Circannual vitamin D serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe

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Methods. Fifty-four Italian patients (IP) and 64 RA Estonian patients (EP) were evaluated for serum 25(OH)D levels in winter and summer time.

Results. 25(OH)D levels were found significantly higher in IP versus EP (p = 0.0116) both in winter and in summer. Differences were observed also in controls. The variations (increase) of 25(OH)D levels between winter and summer were found significant in both IP and EP. Differences were observed also in controls.

No significant differences were found concerning 25(OH)D levels between RA patients and their controls in either country.

Interestingly, a significant negative correlation between 25(OH)D and DAS28, was found in summer only in IP (r = -0.58, p < 0.001) and in winter in EP (r = -0.4, p < 0.05).

Conclusion. Significantly lower 25(OH)D serum levels were observed in RA patients from North versus South Europe with a circannual rhythm in winter and summer time. In addition, 25(OH)D values showed a significant correlation (negative) with RA clinical status (DAS28) in both North and South European RA patients, suggesting possible effects of vitamin D among other factors on disease activity.

Introduction

It is clear that both genetic and environmental factors affect prevalence of autoimmune diseases. The data link vitamin D and insulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), inflammatory bowel diseases (IBD), and rheumatoid arthritis (RA) (1, 2).

The fact that vitamin D has been implicated as a factor in several different autoimmune diseases suggests that vitamin D might be one of the environmental factors that among others normally participates in the control of self tolerance (2).

Vitamin D receptor is found in significant concentrations in the T lymphocyte and macrophage populations (3). However, its highest concentration is found in the immature immune cells of the thymus and the mature CD-8 T lymphocytes.

The significant role of vitamin D compounds as selective immunosuppressants is also illustrated by their ability to either prevent or markedly suppress animal models of autoimmune diseases (4).

RA is an autoimmune disorder of multifactorial etiology in which both genetic and nongenetic factors (i.e. infectious, hormonal, environmental) contribute to disease susceptibility. Vit D may exert immunomodulatory effects and hypovitaminosis D together with higher prevalence of RA seems common amongst North when compared to South Europe (5).

Greater intake of vitamin D was associated with a lower risk of rheumatoid arthritis (RA), as well as lower vitamin D was found associated with higher disease activity (6, 7).

In the present study, we decided to evaluate serum 25-hydroxyvitamin D [25(OH)D] levels in female RA patients from North (Estonia) and South (Italy) Europe and to correlate them with the disease activity score (DAS28) during summer and winter time.

Patients and methods

A total number of 54 Italian RA patients (IP, 58.5 ± 1.1 years) and 64 Estonian RA patients (EP, 56.3 ± 2.3 y), were evaluated in winter and summer.
Table I. RA patients and control characteristics. 25(OH)D serum levels and DAS28 scores in Italian and Estonian RA patients in winter and in summer. 25(OH)D serum levels in Italian and Estonian controls. Average ± SE.

<table>
<thead>
<tr>
<th></th>
<th>Italy** RA patients</th>
<th>Estonia** RA patients</th>
<th>Italy** Controls</th>
<th>Estonia** Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n°)</td>
<td>53</td>
<td>64</td>
<td>38</td>
<td>30</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>58.5 ± 2.1</td>
<td>56.3 ± 2.3</td>
<td>59.9 ± 0.9</td>
<td>51.1 ± 3.8</td>
</tr>
<tr>
<td>25(OH)D Winter (nmol/L)</td>
<td>58.9 ± 5.3</td>
<td>35.1 ± 1.9</td>
<td>54.5 ± 3.5</td>
<td>43.3 ± 2.6</td>
</tr>
<tr>
<td>25(OH)D Summer (nmol/L)</td>
<td>65.2 ± 5.5</td>
<td>46.4 ± 2.3</td>
<td>68.9 ± 6.1</td>
<td>47.4 ± 3.1</td>
</tr>
<tr>
<td>DAS28 winter</td>
<td>3.73 ± 1.69</td>
<td>4.19 ± 1.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS28 Summer</td>
<td>3.48 ± 0.25</td>
<td>3.99 ± 1.46</td>
<td></td>
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</tr>
</tbody>
</table>

*ANOVA: winter versus summer p = 0.0005. **ANOVA: Italy versus Estonia p = 0.0016.

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for 25-hydroxyvitamin D 25(OH)D, as well as for disease activity score (DAS
28). Clinical evaluations and blood samples were collected at the end of
each season. In particular, the sample collection was carried out mainly from
December to February in the winter, and mainly from July to August in the
summer.

Normal female controls included 35 (IC, 59.9 ± 0.9 y) and 30 (EC, 57.1 ± 3.8 y)
age-matched subjects, respectively. No vitamin D or calcium, nor drugs
affecting calcium metabolism were administered from 2 months before the study
starting. No liver or kidney insufficiency was present. Treatment with low
dose glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) was
constant from at least 3 months.

