=0.224.
(-57.5 [-80.4-35.9] ml/year), in comparison with asthmatics with normal vitamin D rate (12 [-16-23.6] ml/year, p=0.001; figure C). There was no differences in femoral/vertebral T-scores and FEV₁ decline in subjects treated with different ICS doses. Furthermore, femoral-t-score changes were not associated to the use of a medium (β=0.233; p=0.450) or a high (β=-0.75; p=0.856) dose of ICS when compared to subjects treated with low ICS dose. The same was observed for vertebral-t-scores (medium dose: β=-0.046; p=0.930; high dose: β=-0.388; p=0.582). Also FEV₁ decline was not associated to medium (β=-15.01; p=0.527) or high (β=-8.59; p=0.815) ICS doses use, when compared to subjects treated with low ICS doses.

**Discussion**

Although the number of patients analyzed was limited, this is the first study highlighting a significant relationship between lung function decline and BMD deterioration in time. The link seems to be a vitamin D low level. In fact, femoral T-score decrease in time was associated to a low vitamin D level, confirming, what we already knew, namely, that vitamin D insufficiency was clearly associated to a reduction of BMD (2,14). Besides, a greater FEV₁ decline was found in subjects with a vitamin D value below normal cut-off in accordance to what was found by other authors in larger groups of asthmatics (15). Such result, therefore, suggests that vitamin D deficiency may play an important role in the progressive combined deterioration of lung function and BMD. No associations were observed between BMD/lung function deterioration in time and medium or high ICS doses when compared to low doses. As already said, only a long-term treatment with high ICS doses and, above all, a prolonged use of systemic corticosteroids (for exacerbations) seem to influence a BMD decrease (6,7,9,10,18). Conversely, a continuous therapy with ICS may slow down lung function decline in asthma and not, on the contrary, favor a deterioration (19). Therefore, it is unlikely that ICS might influence a development of concomitant osteopenia/osteoporosis and progressive airway obstruction. It is unclear how vitamin D might affect such combined loss in lung function and BMD in time. Probably, hypovitaminosis D adversely affects calcium metabolism, osteoblastic activity, matrix ossification, bone remodeling and bone density (14). Probably, vitamin D deficiency can also lead to a secondary hyperparathyroidism, a progressive hyperplasia of the parathyroid glands and an increased production of parathyroid hormone, inducing an
low vitamin D levels and FEV1/BMD loss

alteration of calcium homeostasis (20). However, even if the association between 25OHD and BMD is still controversial (6), adequate vitamin D level can play a protective role in the incidence and development of osteoporosis (2), confirming that vitamin D deficiency can be an important risk factor for osteoporosis (14). On the other hand, a vitamin D low level may favor exacerbations and airway remodeling in asthma, probably through a worsening of oxidative stress and DNA damage (21). Furthermore, vitamin D deficiency can interfere with the immunological pathway leading to development/worsening of bronchial inflammation and thus to airway remodeling in asthma (22-25). In fact, the action of vitamin D is related to adaptive immunity with a Th2 response and production of anti-inflammatory cytokines like interleukins 4 and 5, and with Th17 and B-lymphocyte suppression (22), factors involved in airway remodeling. Furthermore, the anti-fibrotic and anti-proliferative effects of vitamin D at airway level have been described in several researches (24,25). Particularly, vitamin D has been shown to decrease smooth muscle cells proliferation, migration as well as cytokine secretion (25), thus suggesting its important role to prevent lung function decline in asthma. This was also confirmed by a longitudinal study, conducted for approximately 11 years, observing that low serum 25(OH)D levels were associated with a higher lung function decline in adults with asthma (15).

In conclusion, according to our data, there is an association between FEV1, decline and BMD deterioration. This association does not seem to be related to ICS use but to a low vitamin D level, confirming its possible role in the progressive deterioration of asthma and BMD in time.

Conflict of Interest None of the authors has any conflict of interest to declare in relation to this work.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required

References