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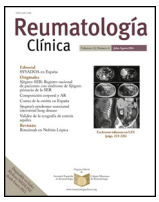

Review Article

Is There Really a Relationship Between Serum Vitamin D (25OHD) Levels and the Musculoskeletal Pain Associated With Statin Intake? A Systematic Review☆

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ABSTRACT

Introduction: Musculoskeletal pain associated to statin use, is the most common adverse event, leading to cessation of treatment. Several studies proposed Vitamin D deficiency to increase the risk of pain associated to statin intake.
Objectives: To evaluate whether vitamin D status is linked to musculoskeletal pain associated to statin use.
Methods: We performed a systematic review based on electronic searches through MEDLINE, Cochrane Central and EMBASE to identify studies that (1) included patients on statin therapy, (2) with vitamin D serum levels assessment, (3) in relation to musculoskeletal pain.
Results: The electronic search identified 127 potentially eligible studies, of which three were included and analyzed in the present study. The heterogeneity of studies did not allow metaanalysis. A systematic review and two cohort studies not included in the previous systematic review, revealed a statistically significant association of vitamin D deficit in patients with musculoskeletal pain on statin therapy.
Conclusion: The displayed evidence suggests a significant association between 25OHD serum levels <30 ng/ml and the presence of musculoskeletal pain in patients on statin therapy.

¿Existe relación entre los niveles séricos de vitamina D (25OHD) y el dolor musculoesquelético relacionado con la ingesta de estatinas? Revisión sistemática

Palabras clave:
Vitamina D
Estatinas
Dolor musculoesquelético

RESUMEN

Introducción: El dolor musculoesquelético (DME) asociado a estatinas es el efecto adverso más frecuente y responsable de su abandono. Diversos trabajos sugieren que el déficit de vitamina D incrementa el riesgo de padecer dolor asociado a estatinas.
Objetivos: Evaluar una posible asociación entre el nivel de vitamina D y la presencia de DME en pacientes en tratamiento con estatinas.
Métodos: Se realizó una búsqueda bibliográfica en Medline, Cochrane Central y EMBASE para identificar estudios que: 1) incluyeran pacientes tratados con estatinas; 2) en los que valoraran niveles séricos de vitamina D, 3) en relación con DME.
Resultados: Se identificaron 127 estudios de los que se incluyeron y analizaron finalmente 3. La heterogeneidad de los estudios no permitió realizar metaanálisis. Una revisión sistemática y 2 estudios de cohorte no incluidos en la revisión previa mostraron una asociación significativa entre el déficit de vitamina D y el DME.

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Conclusiones: La evidencia sugiere una asociación significativa entre niveles séricos de 25OHD <30 ng/ml y la presencia de DME.

Introduction

Statins have demonstrated their efficacy both in the prevention of cardiovascular mortality and its overall reduction.[1] As a consequence, the number of patients receiving statin therapy has grown substantially and continues to increase. However, nearly 15%–30% of them will develop musculoskeletal pain (MSP) as the major adverse effect, which often leads to their discontinuing the treatment.[2] The mechanism of the production of the pain is unknown and, potential factors include genetic predisposition, a possible mitochondrial dysfunction, a dysfunction involving coenzyme Q synthesis and/or cholesterol).[3]

Recent studies have suggested that vitamin D deficiency would be associated with MSP induced by statins and, that this could be reversible with vitamin D supplementation and the subsequent normalization of serum 25-hydroxyvitamin d (25OHD) levels.[4,5]

We performed the present systematic review of the literature for the purpose of determining whether serum 25OHD levels were associated or not with a higher prevalence of MSP related to the intake of statins.

Materials and Methods

Source of Data and Search Strategy

A systematic search was performed in 3 databases: Medline, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (up to October 2015), through the documentation service of the Sociedad Española de Reumatología (SER).

Moreover, we performed a manual search of the abstracts from meetings of the American College of Rheumatology (ACR) and the European League Against Rheumatology (EULAR) of the last 3 years. We included studies in English and Spanish.

