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Research paper

Randomized, placebo-controlled, double-blind clinical trial on the contributions of vitamin D in the control of cardiovascular risk factors, depressive symptoms and suicide risk

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ABSTRACT

Objectives: To evaluate the contributions of vitamin D supplementation to the control of cardiovascular risk factors and the treatment of depressive symptoms, including suicide risk.

Methods: A randomized, placebo-controlled, double-blind clinical trial was conducted with 224 adults (18–61 years) diagnosed with major depressive disorder, recruited from psychiatric clinics of two universities in Northeast Brazil. Participants were randomized to receive vitamin D supplementation (50,000 IU/week; $n = 112$) or placebo (n = 112) for six months. Assessments included depressive symptoms, suicide risk, clinical/laboratory cardiovascular parameters, and serum vitamin D at baseline and day 180. Statistical analysis used chi-squared or Fisher's exact test, McNemar's test, Student's *t*-test or Mann-Whitney test, with odds ratios (OR) and 95 % confidence intervals (CI). Significance level was set at 5 %.

Results: Vitamin D supplementation significantly increased serum concentrations to adequate physiological levels and led to marked reductions in depressive symptoms ($p = 0.001$) and suicide risk (p = 0.001). Additionally, 13 of 15 evaluated cardiovascular risk factors showed normalization or significant reduction, without adverse events related to calcium metabolism or other side effects. Improvements included better lipid profile, glycemic control, and inflammatory markers. Clinically, these findings suggest potential for vitamin D as an adjuvant therapy in depression management, contributing to both mental health and cardiometabolic stability.

Strengths and limitations: Strengths include the rigorous double-blind, randomized design, probabilistic sampling, and comprehensive clinical-laboratory evaluation. Limitations involve the single-region sample, lack of long-term follow-up after supplementation, and the exclusion of patients with severe comorbidities, which may limit generalizability.

Conclusion: Weekly administration of 50,000 IU of vitamin D for six months proved effective in reducing depressive symptoms and suicide risk while improving cardiovascular health markers, highlighting its promise as an accessible, low-cost adjunctive therapy in psychiatric and primary care settings.

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1. Introduction

Depression is one of the main causes of disability throughout the world and reported to have affected more than 300 million individuals in 2015, which corresponds to 4.4% of the global population [1]. Depression is also considered a cardiovascular risk factor, increasing the relative risk of coronary artery disease as well as cardiovascular morbidity and mortality rates [2,3,4]. Moreover, data from the World Health Organization reveal that depression is responsible for the highest number of deaths by suicide, reaching nearly 800 thousand per year [1]. Studies suggest that psychiatric disorders, such as schizophrenia, alcoholism and depression, may be associated with low serum levels of 25-hydroxyvitamin D [25(OH)D] [5–7]. Recent studies report that vitamin D deficiency may be related to an increase in the depression rate from 8 to 14% [5–6].

Vitamin D receptors have been identified in areas of the brain involved in depression, such as the prefrontal cortex, hypothalamus and substantia nigra, leading some researchers to consider it a neurosteroid hormone [7]. Vitamin D has also been reported to increase the expression of genes that encode tyrosine hydroxylase, which is a precursor of dopamine and norepinephrine [7–8].

Some controlled clinical trials investigating the effects of vitamin D on depressive symptoms found that supplementation for eight weeks was beneficial but nonsignificant, demonstrating a tendency of a possible role of this hormone in the management of depression. Recent meta-analyses conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reported a statistically significant reduction in depressive symptoms and a clinically significant reduction in depression following vitamin D supplementation [7–8].

From the cardiovascular standpoint, several studies have reported vitamin D to be a molecule with various endocrine, paracrine and autocrine effects in different tissues and organs. The hormone also plays an important role in the maintenance of skeletal homeostasis, with a special role of the skin in the metabolic control of the hydroxylase CYP2R1 in the liver and the specificity of 1α- hydroxylase in different tissues and cell types. Moreover, vitamin D receptors (VDRs) exert genomic, non-genomic and epigenomic effects [9].

Associations between low vitamin D levels and an increased risk of cardiovascular disease (CVD) have been described in several studies and corroborated by meta-analyses, lending support to the notion that low vitamin D levels are associated with CVD. Thus, vitamin D can be considered essential to cardiovascular integrity, especially for the regulation of vascular tone and as an antifibrotic and antihypertrophic signaling pathway in the heart and arteries [9–12].

Although current evidence demonstrates the positive effects of vitamin D supplementation on depressive symptoms and the control of cardiovascular risk factors in particular population groups, studies on the possible effects of supplementation in individuals with greater vulnerability to the two conditions (patients in treatment for depression with cardiovascular risk factors) and an increased risk of suicide are needed. Therefore, the aim of the present randomized, placebo-controlled, double-blind study was to investigate the therapeutic effects of vitamin D at a weekly dose of 50,000 IU for six months in a sample of Brazilian patients under care at psychiatric clinics with a diagnosis of depression, cardiovascular risk and suicide risk in comparison to a control group (placebo once per week for six months). The hypothesis is that vitamin D supplementation is capable of reducing the degree of depressive symptoms as well as diminishing cardiovascular risk and suicide risk.

