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REVIEW ARTICLE

VITAMIN D DEFICIENCY AND CARDIOVASCULAR MORTALITY IN CHRONIC KIDNEY DISEASE: INTEGRATIVE REVIEW

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ABSTRACT

Objective: To analyze scientific studies that have addressed vitamin D deficiency and cardiovascular mortality in people with chronic kidney disease. **Method**: This is an integrative literature review conducted through the LILACS, PubMed and Medline databases, and through the SciELO electronic library, using the 'vitamin D deficiency', 'cardiovascular mortality' and 'chronic kidney disease' descriptors, with 14 articles being selected for analysis. **Results**: By analyzing the selected articles, it was possible to identify that vitamin D deficiency and cardiovascular mortality are very common conditions in chronic renal patients and, for this reason, there are hypotheses that correcting this deficiency may have beneficial effects on the disease and cardiovascular mortality in this population. **Conclusion**: There is an intrinsic relationship between vitamin D deficiency and cardiovascular mortality. However, it is still debatable whether vitamin D supplementation reduces cardiovascular mortality in chronic renal patients. Such hypothesis needs to be tested in clinical trials, which gives cause for the need to develop further research on the theme.

Keywords: Vitamin D deficiency. Mortality. Chronic Kidney Disease.

INTRODUCTION

Chronic non-communicable diseases (CNCDs) are one of the main causes of death in Brazil and in the world, accounting for 70% of the worldwide mortality rate and 38 million deaths per year[1]. One of the most prevalent CNCDs in Brazil and globally is chronic kidney disease (CKD), which has many causes and risk factors for its development, being characterized by damage to the structure of the kidneys, as well as by a progressive, irreversible and insidious loss of function for more than three months, resulting in multiple negative outcomes[2].

CKD is considered a public health problem in Brazil and worldwide, with an increasing global trend of people with the disease. Given its high prevalence, the Global Burden Disease Study[3] pointed out that CKD had one of the highest growth in mortality rates in the world, staying behind diabetes and dementia, going from the 21st place in 1990 to the 12th place in 2015.

CKD, without proper treatment, evolves to its final stage, known as end-stage renal disease (ESRD), and, along with its complications, especially cardiovascular disease (CVD), requires replacement renal therapy (RRT). People with CKD have an increased risk of cardiovascular mortality, which is thus the main cause of death among these patients, and it is more likely that death will occur due to cardiovascular events than due to progression to ESRD. Morbimortality related to cardiovascular disease in people with chronic kidney disease is higher than in those without the latter. Cardiovascular mortality and morbidity are inversely related to renal function, more explicitly in the terminal stage of the disease[4].

Another complication from CKD is the

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mineral and bone disorder, which can lead to vitamin D deficiency and cause an imbalance in calcium metabolism. The non-classic effects of vitamin D on the myocardial and vascular functions have been highlighted in some studies[5-6].

Although the mechanisms have not yet been fully elucidated, an association between the prevalence of vitamin D deficiency in people with CKD and increased risk of mortality from cardiovascular causes is suggested, that is, there might be a relationship between low serum levels of vitamin D and the increase in cardiovascular mortality in this population[7].

In light of the foregoing, the following research question was elaborated: What evidence is available in the literature on vitamin D deficiency in people with chronic kidney disease and on mortality from cardiovascular causes?

Thus, the objective of the study was to analyze scientific studies that have addressed vitamin D deficiency and cardiovascular mortality in people with chronic kidney disease.

METHODS

With a view to achieving the proposed objective, an integrative literature review was chosen, a research method that consists of building a broad analysis of publications, and that contributes to discussions about research methods and results, as well as reflections for conducting future studies.

Six steps[8] were taken for the operationalization of this review: 1- elaboration of the research question; 2- selection of the studies that will compose the sample; 3- definition of the characteristics of the studies; 4- critical analysis of the studies included; 5- synthesis of results; and 6- presentation of the review.

