The role of IL-17A in postmenopausal inflammatory events, such as in osteoporosis

1 Ildikó Molnár, MD, CSc, 2 Ilona Bohaty, MD, 1Éva Somogyiné-Vári
1Immunoendocrinology and Osteoporosis Centre,
2Regional Centre of Hungarian National Blood Transfusion Service,
Debrecen, Hungary
IL-17 cytokine

IL-17 (called as IL-17A) is characterized by:
- T-cell-derived cytokine
- secreted from Th17 cells, which are distributed from other effector CD4+ T helper cells, such as Th1, Th2 and regulatory T (Treg) cells.

Sources of IL-17:
- Cells of innate and adaptive immunity (T and B cells, NK, NKT, γδ T cells, neutrophils, basophils, mast cells, monocyte-macrophages, dendritic cells).
- Epithelial, endothelial, vascular and stromal cells.

IL-17 initiated cytokine/chemokine productions:
- IL-6, TNFα, IL-1β, IL-8, CXC1, CXC2, CXC8, CCL2, MCP-1
Increased IL-17 production-related diseases

- Local inflammation (cytokine interplay chemokine)
  - Autoimmunity
  - Allergy
  - Host defense mechanism (infection, transplantation)
  - Tissue repair
- Bone loss (osteoporosis)
- Arteriosclerosis (cardiovascular diseases)

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Immune dysfunction associated with estrogen deficiency

- Estrogen deficiency leads to T cell activation.
- T cell activation results in osteoclast and osteoblast
  - IL-1↑, TNFα↑, RANK ligand↑, TGFβ↓, IFNγ↑
- Neutrophil recruitment and IL-6 secretion
- Peripheral mononuclear cells

- IL-17↑ in spleen
- Th17 activates neutrophil recruitment and IL-6 secretion
- Estrogen receptor

BONE LOSS

IL-6 secretion

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Patients and methods

- Pre- (n=22, mean age 41 yr) and postmenopausal (n=72, mean age 65 yr) women were studied.
- Serum levels of IL-17A, IL-6, MCP-1 (macrophage-chemoattractant protein-1), sRANK (soluble receptor activator of NF-κB) ligand and OPG (osteoprotegerin) were measured by enzyme-linked immunosassay (ELISA).
- Serum levels of estradiol were measured by chemiluminescence assay in fully automatized manner.
- Bone mineral density was detected by dual-energy X-ray absorptiometry (DXA) using Hologic Discovery equipment.
We studied in pre- and postmenopausal women:

- The relationship among serum IL-17A levels, estrogen deficiency and postmenopausal period.
- The relationships among serum IL-17A, sRANK ligand, OPG levels and bone mineral densities.
- The relationship between vitamin D$_3$ deficiency and serum IL-17A levels.
- The relationship between serum IL-17A and IL-6 or MCP-1 levels.

Synergism between bone loss and arteriosclerosis via IL-17 cytokine.
The relationship among serum IL-17A levels, estrogen deficiency and postmenopausal period.
Serum IL-17A levels were significantly higher in women with estrogen deficiency.

Figure 7

Serum IL-17A levels (ng/ml)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol levels below 83 pmol/l</td>
<td>3.01 ± 0.38</td>
</tr>
<tr>
<td>Estradiol levels in the normal range</td>
<td>3.43 ± 0.56</td>
</tr>
</tbody>
</table>

P < 0.001

OR: 17.74  RR: 5.64  CI95%: 3.52-79.62
Increased serum IL-17A levels showed an age-related dependency in postmenopause.

<table>
<thead>
<tr>
<th>Age-Related Groups</th>
<th>Serum IL-17A Levels (ng/ml)</th>
<th>Mean ± SD</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td></td>
<td>3.59 ± 0.65</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>60-69</td>
<td></td>
<td>3.31 ± 0.4</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>70-79</td>
<td></td>
<td>3.63 ± 0.46</td>
<td></td>
</tr>
<tr>
<td>80-89</td>
<td></td>
<td>3.97 ± 0.77</td>
<td></td>
</tr>
</tbody>
</table>

Figure 8
Correlation between serum IL-17A levels and the post-menopausal period of women aged 60 to 89 years.

![Figure 9](image link)
Inreased serum IL-17A levels showed a dependency on the history of hysterectomy in postmenopause.

(mean ±SD)  3.57  3.29
± 0.59  ± 0.39

P<0.026

Serum IL-17A levels (ng/ml)

Yes hysterectomy
No hysterectomy

Patient groups

n=54  n=18

Figure 10
Increased serum IL-17A levels showed a postmenopausal age-related dependency on the history of hysterectomy.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean ± SD</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10 yr</td>
<td>3.34 ± 0.68</td>
<td>17</td>
</tr>
<tr>
<td>11-20 yr</td>
<td>3.49 ± 0.47</td>
<td>3</td>
</tr>
<tr>
<td>21-30 yr</td>
<td>3.25 ± 0.26</td>
<td>20</td>
</tr>
<tr>
<td>31-40 yr</td>
<td>3.62 ± 0.46</td>
<td>14</td>
</tr>
<tr>
<td>41-50 yr</td>
<td>3.13 ± 0.28</td>
<td>7</td>
</tr>
<tr>
<td>51-60 yr</td>
<td>4.3 ± 1.09</td>
<td>3</td>
</tr>
<tr>
<td>61-70 yr</td>
<td>3.55 ± 0.56</td>
<td>3</td>
</tr>
</tbody>
</table>

$P < 0.008$

Figure 11.
Relationship between serum IL-17A levels and bone mineral densities (BMDs).
Increased serum IL-17A levels were associated with relevant bone loss in postmenopause compared to those in premenopause.

