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BLOOD PRESSURE CHANGES AFTER SUPPLEMENTATION OF VITAMIN D IN PATIENTS WITH CHRONIC KIDNEY DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: To analyze the effects of vitamin D supplementation on blood pressure (BP) in patients with Chronic Kidney Disease (CKD). **Method**: For this systematic review, searches were performed in the databases PUBMED, COCHRANE LIBRARY, BVS, Embase and Web of Science for clinical trials about vitamin D supplementation in populations with CKD. The analysis of the articles had as selection criteria the outcome of searching for changes in blood pressure. Qualitative assessment for risk of bias in the studies included. **Results**: In the primary search in the databases, 204 articles were found. After screening and qualitative analysis, 8 works remained for final compilation, with a total population of 474 participants, of which 254 belong to the intervention group and 220 to the control group. **Discussion**: Vitamin D supplementation in patients with CKD shows no significant changes in blood pressure. **Conclusion**: No correlation was found between vitamin D supplementation and BP alteration in patients with CKD, however, the literature was sparse on the subject, so further research is needed to better understand the theme.

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INTRODUCTION

Chronic Kidney Disease (CKD) is characterized as a generally irreversible syndrome and with a progressive character. Approximately, CKD prevalence in the world is between 8 and 16%, with an increase in the group of over 64 years patients, which can reach 23-38% in this specific population. Then, it is suggested that, with an increase of age, there is also an increase of CKD prevalence (Pereira *et al.,* 2017; Zhong *et al.,* 2017). In addition, patients suffering from CKD have changes in the renal structure, which can affect the glomerular apparatus, the endocrine part of the kidneys or the tubular region. Thus, it implies reducing in the renal filtration capacity or even complete failure. Therefore, changes in mineral metabolism cascade can be found, because there is an increase in parathyroid hormone (PTH) release by the parathyroid glands. However, in addition to this alteration, it is common to find diseases and cardiovascular alterations (hypertension, hypertriglyceridemia, diabetes, low levels of cholesterol and high-density lipoproteins) that, in correlation with another factors, have shown a high rate of morbidity and mortality in this group (Gluba-Brzózka *et al.,* 2018; Kim *et al.,* 2017). In cross-sectional studies, it has been observed that vitamin D deficiency is common in patients with CKD. This is a prehormone that the active form found in the body is 1.25-OH-vitamin D. Several Brazilian and international guidelines that address CKD, recommend vitamin D supplementation for patients, due to the existing deficiency associated with this substance and its effect on the release of PTH (Batacchi *et al.,* 2017; Gluba-Brzózka *et al.,* 2018). Hypertension is a multifactorial disease that is influenced by genetic and environmental factors. Vitamin D deficiency has a direct effect on activation on the Renin-Angiotensin-Aldosterone System (RAAS) and on the vascular endothelium. Consequently, these changes have a fundamental role for both persistence and the genesis of this disease. Because of this, it is important to analyze vitamin D supplementation in patients with CKD, as a form to evidence clinical status

improvement, which may be related to beneficial survival results for these patients (Fonseca, 2015; Gluba-Brzózka *et al.,* 2018). Given this context, this article aims to assess the effects of vitamin D supplementation on blood pressure in patients who have been diagnosed with CKD.

METHOD

This systematic review complies with the recommendations and criteria described in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher *et al.,* 2009) and the Cochrane Handbook (Higgins *et al.,* 2011).