25(OH)D concentrations were measured by a competitive radioimmuno-
assay (DiaSorin, Stillwater, Minnesota, USA). The current standard of disease
activity evaluation was the EULAR Disease Activity Score (DAS), as well as the
defined DAS 28 based on a 28-
joint assessment (8).

Informed consent from all the patients, as well as the Ethical Committee
approval were obtained. Statistical ana-
lysis was performed by r Pearson cor-
relation, t-Student with Bonferroni cor-
rection and by repeated ANOVA mea-
sures (summer and winter) with two factors (country and clinical status).

Log transformed data were used for the
analysis. Significant level was considered to be p = 0.05.

Results

As reported in Table I, 25(OH)D levels
were found significantly higher in IP
versus EP (p = 0.0016) both in winter
and in summer. Differences were ob-
erved also among the controls both in
winter and in summer (Table I).

The variations (increase) of 25(OH)D levels between winter and summer
time (Table I), were found significant in both IP and EP (p = 0.0005).
Differences were observed also in the con-
trols between winter and summer.

No significant differences were found concerning 25(OH)D levels between
Italian and Estonian RA patients and
their controls.

Interestingly, a significant negative correlation between 25(OH)D and
DAS28, was found in summer in IP
(r = -0.57, p < 0.0001) and in winter in
IP (r = -0.40, p < 0.05).

However, the mean DAS28 scores were found generally higher in EP vs
IP (NS) and the difference was more
evident in winter (Table I).

Discussion

Significantly lower 25(OH)D serum
levels were observed in RA patients
from North (Estonia) versus South
(Italy) Europe with a circannual rhythm, namely in winter and summer
time. In addition, low 25(OH)D values showed in summer a significant moder-
ate negative correlation with RA clinical
status (DAS28) in South European
patients, whereas in Estonian RA patients the significant negative corre-
lation was found in winter, suggesting
possible effects of vitamin D, among
other factors, on RA disease activity.

Vitamin D may exert immunomodula-
tory effects and hypovitaminosis D
together with higher prevalence of RA
seems common amongst Northern
patients when compared to South
Europe (7).

As a matter of fact, hypovitaminosis D
linked to higher latitude further charac-
terizes Greenlanders versus Danes
(plasma 25(OH)D < 40 nmol/l) (9).

A possible beneficial role for ultravo-
etradiations (UVR) on three Th1-
mediated autoimmune diseases: multi-
ple sclerosis, type 1 diabetes and RA in
relation to recent developments in pho-
toimmunology has been analyzed (2).

Recent work suggests that UVR expo-
sure may be one factor that can attenu-
ate the autoimmune activity leading to
these three diseases through several
pathways involving UVB and UVA
irradiation, UVR-derived vitamin D
synthesis and other routes such as
alpha-melanocyte-stimulating hormone,
and melatonin (2, 10). Therefore, eco-
logical features, particularly a gradient
of increasing prevalence of RA (Fin-
land nearly 0.8 % and 0.3 % in Italy)
and other autoimmune diseases with
higher latitude, provide some support
for a beneficial role of UVR (11-15).

In addition, there may be a higher vita-
mion D requirement for patients at risk
for developing autoimmunity and those
that already have an autoimmune dis-
 ease such as systemic lupus erythemato-
sus (SLE) (16).

The optimal amount of vitamin D to
support the immune response may be
different from the amount required to
prevent vitamin D deficiency or to
maintain calcium homeostasis. New
evidence from human, animal, and in
vitro mechanistic experiments suggest
that vitamin D may play a role in the
etiopathology of autoimmunity (4).

Therefore, although chronic excessive expo-
sure to sunlight increases the risk of
melanoma skin cancer, the limited
and/or avoidance of all direct sun expo-
sure (i.e. darkness) increases the risk of
vitamin D deficiency, which in turn can
play a role in autoimmunity (17).

Interestingly, polymorphisms in the vit-
amin D receptor (VDR) have been cor-
related with increased susceptibility of
RA (18). Furthermore, a recent study in
North European people (Finnish) re-
ported the association between poly-
morphism of VDR gene and individual risk of hand osteoarthritis (OA) (19). However, recently, a significant clinical improvement was strongly correlated with the immunomodulating potential in vitamin D-treated RA patients (20).

In conclusion, prolonged daily darkness, different genetic background (i.e. vitamin D receptor polymorphism) and nutritional factors, may explain lower 25(OH)D levels observed in North Europe (i.e. Estonia). Low 25(OH)D levels might be also partially linked, among other factors, to the recognized local increased prevalence of autoimmune diseases such as RA by considering the potential immuno-suppressive role of Vit D (2,10).

References
8. VAN GESTEL AM, HaAGSMA CI, VAN RIEL PLCM: Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998; 41: 1848-50.