2. Methods

2.1. Study design

The protocol for this clinical trial was previously published [13] and the trial was registered in the clinical trials platform (http://www.ensaiosclinicos.gov.br/rg/ with registration number RBR-6yj8sj and Universal Trial Number U1111-1217-9237, July 23rd, 2018). The project received approval from the Human Research Ethics Committee of *Universidade Federal de Pernambuco* (certificate: 2,464,997 on 01/01/2018) and the study was conducted in accordance with the ethical precepts stipulated in the Declaration of Helsinki. The project followed the CONSORT guidelines for Clinical Trials

All patients gave written informed consent. The study was organized, coordinated and executed by researchers of the Department of Neuropsychiatry of *Universidade Federal de Pernambuco*, who were also in charge of data management and statistical analysis.

2.2. Patients

Patients were recruited from two psychiatric clinics of Brazilian university hospitals:

- Hospital affiliated with *Universidade Federal de Pernambuco* (UFPE)
- Oswaldo Cruz University Hospital of *Universidade de Pernambuco* (UPE)

The eligibility criteria were adults (18 to 60 years of age) with a diagnosis of depression by a psychiatrist based on the International Classification of Diseases (ICD-10) [14] as F33.0 (mild recurrent depressive disorder), F33.1 (moderate recurrent depressive disorder), F33.2 (severe recurrent depressive disorder without psychotic symptoms, including recurrent major depression, endogenous depression and manic-depressive psychosis in the depressive form without psychotic symptoms), F33.8 (other recurrent depressive disorders) and F33.9 (recurrent severe depressive disorder without psychotic symptoms, including recurrent major depression without specification or unipolar depression) in routine care at the psychiatric clinics. Severity of the disease could be mild, moderate or severe based on the assessment of the psychiatrist. The patients were taking antidepressants prescribed by their psychiatrists. No restrictions were imposed on the type of antidepressant, and therefore, information about the medication of choice and dosage were not detailed in this article and were only recorded in the patient's medical record for clinical purposes. All participants who used antibiotics were excluded.

For inclusion, the patients also needed to have a score > 6 points on the Montgomery-Asberg Depression Rating Scale [15]. The exclusion criteria were cognitive impairment (determined using the Mini Mental State Examination) [16], individuals already on vitamin D supplementation, a past history of psychiatric comorbidities, chronic kidney disease, hypercalcemia or neoplasms and pregnant or nursing women.

2.2.1. Sample size calculation

The sample power was calculated to compare the two groups regarding the reduction in depression symptoms and suicide risk from baseline to post-intervention. The calculations indicated a power of 99.9% with a 5% error and a two-sided test. The calculations were performed using G*Power version 3.1.9.4.

The first patients were recruited on January 1st, 2021, with the last follow- up assessment was conducted in May of 2021. The flowchart showing the screening, inclusion and analyses is displayed in online supplementary Fig. 1. Patient compliance in taking Vitamin D supplements was assessed bi-monthly during cardiovascular follow-ups or by telephone. All patients had access to the author's contact information.

2.3. Randomization

Two pharmacists participated in the randomization and were aware of the allocation of the participants to the two groups (vitamin D supplement or placebo). Data were collected from the patients until May 30th, 2021.

The initial (baseline) assessment involved the following:

- Completion of identification chart and sociodemographic inventory: standard chart with the patient history, results of physical and cardiological exams and questionnaire addressing activities that involve exposure to sunlight;
- Application of the Montgomery-Asberg Depression Rating Scale [15];
- Application of the Columbia Suicide Severity Rating Scale, which addresses the risk of suicide [17];
- Collection of biological material: Collection of venous blood (10 ml) from a peripheral vein for the determination of fasting blood sugar, cholesterol (total and fractions), urea, creatinine, total proteins, albumin, homocysteine, high sensitivity C-reactive protein, lipoprotein A, ionic calcium and phosphorus as well as levels of total testosterone, thyroid- stimulating hormone (TSH), concentration of 25-hydroxyvitamin D and parathyroid-stimulating hormone (PTH). Urine was collected for the determination of 24-h urinary calcium and microalbuminuria. Fis exams were performed in the laboratories of the hospitals at which the study was developed (online supplementary document 2).
- Cardiological assessment: Cardiological and imaging exams (electrocardiogram, ergometric test, electrocardiographic monitoring [24- h Holter] and Doppler ultrasound of the carotid and vertebral arteries) (online supplementary document 2). Systemic hypertension was defined as arterial blood pressure $\geq$ 140 $\times$ 90 mmHg in two separate measurements or chronic use of anti-hypertensive therapy. Peripheral obstructive arterial disease was assessed through Ankle-Brachial Index (ABI), with a result <0,9 compatible with the condition. Carotid atherosclerosis was assessed through carotid Doppler ultrasound with Intima-Media Thickness (IMT) $\geq$ 0,9 or presence of plaque as a threshold. Transthoracic echocardiography was performed to assess left ventricular ejection fraction and left ventricular hypertrophy; an ejection fraction $\geq$50 % was considered normal and left ventricular mass indexed by body surface area $>$ 131 g/m^2 for men and $>$ 108 g/m^2 for women was considered increased and abnormal. Arrhythmia was assessed during 24-h Holter, with findings of sinus tachycardia, paroxysmal supraventricular tachycardia (PSVT), ventricular tachycardia, bradycardia, atrial fibrillation, atrial flutter, atrioventricular block and left or right bundle branch block being classified as positive for arrhythmia. Coronary artery disease was assessed through clinical findings of typical angina or positive results in ergometric test, myocardial scintigraphy or coronary artery calcium score (cut-off point of $\geq$100).

