BMJ Open

Brain changes in neuroimaging of adult patients with vitamin D deficiency: systematic review protocol

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To cite: Porto CM, Leão RdCH, Sousa RA, *et al*. Brain changes in neuroimaging of adult patients with vitamin D deficiency: systematic review protocol. *BMJ Open* 2023;**13**:e052524. doi:10.1136/bmjopen-2021-052524

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-052524).

Received 20 April 2021
Accepted 16 August 2022

Check for updates

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ABSTRACT

Introduction Brain abnormalities detected through neuroimaging are described in patients with vitamin D deficiency, however, it is still not clear which cerebral alterations are more frequent and characteristic in this population. Thus, this review aims to identify and classify which are the main and most frequent brain changes found by neuroimaging in patients with vitamin D deficiency.

Methods and analysis The study protocol was constructed in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols and the leading research question was formulated through Population, Intervention, Comparator, Outcome, Setting. The evidence will be researched at the following electronic databases: PubMed, PsycINFO, Scopus, Web of Science and EMBASE. Two researchers will work in the selection, analysis and inclusion phases of the articles. In the case of divergence, a third-party reviewer will be contacted. The following studies will be included: (1) cohort studies, case–control studies and cross-sectional studies; (2) studies carried out on patients with serum 25-hydroxyvitamin D levels below 30 ng/mL; (3) studies conducted with an adult population; (4) studies using neuroimaging methods. Articles considered eligible will be analysed by the Newcastle-Ottawa Quality Assessment Scale/cross-section studies to evaluate study quality. The survey will be conducted from June to December 2022.

Ethics and dissemination The identification of the main and most frequent brain alterations found through neuroimaging in patients with vitamin D deficiency can guide professionals as to the identification which of the main cerebral pathologies detected through neuroimaging are related to vitamin D deficiency, in choosing more sensitive and specific neuroimaging tests to detect these brain changes, in addition to emphasising the importance of monitoring and maintaining adequate serum levels of vitamin D, in order to reduce possible cognitive sequelae. Results will be announced at national and international conferences.

PROSPERO registration number CRD42018100074.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The protocol was previously registered and submitted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).
⇒ Review based on validated registration data based on confirmation by imaging examinations.
⇒ Statistical analysis methods and risk of bias assessment tools recommended by PRISMA were used.
⇒ Grey literature will not be considered.
⇒ Comparison of studies with different designs cannot be done.

INTRODUCTION

The neuroprotective effect of vitamin D is well addressed in several studies in which many factors are related to this protection, considering that the vitamin D receptors and the enzymes responsible for its hydroxylation were mapped throughout the brain, including the amygdala/limbic system, where behaviour/emotions are regulated. In addition, calcitriol is also involved in the release of brain neurotransmitters and neurotrophic factors,[1 2] highlighting the anti-inflammatory mechanism of vitamin D reducing oxidative stress and release of inflammatory cytokines, attenuating or suppressing the autoimmune response.[3–6]

Vitamin D deficiency is related to several pathologies of cerebral involvement, such as depression,[7 8] all types of dementia, Alzheimer,[9–11] Parkinson's disease[12–14] with systematic review and meta-analysis, from 2017 demonstrating that vitamin D deficiency contributes to dementia,[15] multiple sclerosis,[5 16 17] cerebral small vessel disease[18] it being an independent risk factor for cerebrovascular accident (CVA),[19 20] with vitamin D having a potential anti-inflammatory role in individuals diagnosed with CVA.[6]

Among the cognitive symptoms most commonly related to vitamin D deficiency, cognitive decline and executive dysfunction stand out. In addition, evidence has shown that severe vitamin D deficiency is significantly associated with a greater decline in visual memory. Among older adults, he

observed that those moderately and severely deficient in serum 25-hydroxyvitamin D (25(OH)D) (30 to <50 and <30 nmol/L, respectively) experienced a significantly greater annual decline in verbal memory (immediate and delayed recall of the word list) compared with enough (50 to <125 nmol/L) in an average of 4.8 years.[21]

Several neurodegenerative and vascular mechanisms have been identified explaining the association between vitamin D, cognition and dementia. In these studies, executive dysfunction is more strongly linked to cerebrovascular disease than to neurodegeneration. Low levels of 25(OH)D are associated with an increased risk of stroke, particularly ischaemic.[22]

Some cross-sectional and cohort studies showed an association between low vitamin D concentrations and an increased risk of abnormalities in neuroimaging, with neurodegenerative and cerebrovascular alterations such as white matter hyperintensities,[23–25] with increased ventricular volume[26] related to dementia, as well as infarctions,[18] with reduced hippocampal volumes, as revealed in Framingham Heart Study,[27] as well as in the study in patients with schizophrenia, in which was a significant positive correlation between vitamin D and the regional grey matter volume in the hippocampus.[28]

