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European multicentre pilot survey to assess vitamin D status in rheumatoid arthritis patients and early development of a new Patient Reported Outcome questionnaire (D-PRO)

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ABSTRACT

Objective: To collect data on vitamin D (25(OH)D) serum levels in a large number of rheumatoid arthritis (RA) patients from different European countries, to investigate their relation with disease activity, disability, quality of life, and possibly to construct a new Patient Reported Outcome (PRO) questionnaire in order to self-estimate if they are at risk for vitamin D insufficiency/deficiency-related clinical implications (D-PRO).
Methods: This was a European League Against Rheumatism (EULAR) supported cross-sectional study (project No CLI064) which involved 625 RA patients (mean age 55 ± 11 years, mean disease duration 11 ± 9 years), 276 age and sex matched healthy subjects, and rheumatologists working in academic institutions or hospital centres, as well as PARE organizations (patient representatives) from 13 European countries. Serum samples for 25(OH)D level measurement were collected during winter time and analyzed in a central laboratory using chemiluminescence immunoassay (DiaSorin). Patient past medical history was recorded. RA patients were provided with three questionnaires: the Rheumatoid Arthritis Impact Diseases score (RAID), the Health Assessment Questionnaire (HAQ), and the new D-PRO questionnaire at the time of 25(OH)D serum sampling. D-PRO questionnaire consisted of three domains, Symptom Risk Score (SRS), Habitus Risk Score (HRS) and Global Risk Score (SRS + HRS = GRS), constructed with items possibly related to vitamin D deficiency. D-PRO was correlated with both clinical and PRO scores. DAS28-CRP was also evaluated. Statistical analysis was performed by non parametric tests.

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Results: Mean serum concentration of 25(OH)D in RA patients (17.62 ± 9.76 ng/ml) was found significantly lower if compared to the levels obtained in matched controls (18.95 ± 9.45 ng/ml) ($p = 0.01$), with statistically significant differences among several European countries. Negative correlations were found between 25(OH)D serum levels and DAS28-CRP ($p < 0.001$), RAID ($p = 0.05$) and HAQ ($p = 0.04$) scores in the RA patients group. Negative correlations were also found in the cohort of enrolled RA patients between 25(OH)D serum concentrations and SRS ($p = 0.04$), HRS ($p = 0.02$) and GRS ($p = 0.02$) domains of the D-PRO questionnaire.
Conclusions: This first multicentre European survey add new evidences that vitamin D insufficiency/deficiency is frequent in RA patients with statistically significant differences among several countries. Vitamin D serum concentrations seem to correlate negatively and significantly with the D-PRO Global Risk Score, clinimetric indexes for quality of life, disease activity and disability in present cohort of RA European patients.

1. Introduction

Experimental and clinical data provided evidence that vitamin D deficiency can be an important environmental risk factor influencing prevalence and severity of several autoimmune diseases especially in people of particular geographical, climate and ethnic background [1–4].

The term vitamin D refers to a precursor of the 1,25-hydroxy-vitamin D ($1,25(OH)_2D_3$) (calcitriol), the only natural form able to induce biological effects within the body, which is known to act at subnanomolar concentrations as an endocrine hormone. The D hormone ($1,25\text{-}(OH)_2D_3$) is a member of a group of steroid molecules generated from cholesterol (cholecalcipherol) with a plethora of biological actions and immune modulatory effetcs, orchestrated via the integrated operation of the D hormone endocrine system [5–6].

Individual vitamin D status is usually assessed by measurement of 25(OH)D (calcifediol) in serum, since calcitriol has a very short half-life that does not allow reliable measurements [7–8]. Accordingly, calcitriol deficiency may exist even when normal or even elevated calcifediol levels are present into circulation [9].