After the initial (baseline) assessment, simple randomization (heads or tails) was performed, resulting in two groups of 112 participants each – Vitamin group and placebo group. The administration of vitamin D and placebo was performed by the nurse involved in the study in capsules of equal size and color designed for the clinical trial.

All instructions were precise and written in the form of a manual to ensure the execution of all procedures determined for the clinical trial, including patient recruitment, allocation to the study groups, administration of the intervention, registration systems, criteria for interrupting the intervention, etc. All activities performed during the clinical trial were previously established in the form of a list of tasks distributed to the research team.

Assessments involving scales, exams and the recording of information were performed at the time of randomization (first assessment – baseline) and after 180 days (final assessment – follow-up).

As the region in which the clinical trial was conducted (Northeast Brazil) is sunny throughout the entire year, with the absence of well-defined seasons, seasonality did not exert an influence on exposure to sunlight or the synthesis of vitamin D [18].

2.4. Outcomes

The primary outcomes were the contributions (therapeutic effects) of vitamin D supplementation to reductions in the severity of depression, the risk of suicide and cardiovascular risk factors (see supplementary document 2 for risk factors considered).

2.5. Safety and side effects

For the analysis of safety, all adverse events that occurred in the 12 months from the onset of the clinical trial were recorded. All known side effects of vitamin D were considered and we monitored serum concentrations of ionic calcium, PTH, phosphorus, 24-hour urinary calcium at the onset of the study, after 90 days and after 180 days of vitamin D supplementation or placebo.

The dosage of vitamin D for supplementation considered for the study (50,000 IU weekly) met the criteria established in previous studies that presented positive results with regards to the reduction in depressive symptoms [19]. Vitamin D3 is quite safe when administered with the prescribed posology. Doses of up to 10,000 IU per day for five months did not induce signs of toxicity, such as hypercalcemia and hypercalciuria [19]. Antidepressants with a greater risk of severe cardiovascular side effects were avoided [20].

2.6. Statistical analysis

The data were entered onto an EXCEL spreadsheet and the Statistical Package for the Social Sciences (SPSS, version 25) was used for the statistical calculations. The data were submitted to descriptive and inferential analyses. Descriptive analysis involved the calculation of absolute and relative (percentage) frequencies for categorical and numerical variables.

Comparisons between groups and the determination of associations between two categorical variables were performed with either Pearson's chi- squared test or Fisher's exact test, when appropriate. McNemar's test was used for comparisons between assessments. Comparisons between two categories involving numerical variables were performed with either the equal variance Student's t-test for data with normal distribution or the Mann-Whitney test for data were non-normal distribution. The strength of the associations was measured using odds ratios (OR) and respective 95% confidence intervals (CI) obtained in the bivariate analysis. The margin of error used in the decisions of the statistical tests was 5%.

2.7. Involvement of patients and public

The patients were not involved in the conception or conduction of the clinical trial. All participants were informed of their results in person at appointments or by video appointments or via e-mail due to the restriction to in-person appointments during the Sars-Cov-2 pandemic. The researchers continued to offer care to all patients involved in the study after its conclusion as well as administer all necessary psychiatric and cardiological treatments.

3. Results

3.1. Patients

All participants were in treatment for depression and maintained their prescribed medications and other treatment routines, including psychotherapy. The assessment of the chronicity of depressive symptoms and suicidal behavior was performed at baseline and at the end of the intervention by the same researcher. The assessment of cardiovascular risk factors was performed by the same health team and laboratory analyses were always conducted at the same institution. Patients with at least six months of treatment for depression were included and randomized. Total follow-up time was six to twelve months.

Women, individuals with self-declared brown skin color, married individuals, individuals older than 50 years of age, those with nine to 12

years of schooling, those with a diagnosis of major depressive disorder for at least six years and those with a family history of major depressive disorder predominated in the sample. The demographic and baseline clinical characteristics were similar between the two groups, with the exception of skin color ($p^{(1)} = 0.025$) (Table 1).

3.2. Assessment of vitamin D deficiency, presence of depressive symptoms and risk of suicide

Table 2a and 2b displays the distribution of vitamin D deficiency, depressive symptoms and suicide risk per group at both assessment times. Vitamin D deficiency reduced from 82.1% at baseline to zero at follow-up in the supplementation group, whereas vitamin D deficiency increased from 84.8% to 96.4% in the placebo group. Most participants were classified as having moderate/severe depressive symptoms at baseline (92.0% in the supplementation group and 82.1% in the placebo group). After the intervention, the number of patients with moderate/severe depressive symptoms decreased to 62.5% in the supplementation group and increased to 100.0% in the placebo group. The risk of suicide reduced from 77.7% to 43.8% in the supplementation group and increased from 78.6% to 85.7% in the placebo group. At baseline, "depressive symptoms" was the only variable with a significant difference ($p < 0.05$) between groups. At the follow-up assessment after the intervention, significant differences between groups were found for all three variables.

Thus, positive outcomes were found at the end of the intervention in the group of patients supplemented with vitamin D for both the remission of depressive symptoms (p [2] < 0.001) and the reduction in the risk of suicide (p (1) < 0.001) (Table 2a and 2b).