**Figure 13**

![Graph showing serum IL-17A levels in postmenopausal and premenopausal women.](image)

- Postmenopausal women:
  - Osteopenia: -1 > T-score > -2.5 (n=31)
  - Osteoporosis: T-score < -2.5 (n=41)

- Premenopausal women:
  - Normal: T-score > -1 (n=22)

Line chart illustrating the distribution of serum IL-17A levels with mean ± SD: 3.31 ± 0.08 ng/ml, 3.65 ± 0.61 ng/ml, and 2.88 ± 0.08 ng/ml. Statistical significance with p-values: P<0.027, P<0.013, P<0.0001.
Serum IL-17A levels were significantly higher in post-menopausal osteoporotic women in the lumbar and femoral total regions.

![Serum IL-17A levels](image)

**Figure 14**

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Serum IL-17A levels correlated inversely with bone mineral densities in postmenopause.

Figure 15

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Relationship between serum IL-17A and sRANK ligand or OPG levels.
Increased serum IL-17A and sRANK ligand levels were detected in osteoporotic women.

**Figure 17**

- **A** IL-17A levels
  - Premenopausal women, n=18.
  - Postmenopausal osteopenic women, n=31.
  - Osteoporotic women, n=41.

- **B** sRANK ligand levels

- **C** OPG levels
  - Premenopausal women, n=18.
  - Postmenopausal osteopenic women, n=31.
  - Osteoporotic women, n=41.
Serum IL-17A levels correlated positively with sRANK ligand and did not with OPG serum levels, but with the ratio of sRANK ligand and OPG serum levels.

Figure 18
Vitamin D$_3$ deficiency and serum IL-17A levels.
Serum IL-17A levels were significantly higher in post-menopausal women with vitamin D$_3$ deficiency.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vitamin D$_3$ deficiency (n=18) &lt;50 nmol/l</th>
<th>Vitamin D$_3$ insufficiency (n=25) 51-75 nmol/l</th>
<th>Vitamin D$_3$ sufficiency (n=11) &gt;75 nmol/l</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59±17</td>
<td>61±13</td>
<td>61±12</td>
<td></td>
</tr>
<tr>
<td>BMI* (kg/m$^2$)</td>
<td>29±5</td>
<td>29±6</td>
<td>29±6</td>
<td></td>
</tr>
<tr>
<td>Vitamin D$_3$ (nmol/l)</td>
<td>16,84±6,06</td>
<td>35,08±5,79</td>
<td>68,95±44</td>
<td></td>
</tr>
<tr>
<td>IL-17A (ng/ml)</td>
<td>13,35±2,9 $^\circ$</td>
<td>12,07±2,61</td>
<td>11±1,9 $^\circ$</td>
<td>0.033</td>
</tr>
<tr>
<td>MCP-1** (ng/ml)</td>
<td>17,35±2,9</td>
<td>16,62±2,07</td>
<td>16,18±1,23</td>
<td></td>
</tr>
<tr>
<td>IL-6 (ng/ml)</td>
<td>26,11±12,66</td>
<td>26,25±12,23</td>
<td>22,68±13,52</td>
<td></td>
</tr>
</tbody>
</table>

*Body mass index (BMI)  **Monocyte chemoattractant protein-1 (MCP-1)  

Table 1
Serum IL-17A levels correlated inversely with vitamin D$_3$ serum levels in postmenopause.

Figure 20
Relationship between serum IL-17A and IL-6 or MCP-1 levels.
Serum IL-17A levels correlated positively with serum MCP-1 levels in postmenopause.

\[ Y = (X \times 0.81) - 1.43 \]

\[ P < 0.0001 \quad r = 0.6745 \]
Serum IL-17A levels correlated positively with serum IL-6 levels in postmenopause.

\[
Y = 8.47 + (X \times 1.46)
\]

\[P < 0.0001 \quad r = 0.6693\]
Synergism between bone loss and arteriosclerosis via IL-17 cytokine.


Figure 24
Conclusions

- The high prevalence of increased serum IL-17A levels was connected to postmenopausal estrogen deficiency and showed a postmenopausal period-related dependency.
- Postmenopausal osteoporosis was associated with increased serum IL-17A and sRANK ligand levels, but only weakly increased serum OPG levels.
- Vitamin D₃ deficiency was associated with higher serum IL-17A levels in postmenopause.
- The strong correlation between serum IL-17A and IL-6 or MCP-1 highlighted the relationship between osteoporosis and arteriosclerosis, as well as cardiovascular diseases.
Thank you for your attention!
Participated in this work:

Regional Centre of Hungarian National Blood Transfusion Service, Debrecen, Hungary

Ilona Bohaty MD

EndoMed, Immunoendocrinology and Osteoporosis Centre

Éva Somogyiné-Vári