In a cross-sectional study performed with 110 elderly patients evaluated by MRI, the serum concentration of 25(OH)D was independently and inversely associated with intracranial volume.[29]

However, two other studies found no correlation between abnormalities in neuroimaging and vitamin D deficiency.[30 31] The Atherosclerosis Risk in Communities brain MRI study performed with adult patients did not show a cross-sectional association between lower levels of vitamin D and the severity score of white matter hyperintensity, prevalent high-grade White Matter Hyperintensities (WMHs) score (≥3) or prevalence of infarctions. However, 40% of the patients were lost in this study, which may have influenced the findings.[30] In the other prospective population cohort study from Cardiovascular Health Study performed with 1658 elderly patients, the serum 25(OH)D status was not significantly associated with the development of any neuroimaging abnormalities assessed by MRI, but those elderly with vitamin D deficiency were linked to an increased risk of infarction compared with those with normal vitamin D levels.[31]

In systematic review and meta-analysis carried out with the objective of evaluating cerebral morphometric alterations associated with vitamin D deficiency or sufficiency, it was found that low serum vitamin D levels were associated with cerebral volume reduction, with larger lateral ventricles, however, this review included experimental studies, not restricting the research to the original studies performed with humans.[32]

Important advances were also related to vitamin D and its neuromodulatory role in pain from the reduction of chronic pain. Regarding pain sensitisation mechanisms, vitamin D seems to stimulate anti-inflammatory processes in some cases and thus alleviate the painful sensation of many diseases.[33] The mechanism by which pain reduction would occur is related to the fact that the active form of vitamin D (1,25(OH)2D) would act on Th2 cells by increasing the synthesis of interleukin 4 (IL-4) and transforming growth factor-β (TGF-β). Knowing that TGF-β decreases the expression of pro-inflammatory cytokines, such as interferon-γ (IFN-γ), IL-1 and TNF-α. Both TGF-β and IL-4 are found in microglial cells. In this case, vitamin D inhibits the action of PGE 2 by inhibiting its precursor, cyclo-oxygenase-2.[34] Additionally, studies have shown that 1,25(OH)2D prevents the synthesis of inducible nitric oxide synthase, an enzyme that produces large amounts of nitric oxide when stimulated. These regulatory pathways are involved in the sensitisation of pain and 1,25(OH)2D and appear to regulate important molecules involved in this process, confirming their neuroimmunomodulatory role.

The role of vitamin D in improving neuromuscular function is also theorised, in which it is known that 1α,25(OH)2D can bind to its receptor in muscle tissues, allowing protein synthesis and cell growth. muscles, thus being able to improve muscle strength and function and consequently postural and dynamic balance.[35]

Due to the important role of vitamin D and its receptor in various organs, such as the brain, as well as the existence of a large body of evidence associating its deficiency with several pathologies related to the central nervous system and also considering the ease and low cost of its supplementation, studies aimed at understanding and evaluating brain abnormalities related to vitamin D deficiency are essential.

However, it is important to state that there is still no consensus on the correlations under study. This review proposes to present a descriptive picture on the following research question: what is the frequency of brain and cognitive changes in neuroimaging tests in adult patients with vitamin D deficiency?

METHODS AND ANALYSIS

Inclusion criteria for study selection

Patient and public Involvement

No patient involved.

Design and registration of the study

The methods of the review protocol were drafted in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[36] The systematic review article will follow the guidelines of the Systematic Review and Meta-Analysis Protocols.[37]

The leading research question was based on the Population, Intervention, Comparator, Outcome, Setting strategy[38]: 'What is the frequency of brain and cognitive changes in neuroimaging tests in adult patients with vitamin D deficiency?'.

Inclusion criteria for study selection

The following studies will be included: (1) cohort studies, case–control studies and cross-sectional studies; (2) studies

carried out on patients with serum 25(OH)D levels below 30 ng/mL; (3) studies conducted with an adult population; (4) studies using neuroimaging methods. There will be no restrictions regarding the gender or ethnicity of the participants or the publication date and language of the article. Review studies and editorial notes will be excluded from the analysis.

Types of patients

Individuals aged over 18 years with vitamin D deficiency who underwent neuroimaging.

Exposure

The exposure of interest is vitamin D deficiency. Thus, studies reporting neuroimaging in patients with low serum vitamin D levels will be included in the review.

Search methods for the identification of studies

Information sources

The research will be conducted in the following electronic databases: EMBASE, Medline via PubMed, Web of Science and Scopus and PsycINFO. After the search is carried out, the snowball sampling strategy will be adopted for data recovery.[39] Grey literature will not be considered.