Search Strategy: Potential studies have been identified through an embracing strategy. Searches for articles to integrate this systematic review were performed in the following databases: Pubmed and Cochrane Library on July 27, 2020, Virtual Health Library on October 02, 2020, Embase and Web of Science on December 12, 2020 October 2020. Pubmed Strategy: ((("Renal Insufficiency, Chronic"[Mesh] OR (Chronic Renal Insufficiencies) OR (Renal Insufficiencies, Chronic) OR (Chronic Renal Insufficiency) OR (Kidney Insufficiency, Chronic) OR (Chronic Kidney Insufficiency) OR (Chronic Kidney Insufficiencies) OR (Kidney Insufficiencies, Chronic) OR (Chronic Kidney Diseases) OR (Chronic Kidney Disease) OR (Disease, Chronic Kidney) OR (Diseases, Chronic Kidney) OR (Kidney Disease, Chronic) OR (Kidney Diseases, Chronic) OR (Chronic Renal Diseases) OR (Chronic Renal Disease) OR (Disease, Chronic Renal) OR (Diseases, Chronic Renal) OR (Renal Disease, Chronic) OR (Renal Diseases, Chronic))) AND "Vitamin D"[Mesh]) AND ("Hypertension"[Mesh] OR (Blood Pressure, High) OR (Blood Pressures, High) OR (High Blood Pressure) OR (High Blood Pressures)). Cochrane Library Strategy: (Renal Insufficiency, Chronic) OR (Chronic Renal Insufficiencies) OR (Renal Insufficiencies, Chronic) OR (Chronic Renal Insufficiency) OR (Kidney Insufficiency, Chronic) OR (Chronic Kidney Insufficiency) OR (Chronic Kidney Insufficiencies) OR (Kidney Insufficiencies, Chronic) OR (Chronic Kidney Diseases) OR (Chronic Kidney Disease) OR (Disease, Chronic Kidney) OR (Diseases, Chronic Kidney) OR (Kidney Disease, Chronic) OR (Kidney Diseases, Chronic) OR (Chronic Renal Diseases) OR (Chronic Renal Disease) OR (Disease, Chronic Renal) OR (Diseases, Chronic Renal) OR (Renal Disease, Chronic) OR (Renal Diseases, Chronic) in Title Abstract Keyword AND (Vitamin D) in Title Abstract Keyword AND (Hypertension) OR (Blood Pressure, High) OR (Blood Pressures, High) OR (High Blood Pressure) OR (High Blood Pressures) in Title Abstract Keyword - in Trials (Word variations have been searched). BVS Strategy: (tw:(“Insuficiência Renal Crônica” OR “Doença Crónica Renal” OR “Doença do Rim Crônica” OR “Doença Renal Crônica” OR “Doenças Crônica do Rim” OR “Doenças Crônicas do Rim” OR “Doenças Crônicas Renais” OR “Doenças do Rim Crônicas” OR “Doenças Renais Crônicas” OR “Insuficiência Crônica do Rim” OR “Insuficiência Crônica Renal” OR “Insuficiência do Rim Crônica” OR “Insuficiências Crônicas do Rim” OR “Insuficiências Crônicas Renais” OR “Insuficiências do Rim Crônicas” OR “Insuficiências Renais Crônicas” OR “Nefropatia Crônica” OR “Nefropatias Crônicas” OR “Renal Insufficiency, Chronic” OR “Chronic Kidney Diseases” OR “Chronic Kidney Insufficiency” OR “Chronic Renal Diseases” OR “Chronic Renal Insufficiency” OR “Kidney Insufficiency, Chronic” OR “Insuficiencia Renal Crónica” OR “Enfermedad Crónica del Riñón” OR “Enfermedad Crónica Renal” OR “Enfermedad del Riñón Crónica” OR “Enfermedad Renal Crónica” OR “Enfermedades Crónicas del Riñón” OR “Enfermedades Crónicas Renales” OR “Enfermedades del Riñón Crónicas” OR “Enfermedades Renales Crónicas” OR “Insuficiencia Crónica del Riñón” OR “Insuficiencia Crónica Renal” OR “Insuficiencia del Riñón Crónica” OR “Insuficiencias Crónicas del Riñón” OR “Insuficiencias Crónicas Renales” OR “Insuficiencias del Riñón Crónicas” OR “Insuficiencias Renales Crónicas” OR “Insuffisance rénale chronique” OR “IRC (Insuffisance Rénale Chronique)” OR MH:C12.777.419.780.750$ OR MH:C13.351.968.419.780.750$)) AND (tw:(“Vitamina D” OR “Vitamin D” OR “Vitamina D” OR “Vitamine D” OR MH:D04.210.500.812.768$)) AND (tw:(“Hipertensão” OR “Hipertensão Arterial” OR “Hipertensão Arterial Sistêmica” OR “Pressão Arterial Alta” OR “Pressão Sanguínea Alta” OR “Hypertension” OR “Blood Pressure, High” OR “Hipertensión” OR “Presión Sanguínea Alta” OR “Hypertension artérielle” OR “Hypertension” OR “Hypertension chronique” OR “Hypertension permanente” OR MH:C14.907.489$)). Embase Strategy: 'chronic kidney failure'/exp OR 'chronic kidney failure' AND 'vitamin d deficiency':ti,ab,kw OR 'vitamin d':ti,ab,kw AND hypertension:ti,ab,kw OR 'elevated blood pressure':ti,ab,kw OR 'arterial pressure':ti,ab,kw OR 'blood pressure':ti,ab,kw AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [article]/lim AND [humans]/lim AND [embase]/lim Web of Science Strategy: TI=(hypertension OR "elevated blood pressure" OR "arterial pressure" OR "blood pressure") AND TI=("vitamin d deficiency" OR "vitamin d") AND TI=("chronic kidney failure" OR "Chronic Renal Insufficiency" OR "Chronic Kidney Insufficiency")
After the selection of potentially relevant studies, the full texts methodological quality was analyzed by two independent researchers and the disagreement between the reviewers was resolved by discussion and a third author was consulted.