See the search strategy (Appendix A) (available at the website).

Inclusion Criteria

- *By population:* adult patients (≥18 years) with any underlying disease being treated with statins (of any type or dose).
- *By factor:* evaluation of serum 25OHD levels.
- *By outcome:* musculoskeletal pain.
- *By type of study:* systemic reviews (SR), cohort and/or longitudinal studies that have been published after the most recently updated SR. Designs that evaluate risk factors (association).
- *By sample number*: >20 per group.

Review Methodology

Independently, 2 reviewers (CAP/MBN) reviewed the identified abstracts (inclusion criteria and quality of the selected studies), and differences in criteria were resolved by consensus. The citations were handled using ENDNOTE X, version 7.2.

The quality of the studies was evaluated utilizing New Castle-Ottawa Scale (NOS)[6] and the Checklist SIGN (SR). Differences in criteria were resolved by consensus.

Statistical Analysis

We did not perform a meta-analysis, but did identify a SR[2] that utilized weighted mean difference, and used the statistical heterogeneity measured by Cochran *Q* test and I^2.

The results are presented in narrative form.

Results

The combined search identified 127 studies, 119 of which were excluded as they did not meet the inclusion criteria, and another 5 were ruled out as they were duplicates. Finally, 3 studies were included (Fig. 1): 1 of which was a SR, by Michalska-Kasiczak et al.,[2] that contained 7 studies,[1,7–12] as well as, another 2 that were cohort studies, which had been published more recently, Mergenhagen et al.[13] and Morioka et al.[14]

With regard to quality, the SR is acceptable (SIGN), as are the cohort studies (NOS 6–7) (Table 1).

The total population of the studies was 3927 patients, 1038 of whom (26.43%) had MSP, whereas the rest, 2889 (73.53%), were asymptomatic. The mean age of the patients was 61.7 years, and ranged between 58 and 69 years. There were 1026 women and 1527 men; there were no population-based data from the 3 studies.[1,7,12]

The drug most widely used was simvastatin[2,12,13]; it was followed in frequency by atorvastatin,[2,12] pravastatina,[2,8] and

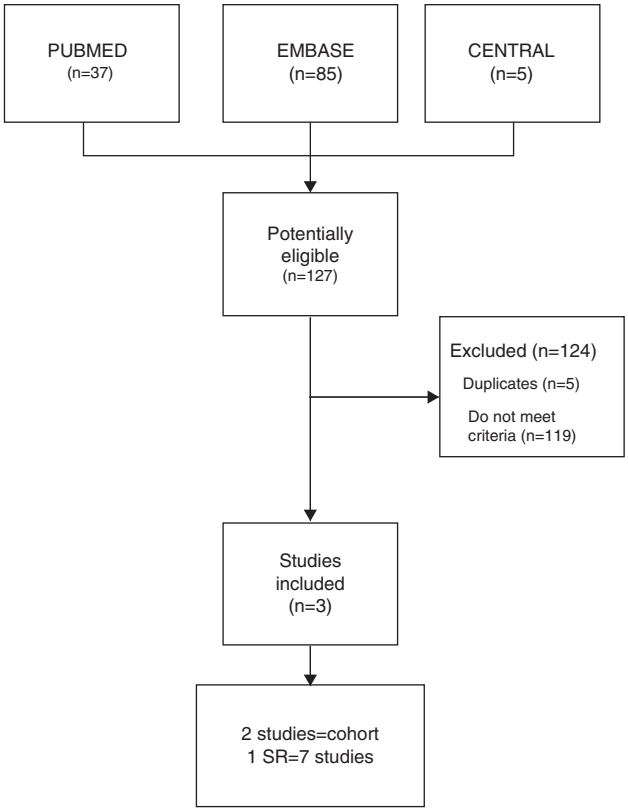

Fig. 1. Flow chart. SR, systemic review.