To structure the review question – first stage –, the PICO strategy was used, in which P refers to the population, made up of people with chronic kidney disease; I- Intervention, presentation or topic of interest – vitamin D deficiency –; C- Comparison – there will be none; O- Outcome or results – related to cardiovascular mortality. Thus, the research question was structured as follows: What evidence is available in the literature on vitamin D deficiency in people with chronic kidney disease and on mortality from cardiovascular causes?

To search for studies in the databases – second stage –, health descriptors (DeCS) combined with each other by the Boolean operator "AND" were used. It is noteworthy that for bases that primarily use the English language, the descriptors were combined in the same language, compatible with MESH. Thus, the descriptors used were: *doença renal crônica* (Chronic Kidney disease [CKD]), *mortalidade* (mortality) and *deficiência de vitamina D* (vitamin D deficiency).

Data were collected between the months of June and August 2020 by two authors, independently and concurrently, in the LILACS (Latin American Health Literature), MEDLINE (Medical Literature Analysis and Retrieval System Online), and PubMed (US National Library of Medicine) databases, and in the SciELO (Scientific Electronic Library Online) electronic library. These databases were chosen due to their scientific relevance and the relationship of the theme with the indexed content.

A total of 79 potential studies were found, 19 of which in LILACS; three in MEDLINE; 56 in PubMed, and one in SciELO, with the search being run without using filters.

For the sample selection process – third stage –, the following inclusion criteria were established: articles available online in full for reading, and in Portuguese and English. As exclusion criteria, case/experience reports, theses, dissertations, book chapters, news, editorials and non-scientific texts were disregarded.

Initially, a skimming was performed for pre-analysis of the chosen material. Those that presented a good methodological design, clearly defined objectives, results that answered the guiding question and published in the period from 2013 to 2020 were included. Duplicate studies were disregarded for selective reading. Based on the publications selected during the search, and in strict compliance with the inclusion and exclusion criteria presented, the title and abstract of each article were read for the final sample to be obtained, resulting in 14 publications, six in LILACS, four in PubMed, three in MEDLINE and one in Scielo, all published between January 2013 and August

2020.

For the critical analysis – fourth stage –, each piece of information obtained through the selected articles was carefully searched, identifying the most relevant data that answered the research question. To this end, the articles were read in full, and the following information was selected: journal, title, authorship, year/country, objective, methodology, result, and conclusion. In addition, the studies were classified in accordance with their level of evidence, namely: Level 1: obtained through meta-analysis of controlled clinical studies and with randomization; Level 2: obtained by studies with experimental design; Level 3: design of quasi-experimental research; Level 4: obtained from cohort and case-control studies; Level 5: obtained from a systematic review of descriptive and qualitative studies; Level 6: obtained from one single descriptive or qualitative study and; Level 7: obtained from opinions of authorities or expert committee reports[9].

The analysis and synthesis of the data extracted from the articles were performed in a descriptive manner, making it possible to observe, count, describe and classify the data, in order to gather the knowledge produced on the theme explored in the review[10].

RESULTS

To summarize and present the results of the review, a chart containing the identification of the studies, as well as their level of evidence, objectives, methods, results and conclusion was created (Chart 1).

In this integrative review, 14 scientific articles were described, as they strictly met the selection of the sample previously established, with six articles found in the LILACS database, four in PubMed, three in MEDLINE, and one in Scielo. As for the language, 85.7% of the selected articles are in English. In accordance with the year of publication, 2013 and 2017 were found to have the highest number of articles produced, with three articles published each year. As for the method of the selected articles, seven were literature reviews, two were systematic reviews with meta-analysis, two were cross-sectional studies, one was a systematic review, and two were randomized clinical trials.

Chart 1. Distribution of studies, in accordance with their identification, level of evidence, objectives, methods, results and conclusion. São Luís, MA, 2020.