Eligibility Criteria: PICO strategy was used (Higgins *et al.,* 2020), where the population corresponds to patients with chronic kidney disease, who receive intervention with vitamin D supplementation. There was no delimitation of a comparison. The searching results were changes in blood pressure levels. The following criteria were adopted for the studies selection: Complete articles, in English, with titles and abstracts that address the theme, found in the aforementioned bases, being clinical trials, with no date specification. Incomplete articles, published in other languages, that are not clinical trials and that do not address the theme were excluded.

Data extraction: Initially, the studies were exported to RAYYAN® (Ouzzani *et al.,* 2016), where duplicates were excluded. The first two screens (selection by title and abstract) were performed by two independent researchers, who selected articles for full reading in a third screen, and potentially included in the final compilation. In cases where there were disagreements, a third researcher was consulted in order to reach consensus. Regarding data extraction, the researchers used a spreadsheet to record: country, population, intervention, comparison and outcome (Table 1).

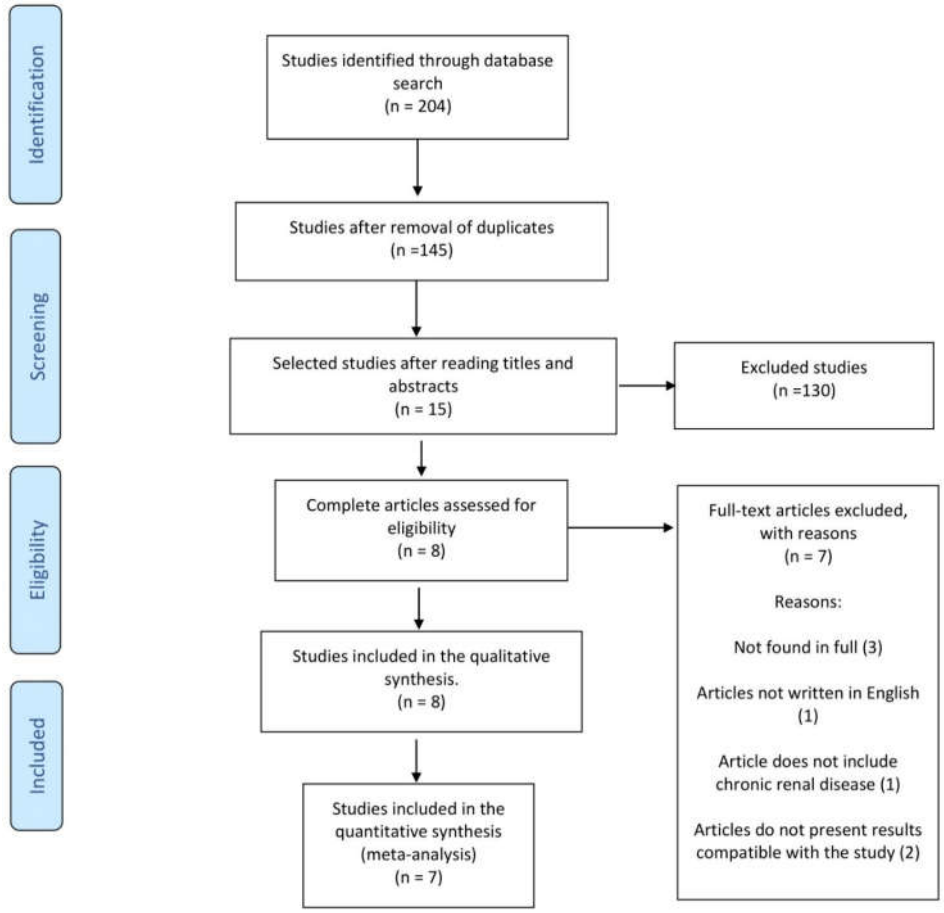
Risk of Bias Assessment: The tool RoB 2 (Risk of Bias 2) (Higgins *et al.,* 2020) was used to assess the included studies quality. The method consists of the assessment of six domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result and overall bias. Each criterion was assessed and classified according to the risk of bias: low risk, some concerns or high risk. This process was performed by two independent researchers and, subsequently, the conflicts were resolved by a third researcher. Finally, with obtained results, figures were generated through the Review Manager Web (RevMan Web, 2020), to illustrate the analysis of risk of bias.