Table 1
Distribution of demographic and clinical characteristics in both groups at baseline, Recife, 2025.

*Variable	*Study groups [1]Supplementation n (%)	Placebo n (%)	Total Group n (%)
Age group (years)			
18 to 30	16 (14.3)	12 (10.7)	28 (12.5)
31 to 40	12 (10.7)	19 (17.0)	31 (13.8)
41 to 50	28 (25.0)	34 (30.4)	62 (27.7)
51 to 61	56 (50.0)	47 (42.0)	103 (46.0)
Sex			
Male	28 (25.0)	23 (20.5)	51 (22.8)
Female	84 (75.0)	89 (79.5)	173 (77.2)
Marital status			
Single	49 (43.8)	49 (43.8)	98 (43.8)
Married/Stable union	63 (56.3)	63 (56.3)	126 (56.3)
Skin color			
White	58 (51.8)	39 (34.8)	97 (43.3)
Brown	40 (35.7)	59 (52.7)	99 (44.2)
Black	14 (12.5)	14 (12.5)	28 (12.5)
Schooling			
Up to 8 years of study	21 (18.8)	27 (24.1)	48 (21.4)
9 to 12 years of study	55 (49.1)	51 (45.5)	106 (47.3)
More than 12 years of study	36 (32.1)	34 (30.4)	70 (31.3)
major depressive disorder			
1 to 5 years	35 (33.0)	36 (32.7)	71 (32.9)
6 to 10 years	40 (37.7)	33 (30.0)	73 (33.8)
More than 10 years	31 (29.2)	41 (37.3)	72 (33.3)
TOTAL	106 (100.0)	110 (100.0)	216 (100.0)
Family history of depressive disorder			
Yes	88 (83.8)	80 (76.2)	168 (80.0)
No	17 (16.2)	25 (23.8)	42 (20.0)
Total	105 (100.0)	105 (100.0)	210 (100.0)

* Significant difference at 5.0% level.
[1] Pearson's chi-squared test.

3.3. Cardiovascular risk factors (clinical findings)

Positive significant ($p < 0.05$) results were found with regards to the control and/or reduction of cardiovascular risk factors in the supplementation group compared to the placebo group for practically all variables analyzed. Among the seven clinical findings investigated, the normalization of six was found in the intervention group: systemic arterial hypertension ($p^{(1)} < 0.001$), carotid atherosclerosis ($p^{(1)} < 0.002$), heart failure based on left ventricular ejection fraction ($p^{(2)} = 0.031$) and left ventricular hypertrophy ($p^{(1)} < 0.001$) and arrythmia ($p^{(1)} < 0.001$). Significant results of the intervention were also found for coronary arterial disease based on the improvement in myocardial ischemia analyzed in this study ($p^{(1)} = 0.038$*). Peripheral obstructive arterial disease was the only condition on which vitamin D supplementation did not have a positive effect (Table 3a and 3b).

3.4. Laboratory cardiovascular risk factors

With regards to cardiovascular risk factors determined by laboratory exams, a significant improvement ($p < 0.05$) was found for nine of the ten variables analyzed after vitamin D supplementation (Table 4a and 4b). In terms of dyslipidemia, the control of this risk factor was demonstrated by the normalization of total cholesterol (TC) and high-density lipoprotein (HDL) (p (1) < 0.001). (See Tables 5a and 5b.)

In the analysis of diabetes mellitus, significant improvements were found in fasting glucose, A1C hemoglobin and insulin resistance using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) after the intervention with vitamin D ($p^{(1)} < 0.001$). The oral glucose tolerance test was the only aspect on which the intervention with vitamin D did not have a positive effect.

In the analysis of thyroid function based on serum levels of high sensitivity TSH, a significant positive effect on hypothyroidism was found in the supplementation group ($p^{(1)} < 0.001$). A significant positive effect was also found for C-reactive protein ($p^{(1)} < 0.001$) following vitamin D supplementation. With regards to parathyroid function (PTH), hyperparathyroidism was reduced from 35.1% to 2.7% from baseline to the follow-up assessment in the vitamin D supplementation group, whereas an increase from 35.5% to 51.4% was found in the placebo group.

Lastly, in the investigation of chronic kidney disease through the analysis of albuminuria and the glomerular filtration rate calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), significant positive results were also found in the vitamin D supplementation group ($p^{(1)} < 0.001$) (Table 4a and 4b).

3.5. Safety aspects

Among the 224 participants enrolled in the present study, four (1.8 %) had a positive diagnosis of COVID-19 based on real-time polymerase chain reaction analysis (online supplementary document 3): two patients in the placebo group and two in the intervention group. The other patients had no signs or symptoms of the disease throughout the trial. Despite this result, the positive patients did not develop the severe form of SARS-CoV-2. Thus, the medications taken during the symptomatic period were only analgesics and did not compromise the results of the trial. During the six months of the trial, there were no adverse events or complications related to treatment among the patients, with no occurrences of hospitalization or suicide attempts. Serum concentrations of ionic calcium were normal in the entire sample and no antidepressants capable of causing side effects that could increase cardiovascular risk were taken.

4. Discussion

Vitamin D supplementation in patients with depression led to the remission of depressive symptoms and the control of cardiovascular risk

Table 2a
Distribution of vitamin D deficiency, depressive symptoms and suicide risk in both groups at baseline assessment and after intervention, Recife, 2025
Continued.