Identification	Objectives	Methods	Results	Conclusion
Duranton[11] *et al.*, 2013 *American Journal of Nephrology* Level of evidence: 5	To assess the association between vitamin D use and causes of mortality and cardiac mortality in patients with CKD.	Systematic review with meta-analysis	The risk of cardiovascular mortality was significantly reduced in patients who received some type of vitamin D derivative.	The use of vitamin D and analogues is associated with reduced mortality in patients with CKD.
Melamed Filho[12] *et al.*, 2013 *Brazilian Journal of Nephrology* Level of evidence: 6	To relate vitamin D deficiency and its participation in the pathogenesis of kidney disease and the outcomes in kidney disease.	Review study	Vitamin D deficiency was associated with the incidence of cardiovascular mortality and all-cause mortality in chronic renal patients.	Low serum levels of 25(OH)D were associated with all-cause mortality, including cardiovascular ones, as well as an increased risk of comorbidities.
Zheng[6] *et al.*, 2013 *BMC Nephrology* Level of evidence: 5	To assess whether vitamin D supplementation reduces mortality in CKD patients with and without dialysis.	Systematic review	Participants who received vitamin D had a lower mortality rate than those who did not receive treatment.	Vitamin D was associated with decreased all-cause mortality and cardiac mortality in patients with CKD.
Mann[13] *et al.*, 2014 *Clinical Kidney Journal* Level of evidence: 6	To assess whether vitamin D supplementation affects the relative risk as to all causes of mortality and cardiovascular mortality in patients with CKD.	Review study	No significant effect of vitamin D treatment was found on the causes of mortality, cardiac mortality or serious adverse cardiac events.	It brings little evidence of the effects of vitamin D supplementation on the causes of mortality and cardiac mortality, as well as of its action on cardiac events compared with placebo.
Parikh[14] *et al.*, 2014 *Seminars in Dialysis* Level of evidence: 6	To discuss the evidence behind the use of forms of vitamin D in patients undergoing dialysis.	Review study	Vitamin D may have pleotropic effects in dialysis patients, effects on organs, and results that are not related to mineral and bone metabolism.	The data show that using vitamin D improves survival, but this association is not seen in observational studies.
Ferreira[15] *et al.*, 2015 *Portuguese Journal of Nephrology and Hypertension* Level of evidence: 6	To discuss the physiology of vitamin D and the consequences of vitamin D deficiency in CKD and kidney transplant recipients.	Review study	All studies showed efficacy in reducing parathyroid hormones (PTH) and positive effects on mortality.	Vitamin D deficiency was associated with cardiovascular disease, which is the main cause of death in CKD.
Sekercioglu[16] *et al.*, 2016 *Renal Failure* Level of evidence: 5	To compare the effects of cinacalcet versus standard treatment in patients with the CKD mineral and bone disorder.	Systematic review with meta-analysis	The results were not conclusive as to the impact and effects of cinacalcet on reducing hospitalization from cardiovascular events, cardiac mortality and all-cause mortality in patients with CKD.	Cinacalcet decreases parathyroidectomy rates in patients with the CKD mineral and bone disorder, but has no influence on mortality.