Data analysis: Quantitative analysis through meta-analysis was performed using the software R 3.4.2 (R Foundation for Statistical Computing, Beijing, China, meta package). Differences in means and their respective standard deviations were used to assess BP. The heterogeneity test of the studies was based on $I2$ – statistic (Higgins *et al.,* 2003). When heterogeneity was significant ($p < 0,05$ or $I2 > 50\%$), the random effect model was used to analyze the effect sizes. However, when heterogeneity was not significant ($p \geq 0,05$ and $I2 \leq 50\%$), the fixed-effect model was used.

RESULTS

Selection and assessment of the studies: After primary search in databases, 204 articles were found, with the removal of duplicates,

145 studies remained. After primary screening (reading titles and abstracts), 15 were selected for full reading. Finally, 8 studies were selected for qualitative analysis and 7 for quantitative analysis, as shown in Figure 1.



Source: Moher et al. adapted (Moher et al., 2009)

Figure 1. PRISMA Flowchart

Table 1. Included studies characteristics

Author(s)	Country	Population	Intervention	Comparison	Outcome
Alvarez et al., 2012	USA	46	Cholecalciferol	Placebo	There was no significant change in BP
Dreyer et al., 2014	UK	38	Ergocalciferol	Placebo	There was no significant change in BP
Ivarsen et al., 2012	Denmark	13	Alfacalcidol	No treated	There was no significant change in BP
Levin et al., 2017	Canada	119	Calcifediol and calcitriol	Placebo	There was no significant change in BP
Marckmann et al., 2012	Denmark	52	Cholecalciferol	Placebo	There was no significant change in BP
Mose et al., 2014	Denmark	50	Cholecalciferol	Placebo	There was no significant change in BP
Susantitaphong et al., 2017	Thailand	68	Ergocalciferol and calcitriol	Ergocalciferol and placebo	There was no significant change in BP
Zoccali et al., 2014	Italy	88	Paricalcitol	Placebo	There was no significant change in BP

Source: Elaborated by the authors.

Included studies: Eight studies were included, one from the USA, one from Italy, one from Canada, one from the UK, one from Thailand and three from Denmark, as shown in Table 1. The total population is of 474 participants, with 254 in the intervention group (vitamin D supplementation) and 220 patients in the control group. Regarding the gender of participants, 68.6% (n = 325) were men and 31.4% (n = 150) were women. The mean age of participants in general was 63.2 years.