Assessment	Variable	Group			*p*-value	OR (95 % CI)
		Supplementation	Placebo	Total Group		
		n (%)	n (%)	n (%)		
	TOTAL	112 (100.0)	112 (100.0)	224 (100.0)		
Baseline assessment	Vitamin D deficiency				$p^{(1)} = 0.589$	
	Present	92 (82.1)	95 (84.8)	187 (83.5)		1.0
	Absent	20 (17.9)	17 (15.2)	37 (16.5)		1.2 (0.6 to 2.5)
After intervention	Vitamin D deficiency				$p^{(1)} < 0.001$*	
	Present	–	108 (96.4)	108 (48.2)		**
	Absent	112 (100.0)	4 (3.6)	116 (51.8)		
p-value		**	$p^{(2)} = 0.001$*	$p^{(2)} < 0.001$*		
Baseline assessment	Depressive symptoms				$p^{(1)} = 0.029$*	
	Moderate/severe	103 (92.0)	92 (82.1)	195 (87.1)		2.5 (1.1 to 5.7)
	Mild	9 (8.0)	20 (17.9)	29 (12.9)		1.0
After intervention	Depressive symptoms				$p^{(1)} < 0.001$*	
Moderate/severe		70 (62.5)	112 (100.0)	182 (81.3)		**
Mild		42 (37.5)	–	42 (18.8)		
p-value		$p^{(2)} < 0.001$*	**	$p^{(2)} = 0.105$		

* Significant difference at 5.0 % level.
** Not possible to determine due to occurrence of null frequencies.
[1] Pearson's chi-squared test.
[2] McNemar's test.

Table 2b
Distribution of vitamin D deficiency, depressive symptoms and suicide risk in both groups at baseline assessment and after intervention, 2025.
Conclusion

Assessment	Variable	Group			*p*-value	OR (95 % CI)
		Supplementation	Placebo	Total Group		
		n (%)	n (%)	n (%)		
Baseline assessment	Suicide risk				$p^{(1)} = 0.872$	
	Present	87 (77.7)	88 (78.6)	175 (78.1)		1.0 (0.6 to 2.0)
	Absent	25 (22.3)	24 (21.4)	49 (21.9)		1.0
After intervention	Suicide risk				$p^{(1)} < 0.001$*	
Present		49 (43.8)	96 (85.7)	145 (64.7)		1.0
Absent						7.7 (4.0 to
		63 (56.3)	16 (14.3)	79 (35.3)		14.7)
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 0.096$	$p^{(3)} < 0.001$*		

* Significant difference at 5.0 % level.
[1] Pearson's chi-squared test.
[2] McNemar's test.

factors. Supplementation also reduced the risk of suicide.

At baseline, depressive symptoms were found 92 % of the patients in the supplementation group and 82.1 % of those in the placebo group. After the intervention, the presence of depressive symptoms diminished to 62.5 % in the supplementation group and increased to 100.0 % in the placebo group. The effect of vitamin D on depressive symptoms was substantial at the end of the treatment period, suggesting the slow onset of its potential anti-inflammatory, immunomodulating and neurosteroidal actions [5].

Moreover, vitamin D is reported to be capable of increasing the expression of genes that encode tyrosine hydroxylase, which is a precursor of dopamine and norepinephrine [5,6]. Other studies report that vitamin D reduces inflammatory cytokines and diminishes the effects of neurodegeneration [21] through the regulation of stocks of intracellular calcium [22].

4.1. Suicide risk

Between 20 and 60% of individuals with depression have different abnormalities with regards to executive functions [23], with cognitive rigidity being closely related to suicidal behavior [24,25] Unlike other dysfunctions in depression, cognitive rigidity has been associated with suicidal behavior, especially in a sample in which non-violent suicide attempts predominated.

From the neurobiological standpoint, neuroinflammatory processes found in individuals with depressive symptoms seem to be a common unifying pathway between depression and suicidal behavior. Evidence suggests that inflammatory processes play a role in suicide, with associations reported between inflammation and depression as well as among infection, increased serum levels of cytokines, inflammatory metabolites, traumatic brain injury and vitamin D deficiency, increasing the risk of suicide. This neuroinflammation activates the microglia, leading to a greater production of inflammatory cytokines and neurodegeneration, activating enzymes that degrade neurotransmitters, such as the enzyme indoleamine 2,3-dioxygenase (IDO) and extracellular matrix metalloproteinases, which attack the extracellular matrix, resulting in myelin injuries and breaking the blood-brain barrier [26,27].