To be continued…

Identification	Objectives	Methods	Results	Conclusion
Magalhães[17] *et al.*, 2017 *PloS One* Level of evidence: 6	To assess the clinical and laboratory characteristics of patients undergoing dialysis, and to identify risk factors that contribute to their mortality.	Cross-sectional study	Most patients had reduced levels of vitamin D and, at the end of one year of follow-up, 14% of the patients died and had as associated risk factors: arteriovenous fistula, old age, and low vitamin D levels.	The combination of clinical assessment, biochemical parameters, and risk factors revealed that mortality in urgent-start dialysis is associated with older age and deficient levels of vitamin D.
Hou[18] *et al*., 2017 *BioMed Research International* Level of evidence: 6	To assess the role of vitamin D in uremic vascular calcification.	Review study	Vitamin D supplementation may have an adjuvant role in reducing arterial calcification by reducing proteinuria, reversing renal osteodystrophy and restoring calcification inhibitors.	Nutritional supplementation of vitamin D may provide a supporting role to improve uremic vascular calcification.
Shardlow[19] *et al.*, 2017 *British Medical Journal Open* Level of evidence: 6	To elucidate whether patients with vitamin D deficiency have the worst results in the early stages of CKD.	Cross-sectional study	Vitamin D deficiency and SHPT were independently associated with all causes of mortality. After adjusting the multivariate models of CKD progression, no association with vitamin D was found.	The findings suggested the hypothesis that detecting and treating vitamin D deficiency, as a possible factor for high PTH, in patients with stage 3 CKD, may increase their survival rate.
Hamano[20], 2018 *Journal of Clinical & Experimental Nephrology* Level of evidence: 4	To analyze associated and predictive factors for chronic kidney disease.	Randomized clinical trial	2+ proteinuria or a greater one is associated with low vitamin D; massive doses of vitamin D exacerbates renal fibrosis in mice.	The prescription of vitamin D in renal transplant recipients was associated with lower morbidity, and low levels of vitamin D predict worse renal results.
Brzózka[21] *et al.*,2018 *Nutrients* Level of evidence: 6	To show the association between vitamin D use in patients on dialysis and with CKD and its relationship with survival.	Review study	Studies show that an association between the use of active therapy with vitamin D in patients with CKD increases survival. The greater the vitamin D deficiency, the greater the risk of cardiac impairment in renal patients.	Vitamin D deficiency is present in the early stages of CKD, and the relationship between vitamin D deficit and impaired cardiac contractile function in chronic renal patients exists.
Chen[22] *et al*., 2019 *Kidney and Blood Pressure Research* Level of evidence: 1	To investigate the relationship between vitamin D blood concentrations and cardiovascular events in patients with CKD on hemodialysis and in the terminal stage.	Randomized clinical trial	The level of free vitamin D was measured in patients followed up for six months. Cardiovascular events were recorded. In patients without any events, the serum level of vitamin D was significantly higher.	Low serum concentrations of vitamin D are associated with major cardiovascular events in patients with CKD on dialysis.
Junarta[23] *et al*., 2019 Nephrology Level of evidence: 5	To investigate the impact of vitamin D supplementation on substitute outcomes and cardiovascular events in CKD trials.	Review study with meta-analysis	It was suggested that vitamin D supplementation in patients with CKD decreased mortality, including cardiovascular mortality. However, the right dose of supplementation from patient to patient still requires further studies when considering different genotypes for vitamin D-binding protein (DBP).	Although the studies suggest positive results, the use of different vitamin D formulations limits their conclusive capacity.

The articles explained that both the causes of chronic kidney disease and its progression, of a systemic and irreversible character, are factors that contribute to raising mortality from cardiovascular causes, as well as to vitamin D deficiency in this population. Vitamin D deficiency and cardiovascular mortality share traditional risk factors, especially in the context of chronic kidney disease, in which the progression of the disease tends to increase risks.

The studies showed that vitamin D deficiency is prevalent in people with chronic kidney disease. In the observational and laboratory studies, supplementation with vitamin D and its analogues showed significant results in increasing survival, significantly reducing all-cause mortality and even cardiovascular mortality in this population. However, these results have not been observed in better designed clinical trials.

DISCUSSION

From the analysis of the articles, a high prevalence of vitamin D deficiency was identified in all CKD stages[13,17-18]. It is known that most of vitamin D is produced through cutaneous synthesis (Vitamin D3 or Cholecalciferol) induced by sunlight (approximately 80%), while the rest comes from food and supplements[24]. And, in this process, the kidney is a key organ in the activation and regulation of circulating levels of vitamin D.

In recent years, vitamin D ceased to be considered just an essential hormone for bone metabolism, whose deficiency leads to the onset of osteopenia, osteoporosis and osteomalacia. A deficiency of it has been shown to be associated with several clinical conditions, such as secondary hyperparathyroidism, diabetes mellitus, increased cardiovascular risk and faster progression of chronic kidney disease[25].