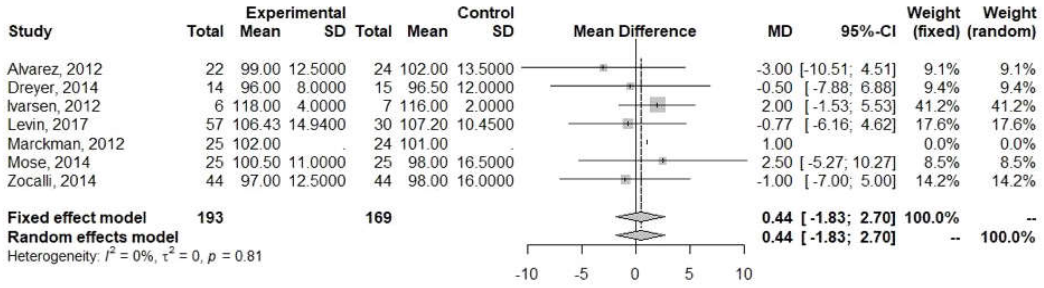
Investigate condition: Based on the objective of the study, and with the selected studies, we sought to analyze the correlation of vitamin D supplementation in patients with CKD and its influence on blood pressure levels. The BP outcome was homogeneous in the studies and the results were grouped in a meta-analysis (Figure 2). The analysis was performed using the fixed-effect model because of the homogeneity of the data. In the meta-analysis, seven studies (Alvarez et al., 2012; Dreyer et al., 2014; Ivarsen et al., 2012; Levin et al., 2017; Marckmann et al., 2012; Mose et al., 2014; Zoccali et al., 2014) were included, comprising a total of 222 subjects in the experimental group and 184 in the control group. Susantitaphong et al. (2017) study was excluded because both experimental group and control group received vitamin D.

Two variants of vitamin D (ergocalciferol and calcitriol) were administrated in the experimental group, while the other group received ergocalciferol and placebo. As can be seen in Figure 2, there were no differences between the control and intervention group in relation to BP, taking into account the fixed-effect model (MD = 0,44; 95%-CI -1,83; 2,70). In Figure 3, it was performed a sensibility analysis removing two articles, Ivarsen et al. (2012), and Marckmann et al. (2012). The first one for having an excessively small sample and the second due to the lack of data dispersion information. However, even so, there was no difference between groups, which means that there was no BP variation between groups.

Assessment of methodologic quality of the selected studies: Analysis of risk of bias was performed in all included studies. It can be seen in figure 4 that the low risk of bias was predominant. The domains of bias due to missing outcome data, bias in measurement of the outcome and overall bias presented 100% of low risk of bias. The bias in measurement of the outcome had 87.5% of low risk of bias

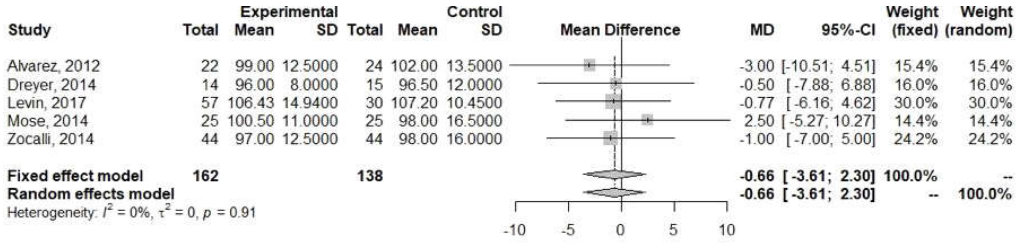
and 12.5% of some concerns (moderate risk). The bias due to deviations from intended interventions presented 87.5% of low risk of bias and 12.5% of high risk of bias. Finally, the bias arising from the randomization process had 62.5% of low risk, 25% of some concerns and 12.5% of high risk of bias.