Table 3a
Distribution of clinical cardiovascular risk factors in study groups at baseline assessment and after the intervention, Recife, 2025
Continued

Assessment	Variable	Group				
		Supplementation	Placebo	Total Group	p-value	OR (95 % CI)
		n (%)	n (%)	n (%)		
Baseline assessment	Systemic arterial hypertension				$p^{(1)} = 0.103$	
	Altered	83 (74.1)	93 (83.0)	176 (78.6)		1.0
	Normal	29 (25.9)	19 (17.0)	48 (21.4)		1.7 (0.9 to 3.3)
	TOTAL	112 (100.0)	112 (100.0)	224 (100.0)		
After intervention	Systemic arterial hypertension				$p^{(1)} < 0.001$*	
	Altered	34 (30.4)	94 (83.9)	128 (57.1)		1.0
	Normal	78 (69.6)	18 (16.1)	96 (42.9)		12 (6.3 to 22.8)
	TOTAL	112 (100.0)	112 (100.0)	224 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 1.000$	$p^{(2)} < 0.001$*		
Baseline assessment	Peripheral obstructive arterial disease				$p^{(1)} = 0.458$	
	Alterado	78 (72.2)	82 (76.6)	160 (74.4)		1.0
	Normal	30 (27.8)	25 (23.4)	55 (25.6)		1.3 (0.7 to 2.3)
	TOTAL	108 (100.0)	107 (100.0)	215 (100.0)		
After intervention	Peripheral obstructive arterial disease				$p^{(1)} = 0.099$	
	Alterado	97 (92.4)	86 (85.1)	183 (88.8)		2.1 (0.8 to 5.2)
	Normal	8 (7.6)	15 (14.9)	23 (11.2)		1.0
	TOTAL	105 (100.0)	101 (100.0)	206 (100.0)		
p-value		$p^{(2)} = 0.001$*	$p^{(2)} = 0.263$	$p^{(2)} < 0.001$*		
Baseline assessment	Carotid atherosclerosis				$p^{(1)} = 0.271$	
	Alterado	40 (36.4)	48 (43.6)	88 (40.0)		1.0
	Normal	70 (63.6)	62 (56.4)	132 (60.0)		1.4 (0.8 to 2.3)
	TOTAL	110 (100.0)	110 (100.0)	220 (100.0)		
After intervention						
	Carotid atherosclerosis				$p^{(1)} = 0.002$*	
	Alterado	28 (25.9)	49 (46.7)	77 (36.2)		1.0
	Normal	80 (74.1)	56 (53.3)	136 (63.8)		2.5 (1.4 to 4.4)
	TOTAL	108 (100.0)	105 (100.0)	213 (100.0)		
p-value		$p^{(2)} = 0.001$*	$p^{(2)} = 0.500$	$p^{(2)} = 0.022$*		
Baseline assessment	Heart failure: left ventricular ejection fraction				$p^{(1)} = 0.446$	
	Reduces	8 (7.2)	11 (10.1)	19 (8.6)		1.0
	Normal	103 (92.8)	98 (89.9)	201 (91.4)		1.4 (0.6 to 3.7)
	TOTAL	111 (100.0)	109 (100.0)	220 (100.0)		

* Significant difference at 5.0 % level.
[1] Pearson's chi-squared test.
[2] McNemar's test.

Vitamin D deficiency may suppress the gene expression of tyrosine hydroxylase, which plays an essential role in the regulation of the biosynthesis of dopamine and the expression of neurotrophic factors. Thus, vitamin D deficiency may be related to a greater frequency of depressive episodes [28] and a higher risk of suicide.

In an attempt to establish a clear correlation between vitamin D deficiency and suicidal behavior, Grudet et al. [29] detected suboptimal levels of vitamin D in up to 90% of individuals with a recent suicide attempt and 60% had a well- established clinical deficiency. As expected, vitamin D in the blood was inversely correlated with levels of proinflammatory cytokines.

Despite this evidence, further data on these associations are needed. In the present study, the reduction in depressive symptoms and consequent improvement in the inflammatory neural response in the group that received supplementation may have been responsible for the significant reduction in suicide risk, which did not occur in the placebo group.

Besides the effects described above with regards to vitamin D and the immune system, calcitriol was also found to lead to a change in the balance of T helper (Th) cells toward the Th2 phenotype, which, in simplified terms, can lead to an anti-inflammatory protective mechanism. As vitamin deficiency is found more in patients with psychiatric diseases, it has been proposed that the lack of vitamin D contributes to the underlying mechanisms of suicide [30].

The fact that cytokine receptors are present in neurons in specific regions of the brain may explain how these cytokines can contribute to behavioral and emotional symptoms relevant to suicide, modulating the concentration of neurotransmitters and their metabolites in different regions of the central nervous system. For instance, interleukin (IL)-6 receptors are expressed in serotonergic neurons in the medulla oblongata as well as in the hypothalamus, hippocampus, cerebellum and selective cortical areas. IL-1β receptors are located in neurons of the hippocampus, amygdaloid complex and thalamus. 5-HT2 receptors are located in the hippocampus and Purkinje cells [30].

High IL-6 was the most robust cytokine finding associated with suicide ideation as well as both non-fatal and fatal suicide attempts. Future studies should investigate the predictive value of high IL-6, consider how it may alter brain function toward suicidal behavior and explore the potential benefits of the reduction in IL-6 with regards to suicide risk [31].

Adversities at the beginning of life are considered one of the main contributors to increased vulnerability to suicidal behavior later in life and predictive of multiple suicide attempts [32,33]. Studying 181 individuals who had recently attempted suicide, Rajalin et al. [33] investigated early life adversities and specific interpersonal problems using the Karolinska Interpersonal Violence Scale (KIVS) and Inventory of Interpersonal Problems (IIP), respectively. The authors found a significant association between suicide attempts and sequelae from these adversities, such as social isolation, low self-esteem and difficulty expressing emotions.