Search strategy

The following descriptors registered in the Mesh will be considered:

"Vitamin D" OR "Vitamin D deficiency" [MeSH Terms] AND ("neuroimaging" OR "Brain Mapping" [MeSH Terms] OR "Magnetic Resonance Imaging" [MeSH Terms] OR "Magnetic Resonance Spectroscopy"[MeSH Terms] OR "Tomography, X-Ray Computed" [MeSH Terms] OR "Tomography, Emission Computed-, Single-Photon" [MeSH Terms] OR "magnetoencephalography" [MeSH Terms] OR "infrared, Near- spectroscopy" [MeSH Terms] OR "Positron-Emission Tomography" [MeSH Terms] OR "radionuclide imaging"[MeSH Terms] OR "nuclear medicine"[MeSH Terms]) combined with one another using the Boolean operator "AND" and "OR. Editorials, news and letters will be excluded. No limits as to year or language will be applied.

Data analysis

Data management

The data obtained will be exported to Endnote V.7.1 and duplicate records will be removed electronically. Tracing and extraction will occur in a database created specifically for the review in Microsoft Excel to ensure that all retrieved references are fully traced.

Selection process

In the initial phase of screening, two authors will independently select the articles through the analysis of the title and summary according to the eligibility criteria. These same researchers will critically appraise the full text of articles. To reduce the risk of bias and lack of potentially relevant studies, researchers will adopt a more tolerant approach at the first screening level. Both researchers will obtain full-text articles for studies that meet the criteria for inclusion of the review. The level of agreement between the two reviewers will be calculated, the reasons for the rejection of articles during the initial screening and the full-text evaluation process will be noted and stored in the database. Any discrepancies will be discussed and resolved by a third-party reviewer.

Data extraction

The data obtained will be condensed and organised into tables created specifically for the review that will bring the following information:

- Characteristics of the study: authors, year of publication, study design, study period.
- General characteristics of the sample: characteristics of the population studied (individuals with vitamin D deficiency), methods of recruitment and sampling, inclusion/exclusion criteria.
- Diagnostic methods and equipment for serum 25(OH)D dosage and for neuroimaging.
- Brain abnormalities found in functional and structural neuroimaging tests: description of the type of brain abnormality, extent and location.
- Pathologies of cerebral involvement with neuroimaging changes most frequent in patients with vitamin D deficiency.

We will consider contacting the corresponding authors for any missing information using a standardised email template.

Risk of bias quality assessment (in individual studies)

In the evaluation of risk of bias, all included articles will be submitted to an analysis of their methodological quality, following Newcastle-Ottawa Quality Assessment Scale/cross-section studies[40] (NOS) protocol. This protocol analyses the articles according to: selection (sample representativeness, sample size, subjects which did not respond, exposure/risk factors), comparability and outcomes (evaluation of outcomes, statistical analysis). The NOS qualitative analysis is determined using the total classification of 10 stars, distributed throughout three domains: selection (maximum five stars), comparability (maximum two stars) and outcomes (maximum three stars).

The strength of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach,[41] the extraction of data and the evaluation of quality will be carried out independently by two authors. The information will be examined and judged independently by a third-party reviewer when necessary.

Ethics and dissemination

The review does not require approval of the ethics committee and informed consent, and the outcome will be released as a literature review. This systematic review protocol received no specific grant from any funding agency in the public, commercial or non-profit sectors.

The review will not require the approval of the ethics committee, as it is a systematic review. The results and conclusions of the review will be taken to national and international symposia and forwarded for submission in a peer-reviewed journal.

In view of the results of the review, it is intended: (1) to identify the most frequent brain changes and cognitive impairments found in neuroimaging tests in the population of individuals with vitamin D deficiency; (2) assess which major brain pathologies detected in neuroimaging tests are related to vitamin D deficiency; (3) assess which neuroimaging tests are most sensitive and specific for detecting brain changes in people with vitamin D deficiency. (4) corroborate the inclusion of the clinical investigation of these tests in patients with vitamin D deficiency.

This study has some important limitations. As this is a review, important associations on the frequency of changes and disease severity cannot be performed. In addition, it is not possible to precisely identify which are the stages and stages of the disease that present greater risks and brain impairments, as well as whether there is remission of changes after conducting treatments. These limitations seem to be important and should be investigated in future studies.

Contributors Data curation: CMP, RdCHL, RAdS, TdPSdS, PRBD, EBS. Formal analysis: RdCHL, RAdS, CMP, TdPSdS. Investigation: CMP, TdPSdS. Methodology: CMP. Project administration: PRBD,TdPSdS. Software: RdCHL, RAdS, CMP. Supervision: TdPSdS, PRBD, EBS. Validation: RdCHL, RAdS, CMP. Visualization: CMP. Writing – original draft: CMP. Writing – review and editing: TdPSdS.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

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