In the context of CKD, it is recognized that vitamin D deficiency is highly prevalent and has been associated with left ventricular hypertrophy and increased mortality, regardless of vascular calcification and stiffness. Most people with CKD present restricted protein and calorie intake, which contributed to the relatively low levels of vitamin D observed in this population[26].

Additionally, as CKD progresses, cutaneous vitamin synthesis lowers because people with this disease go through an increase in skin pigmentation, are less exposed to sunlight, malnourished, present a decrease in renal mass,

in the rate of glomerular filtration and megalin expression, and greater loss of vitamin D urinary metabolites with evident proteinuria[26].

Another finding in this study was that vitamin D deficiency in people with CKD was associated with cardiovascular disease[15,21-22] and increased mortality[12,17,20]. Vitamin D deficiency is related to a wide variety of acute and chronic diseases, such as infectious, autoimmune diseases, stroke, type 2 diabetes, cardiovascular diseases, among others[27].

Most people undergoing dialysis are vitamin D deficient, both in the active and inactive forms. This deficiency, when not treated, leads to secondary hyperparathyroidism and, when they are associated, the mortality rate among chronic renal patients further increases[14]. The impact of vitamin D deficiency on the cardiovascular system of people with CKD is high, with its greatest expression in the renin-angiotensin-aldosterone system, with a consequent increase in blood pressure, causing vascular calcification and having implications for lipid metabolism[28].

Another highlighted aspect[6] is that vitamin D deficiency can increase the risk of death from cardiovascular events. Serum levels of PTH, calcium and phosphorus may be associated with this increased risk, along with dose, treatment length, frequency and limiting factors. However, other studies with more robust methodologies need to be developed.

In the analyzed researches, it was shown that vitamin D supplementation can increase the survival of people with CKD[6,11,14,21-22,23] and help improve arterial calcification[16]. A study[15] concluded that vitamin D deficiency is a common disorder in CKD that, when diagnosed and treated appropriately, increases survival. Using vitamin D analogues that activate selective vitamin D receptors provides better results, since they have immunomodulatory and anti-inflammatory effects.

In contrast, some studies[13,16,19] have stressed the little influence of vitamin D supplementation and the use of Cinacalcet on mortality. A study carried out in Taiwan[18] showed that in laboratory models, vitamin D supplementation activates vitamin D receptors (VDR) in the liver and reduces serum cholesterol levels, thus decreasing the formation of atheroma plaques and improving their modulation by inflammatory agents, consequently mitigating atherosclerosis and the risk of cardiovascular events in people with chronic kidney disease.

Vitamin D deficiency is a potentially modifiable risk factor. However, there is no conclusive evidence that supplementation with vitamin D and its analogues increases the survival of people with CKD[19]. This lack of consensus is the result of the absence of large clinical trials and prospective studies, which confirms the results of some studies[11-12,17]. These researchers warn of the need for clinical trials to validate the benefits of vitamin D. The absence of double-blind studies, controlled clinical trials and randomized clinical trials is pointed out[13].

A study[13] categorically evidences that vitamin D treatment has no quantifiable effect on all-cause mortality in people with CKD compared to using vitamin D and placebo. It notes that a prolonged clinical use of vitamin D supplementation in the population of renal patients contrasts with the inconsistent results of clinical trials, and the elaboration of studies involving people with CKD is what will allow a real assessment of the possible benefits of vitamin D in the context of CKD.

In view of the need to ensure an assistance practice based on scientific evidence, the integrative review becomes a tool in the health field, as it summarizes the available research on a certain theme and guides a practice based on scientific knowledge. Although combining data from different research designs is complex and challenging, conducting an integrative review, by including a systematic and rigorous approach to the process, particularly to data analysis, reduces biases and errors. Therefore, it is imperative to consolidate the integrative review as a valid instrument of Evidence-Based Practice, especially in the Brazilian nursing scenario.

The importance of nursing professionals knowing about this theme is noteworthy as well, and mapping the evidence from this literature review is expected to be able to support practices and add value in the nurses' work process, especially among those who care for people with kidney diseases.