From the physiopathological standpoint, early life adversities are associated with an abnormal cortisol response to stress, persistent high

Table 3b
Distribution clinical cardiovascular risk factors in study groups at baseline assessment and after the intervention, Recife, 2025.
Continuation

Assessment	Variable	Group				
		Supplementation	Placebo	Total Group	p-value	OR (95 % CI)
		n (%)	n (%)	n (%)		
After intervention	Heart failure: left ventricular ejection fraction				$p^{(1)} = 0{,}026$*	
	Reduced	2 (1.8)	9 (8.6)	11 (5.1)		**
	Normal	107 (98.2)	96 (91.4)	203 (94.9)		
	TOTAL	109 (100.0)	105 (100.0)	214 (100.0)		
p-value		$p^{(2)} = 0.031$*	$p^{(2)} = 1.000$	$p^{(2)} = 0.070$		
Baseline assessment	Heart failure: Left ventricular hypertrophy				$p^{(1)} = 0.742$	
	Present	41 (36.9)	43 (39.1)	84 (38.0)		1.0
	Absent	70 (63.1)	67 (60.9)	137 (62.0)		1.1 (0.6 to 1.9)
	TOTAL	111 (100.0)	110 (100.0)	221 (100.0)		
After intervention	Heart failure: Left ventricular hypertrophy				$p^{(1)} < 0.001$*	
	Present	20 (18.5)	43 (41.0)	63 (29.6)		1.0
	Absent	88 (81.5)	62 (59.0)	150 (70.4)		3.1 (1.6 to 5.7)
	TOTAL	108 (100.0)	105 (100.0)	213 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 1.000$	$p^{(2)} < 0.001$*		
Baseline assessment	Arrhythmia				$p^{(1)} = 0.708$	
	Present	70 (63.6)	72 (66.1)	142 (64.8)		1.0
	Absent	40 (36.4)	37 (33.9)	77 (35.2)		1.1 (0.6 to 1.9)
	TOTAL	110 (100.0)	109 (100.0)	219 (100.0)		
After intervention	Arrhythmia				$p^{(1)} < 0.001$*	
	Present	26 (23.9)	86 (81.9)	112 (52.3)		1.0
	Absent	83 (76.1)	19 (18.1)	102 (47.7)		14.4 (7.4 to 28.1)
	TOTAL	109 (100.0)	105 (100.0)	214 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} < 0.001$*	$p^{(2)} = 0.002$*		
Baseline assessment	Coronary artery disease				$p^{(1)} = 0.664$	
	Present	23 (20.7)	25 (23.1)	48 (21.9)		1.0
	Absent	88 (79.3)	83 (76.9)	171 (78.1)		1.2 (0.6 to 2.2)
	TOTAL	111 (100.0)	108 (100.0)	219 (100.0)		
After intervention	Coronary artery disease				$p^{(1)} = 0.038$*	
	Present	14 (12.8)	25 (23.8)	39 (18.2)		1.0
	Absent	95 (87.2)	80 (76.2)	175 (81.8)		2.1 (1.0 to 4.4)
	TOTAL	109 (100.0)	105 (100.0)	214 (100.0)		
p-value		$p^{(3)} = 0.012$*	$p^{(3)} = 1.000$	$p^{(3)} = 0.022$*		

* Significant difference at 5.0 % level.
** Not determineD due to occurrence very low frequencie
[1] Pearson's chi-squared test.
[2] McNemar's test.

levels of proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and IL- 6, and a low-grade increase in other proinflammatory makers, such as C-reactive protein (CRP) [34].

Another mechanism may be that stress in early life would epigenetically modulate inflammatory cells (monocytes/macrophages) so that these cells become hyper-responsive to stress, with the capacity of a null response to inhibitory feedback, and are subsequently more affected by hormonal and behavioral signaling, increasing inflammation [31]. In this case, the anti-inflammatory and antioxidant effects of vitamin D may lead to a reduction in inflammatory signaling.

4.2. Reduction of cardiovascular risk factors

Among the intervention's results regarding the control and/or reduction of cardiovascular risk factors, significant positive effects were found in the group of patients supplemented with vitamin D compared to the placebo group for virtually all variables analyzed. These results corroborate other recent studies that reflect the protective and cardiovascular risk-reducing effects of vitamin D [35,36].

Hypertension is a major public health problem and a risk factor for myocardial infarction, heart failure, kidney failure, and stroke [37]. Observational studies report an inverse association between 25-hydroxyvitamin D levels and blood pressure, with some trials showing benefits from sunlight exposure or supplementation [38,39]. In our trial, vitamin D supplementation in depressed patients reduced blood pressure, aligning with studies demonstrating improved cardiac function and ventricular remodeling [40]. Proposed mechanisms include vasodilation, increased vascular elasticity, RAAS inhibition, reduced parathyroid hormone, and anti-inflammatory vascular effects [40,41].

For peripheral obstructive arterial disease, no improvement in ankle–brachial index was found, despite evidence linking deficiency to higher risk [42,43]. However, carotid intima–media thickness and stenosis improved after supplementation, consistent with vitamin D's potential to modulate endothelial function, reduce oxidative stress, and inhibit smooth muscle cell proliferation [42,43].