Analyzing risk of bias in each article, it can be seen that Alvarez et al. (2012), Dreyer et al. (2014), Marckmann et al. (2012), Mose et al., (2014) and Susantitaphong et al. (2017) demonstrated a low risk of bias in all 6 domains analyzed. Levin et al. (2017) and Zoccali et al. (2014) showed a low risk of bias in almost all domains, and the bias



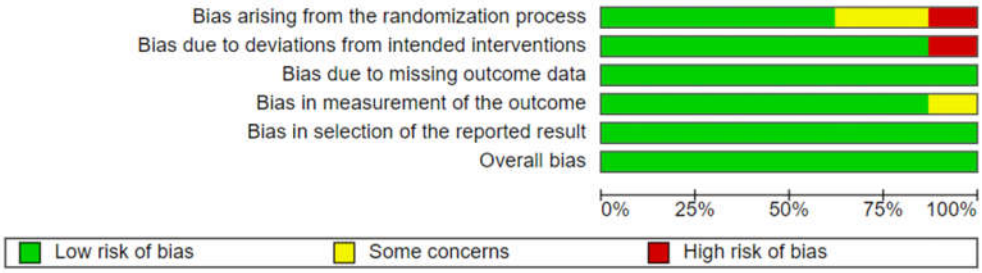
Source: Elaborated by the authors.

Figure 2. Forest plot of articles included in the quantitative analysis



Source: Elaborated by the authors.

Figure 3. Forest plot of articles included in the quantitative analysis, excluded Ivarsen et al. (2012), and Marckmann et al. (2012)



Source: Elaborated by the authors.

Figure 4. Graph of risk of bias

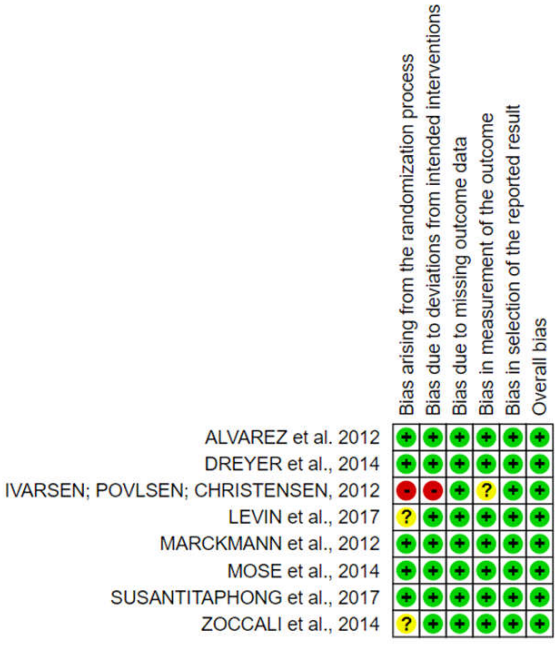


Figure 5. Summary of risk of bias

arising from the randomization process was classified with some concerns. Ivarsern et al. (2012) presented a low risk of bias in the bias due to missing outcome data, bias in selection of the reported result and overall bias, some concerns in bias in measurement of the outcome, and high risk of bias in the bias arising from the randomization process and bias due to deviations from intended interventions (Figure 5). Analyzing risk of bias in each article, it can be seen that Alvarez et al. (2012), Dreyer et al. (2014), Marckmann et al. (2012), Mose et al., (2014) and Susantitaphong et al. (2017) demonstrated a low risk of bias in all 6 domains analyzed. Levin et al. (2017) and Zoccali et al. (2014) showed a low risk of bias in almost all domains, and the bias arising from the randomization process was classified with some concerns.