No real serum 25(OH)D threshold has been documented for rheumatoid arthritis (RA), but preliminary studies suggest that low serum concentrations of vitamin D may be common, and an inverse relationship between serum levels of vitamin D metabolites and disease activity or disability have been reported in RA patients [3,10–11]. Furthermore, it is not unusual for RA patients to have silent signs of vitamin D deficiency (i.e. amplified pain, muscle weakness, changes in hair and nail growth, mood changes etc.) influencing their perception of wellbeing but not attributable to disease itself [12–14]. Similarly, importance of vitamin D deficiency has been demonstrated in many other inflammatory conditions [15–20].

There is also a growing interest in the assessment of RA status from the patient's perspective, and patient reported outcomes (PRO) have been found to be very informative and sensitive. PROs are bringing additional information in the assessment of RA patients, especially in domains of health important from the patient's perspective [21].

The aim of this study was to collect data on vitamin D serum levels in a large number of RA patients from different European countries and to investigate its relation with disease activity, disability, quality of life, and possibly with a new Patient Reported Outcome (PRO) questionnaire constructed and cross-culturally validated for RA patients to self-estimate if they are at risk for vitamin D insufficiency/deficiency (D-PRO).

2. Patients and methods

This was an European League Against Rheumatism (EULAR) supported cross-sectional study (project No CLI064) which involved rheumatologists working in academic institutions or hospital centre and PARE organizations (patient representatives) from 13 European countries (Bulgaria, Croatia, Estonia, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Serbia, Slovakia and Spain). The study was performed in accordance with GCP and Helsinki Declaration, and local Ethical Committee and Patient Informed Consent were obtained before patient enrolment at each national centre.

2.1. Study population and design

It was expected to enrol approximately a total number of 600–700 RA patients (50 from each participating centre). RA patients inclusion criteria were: age 25–65 years; RA diagnosis established by ACR/EULAR criteria [22] at least one year prior to study entry; patients on stable treatment with conventional synthetic DMARDs (i.e. Methotrexate, Leflunomide) during at least 3 months prior to enrolment; use of glucocorticoids ≤7.5 mg/day of prednisone or equivalent, for at least one month prior to enrolment.

Data from 625 RA patients were finally collected, along with blood samples. Blood samples from 276 age and sex matched healthy volunteers were collected in each country to serve as a control for serum 25(OH)D levels.

Due to the circannual variations of vitamin D serum concentrations and its possible influence on disease activity/severity, it was decided to recruit the subjects only during the winter (beginning of December until end of March), known as characterized by the lowest seasonal 25(OH)D serum levels.

In all eligible RA patients, according to detailed study protocol and predefined case reported form, the following item were collected: demographic data, medical/clinical history, and disease activity using the DAS28 score [18]. The DAS28 was based on C-reactive protein (CRP) serum concentration. The DAS28-CRP combines information from the 28 tender and swollen joints, the CRP (in mg/dl) and the patient's general health status (PtGH), measured with a visual analogue scale (VAS 100 mm). Additionally, in order to test possible correlations among new and pre-existing validated PROs, RA patients were provided with three questionnaires: the Rheumatoid Arthritis Impact Diseases score (RAID) [10], the Health Assessment Questionnaire (HAQ) [3], and the new D-PRO (see below) at the time of serum sampling for 25(OH)D level measurement.

2.2. Serum sample collection and Vitamin D measurement

Serum samples for 25(OH)D serum level evaluation were performed centrally in a single laboratory at the Research Laboratory of Genova. Samples were obtained according to standard procedures, divided in 3 cryovial aliquots, labeled with pre-defined patient code and frozen (−80 °C) in each centre. After collection, frozen samples were shipped in dry ice thermal boxes to referring central laboratory where finally they were stored until analysis.

The evaluation of 25(OH)D concentrations was performed in a single run (testing 3 times each sample) by using a chemiluminescence immunoassay and an automatic analyser (LIAISON, DiaSorin, Italy). 25(OH)VitaminD serum concentrations were classified as normal (>30 ng/ml), insufficient (between 20 and 30 ng/ml) or deficient (<20 ng/ml), as already reported [23].