The heterogeneity of the selected studies and even the possibility of biases in described individual studies are uncontrolled

characteristics in this type of study and, therefore, considered as a limitation of the research.

FURTHER CONSIDERATIONS

It is known that vitamin D has an important role in health and, especially, in the context of chronic kidney disease, a chronic non-communicable disease with increased mortality both in Brazil and worldwide.

The analyzed studies showed that the most frequent cause of death in people with chronic kidney disease occurs due to cardiovascular events and, in most deaths, there are significant reductions in the serum levels of vitamin D and its analogues.

Vitamin D deficiency and cardiovascular mortality are very prevalent conditions in people with CKD; thus, there is an intrinsic relationship between both. However, it is still debatable whether vitamin D supplementation reduces cardiovascular mortality in people with this condition, which requires further research and testing by clinical trials.

DEFICIÊNCIA DE VITAMINA D E MORTALIDADE CARDIOVASCULAR NA DOENÇA RENAL CRÔNICA: REVISÃO INTEGRATIVA

RESUMO

Objetivo: analisar os estudos científicos desenvolvidos sobre a deficiência de vitamina D e a mortalidade por causa cardiovascular nas pessoas com doença renal crônica. **Método**: Trata-se de uma revisão integrativa da literatura a partir das bases de dados LILACS, PubMed, Medline e na biblioteca eletrônica SciELO, utilizando os descritores deficiência de vitamina D, mortalidade cardiovascular e doença renal crônica, sendo selecionados 14 artigos para análise. **Resultados:** A partir da análise dos artigos selecionados, foi possível identificar que a deficiência de vitamina D e a mortalidade cardiovascular são condições muito frequentes em renais crônicos e, por isso,discutem-se hipóteses de que a correção desta deficiência pode exercer efeitos benéficos sobre a doença e mortalidade cardiovascular nessa população. **Conclusão**: Há uma intrínseca relação entre a carência de vitamina D e a mortalidade cardiovascular. Entretanto, ainda é discutível se a suplementação de vitamina D reduz a mortalidade cardiovascular nos doentes renais crônicos. Tal hipótese precisa ser testada em ensaios clínicos, ensejando a necessidade de se desenvolver mais pesquisas sobre o tema**.**

Palavras-chave: Deficiência de vitamina D. Mortalidade. Insuficiência Renal Crônica.

DEFICIENCIA DE VITAMINA D Y MORTALIDAD CARDIOVASCULAR EN LA ENFERMEDAD RENAL CRÓNICA: REVISIÓN INTEGRADORA

RESUMEN

Objetivo: analizar los estudios científicos desarrollados sobre la deficiencia de vitamina D yla mortalidad por causa cardiovascular en las personas conenfermedad renal crónica. **Método**: se trata de una revisión integradora de la literatura a partir de las bases de datos LILACS, PubMed, Medline yen la biblioteca electrónica SciELO, utilizando los descriptores deficiencia de vitamina D; mortalidad cardiovascular yenfermedad renal crónica, siendo seleccionados 14 artículos para el análisis. **Resultados:**a partir del análisis de los artículos seleccionados, fue posible identificar que la deficiencia de vitamina D yla mortalidad cardiovascular son condiciones muy frecuentes en enfermos renales crónicos y, por ello, se discuten hipótesis de que la corrección de esta deficiencia puede ejercer efectos benéficos sobre la enfermedady mortalidad cardiovascular enesta población. **Conclusión**: hay una intrínseca relación entre la carencia de vitamina D yla mortalidad cardiovascular. Sin embargo, aúnes discutible sila suplementación de vitamina D reducela mortalidad cardiovascular en los enfermos renales crónicos. Tal hipótesisnecesita ser probada en ensayos clínicos, fomentando la necesidad de desarrollarse más investigaciones sobre el tema**.**

Palabras clave: Deficiencia de vitamina D. Mortalidad. Insuficiencia Renal Crónica.

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