DISCUSSION

Performing the qualitative assessment of the studies found in this review, searching for BP variations in patients with CKD who were administered vitamin D, it was observed that none of the eight studies found significant BP changes. The variations reported in the studies were close to zero, with small increases and decreases in the values, when comparing the control and intervention groups in their respective BP values. BP changes reported were between decrease of 9 mmHg and an increase of 4 mmHg. There was also no significant difference when comparing the variations between systolic and diastolic BP in the same group or between groups (Dreyer et al., 2014; Levin et al., 2017; Marckmann et al., 2012; Mose et al., 2014; Susantitaphong et al., 2017; Zoccali et al., 2014). Analyzed studies samples added together result in a total of 474 participants, of which 53.6% (n = 254) are part of the intervention group and 46.4% (n = 220) are part of the control group. Regarding the gender of the participants, 68.6% (n = 325) were men and 31.4% (n = 150) were women. The mean age of the participants in general was 63.2 years. Finally, the geographical distribution of the sample shows that 46.6% (n = 221) of the participants were from Europe, 24.8 (n = 165) were from North America and 18.6% (n = 88) were from Asia. It should be noted that Denmark hosted 3 of the studies, which means that its sample represents 69.7% (n = 115) of the European sample. Another point to be raised is that only one study was conducted in Asia, in this case in Thailand. These data point to a limited geographical scope.

In general, research was carried out with two distinct groups, a control group, in which placebo was administered, and an intervention group, in which vitamin D was administered. However, some articles presented different ways of building these groups. The article by Ivarsen et al. (2012) did not apply a placebo, the control group just did not receive treatment. Levin et al. (2017) presented two different intervention groups (calcifediol and calcitriol), in addition to a placebo, which allowed the analysis of two different interventions. Susantitaphong et al. (2017) used two groups with the administration of vitamin D, of which one group received only ergocalciferol (control group), while the other group used ergocalciferol associated with calcitriol (intervention group), this method allowed to evaluate differences in using one or two variant of vitamin D. Although the articles cited later present different methods, there were no differences in the results related to BP. Concerning the intervention methods, different vitamin D variants were administered to the participants: cholecalciferol (Alvarez et al., 2012; Marckmann et al., 2012; Mose et al., 2014), ergocalciferol (Dreyer et al., 2014; Susantitaphong et al., 2017), Alfacalcidol (Ivarsen et al., 2012), calcifediol (Levin et al., 2017), calcitriol (Levin et al., 2017; Susantitphong et al., 2017) and paricalcitol (Zoccali et al., 2014). Diverse follow-up periods were also experienced, of which the shortest follow-up time was 8 weeks (Marckmann et al., 2012) and the longest period was 52 weeks (Alvarez et al., 2012). The most applied period was 6 months (Dreyer et al., 2014; Ivarsen et al., 2012; Levin et al., 2017; Mose et al., 2014). All results showed that vitamin D supplementation, independently of variation and time applied, did not cause changes in BP levels. BP variations were not statistically relevant, either in a cross-sectional analysis (comparing the intervention and placebo groups after follow-up), or in a longitudinal analysis (assessing variations within each group between the baseline data and the final results). In addition, the reason why these results were found is discussed and, in some of the texts, it is proposed that vascular changes caused by vitamin D are not expressed in some cardiac risk markers such as BP (Dreyer et al., 2014; Levin et al., 2017; Marckmann et al., 2012; Zoccali et al., 2014). However, changes were found in other markers, such as a reduction in pulse pressure (Ivarsen et al., 2012) and an improvement in the function of the endothelial microcirculation (Levin et al., 2017; Zoccali et al., 2014).

There are evidences that point to the existence of the administered vitamin D activity in vitamin D receptors of the vascular endothelium. These findings suggest an improvement in endothelium-dependent vasodilation that occurs without repercussions in blood pressure levels (Zoccali et al., 2014). Mose et al. (2014) compared results of BP measurements at different periods of the day, searching for changes in 24 hours and in the morning or night periods. There were also no significantly different in BP results between groups. Therefore, this study was limited by the number of articles found in the researched databases, then, by the small population and the small geographical coverage, it is not possible to make more concrete conclusions about the delimited theme. Thus, this research demonstrates the scarcity of literature that addresses the use of vitamin D supplementation to reduce BP in patients with CKD.

CONCLUSION

The findings of this research suggest that vitamin D supplementation does not bring significant positive outcomes in terms of BP reduction. The absence of concrete outcomes, due to the publications and small sample, shows a low scientific interest in addressing the issues. Lastly, it is expected that further studies can be produced with this theme, aiming more concrete results and with larger study groups, so that the evidence produced can lead to more concrete conclusions.

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