Vitamin D exerts cardioprotective actions by improving vascular compliance, modulating RAAS, and suppressing inflammatory cytokines such as IL-6, IL-8, and TNF-α, while increasing IL-10 [44,45]. In this trial, supplementation normalized left ventricular ejection fraction and reduced hypertrophy, likely via VDR-mediated regulation of calcium homeostasis, myocardial contractility, and hypertrophy gene expression [46,47]. Deficiency is associated with higher natriuretic peptides, adverse remodeling, and fibrosis, while supplementation downregulates MMP activity, preserving extracellular matrix integrity [48]

Genetic variations in the VDR gene, such as BsmI polymorphisms, are linked to greater hypertrophy risk [49]. Experimental data show

Table 4a
Distribution of laboratory cardiovascular risk factors in factors in study groups at baseline assessment and after the intervention, Recife, 2025. Continued

Assessment	Variable	Group				
		Supplementation n (%)	Placebo n (%)	Total Group n (%)	p-value	OR (95 % CI)
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 0.049$*	$p^{(2)} = 0.001$*		
Baseline assessment	Diabetes mellitus: Oral glucose tolerance test				$p^{(1)} = 0.360$	
	Altered	95 (88.0)	92 (83.6)	187 (85.8)		1.4 (0.7 to 3.1)
	Normal	13 (12.0)	18 (16.4)	31 (14.2)		1.0
	TOTAL	108 (100.0)	110 (100.0)	218 (100.0)		
After intervention	Diabetes mellitus: Oral glucose tolerance test				$p^{(1)} < 0.001$*	
	Altered	109 (99.1)	86 (80.4)	195 (89.9)		**
	Normal	1 (0.9)	21 (19.6)	22 (10.1)		
	TOTAL	110 (100.0)	107 (100.0)	217 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 0.508$	$p^{(2)} = 0.078$		
Baseline assessment	Diabetes Mellitus: Hemoglobin A1C				$p^{(1)} = 0.167$	
	Altered	84 (75.7)	74 (67.3)	158 (71.5)		1.5 (0.8 to 2.7)
	Normal	27 (24.3)	36 (32.7)	63 (28.5)		1.0
	TOTAL	111 (100.0)	110 (100.0)	221 (100.0)		
After intervention	Diabetes Mellitus: Hemoglobin A1C				$p^{(1)} < 0.001$*	
	Altered	11 (10.0.0)	85 (78.7)	96 (44.0.0)		1,0
	Normal	99 (90.0.0)	23 (21.3)	122 (56.0.0)		33,3 (15,3 to 72,2)
	TOTAL	110 (100.0)	108 (100.0)	218 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 0.001$*	$p^{(2)} < 0.001$*		
Baseline assessment	Diabetes mellitus: Resistance - HOMA-IR				$p^{(1)} = 0.749$	
	Altered	79 (76.0.0)	77 (74.0.0)	156 (75.0.0)		1.1 (0.6 to 2.1)
	Normal	25 (24.0.0)	27 (26.0.0)	52 (25.0.0)		1.0
	TOTAL	104 (100.0)	104 (100.0)	208 (100.0)		
After intervention	Diabetes mellitus: Resistance - HOMA-IR				$p^{(1)} < 0.001$*	
	Altered	41 (38.7)	88 (81.5)	129 (60.3)		1.0
	Normal	65 (61.3)	20 (18.5)	85 (39.7)		9.0 (3.7 to 13.0.0)
	TOTAL	106 (100.0)	108 (100.0)	214 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 0.016$*	$p^{(2)} < 0.001$*		
Baseline assessment	Hyperthyroidism or hypothyroidism - Thyroid function (TSH)				$p^{(1)} = 0.557$	
	Altered	39 (35.5)	43 (39.1)	82 (37.3)		1.0
	Normal	71 (64.5)	67 (60.9)	138 (62.7)		1.2 (0.7 to 2.0)
	TOTAL	110 (100.0)	110 (100.0)	220 (100.0)		

* Significant difference at 5.0 % level.
** Not determined due to occurrence of very low frequencies and very broad confidence interval
[1] Pearson's chi-squared test.
[2] McNemar's test.

calcitriol promotes cardiomyocyte differentiation by inhibiting canonical Wnt signaling [50] and restores Treg/Th17 balance in chronic heart failure, reducing inflammation [51].

These findings reinforce vitamin D supplementation as a potential adjunctive strategy for preventing hypertension-related complications, atherosclerosis, and pathological cardiac remodeling.

Additional evidence shows that vitamin D directly influences vascular smooth muscle cells and cardiomyocytes, protecting against heart failure. Supplementation normalized left ventricular ejection fraction and contributed to a reduction in left ventricular hypertrophy in patients with depression in the present clinical trial.

Vitamin D has been shown to increase vascular compliance, thereby improving endothelial function. This improvement contributes to lowering blood pressure, regulating blood flow in skeletal muscles and coronary microcirculation, and, indirectly, to reducing inflammatory cytokines such as IL-6 and IL-8, which are involved in post-injury myocardial remodeling. Similar to other cardiovascular diseases, vitamin D plays an important role in regulating the renin–angiotensin–aldosterone system (RAAS), which maintains vascular resistance through the synthesis of angiotensin II and controls extracellular fluid homeostasis via aldosterone release. Experimental studies in both animals and humans have shown that calcitriol reduces RAAS activity by suppressing the renin gene [44].

Vitamin D also has anti-inflammatory effects in heart failure pathogenesis. Vitamin D deficiency stimulates the production of pro-inflammatory cytokines such as IL-8 and TNF-alpha. Adequate vitamin D suppresses this pro-inflammatory state by inhibiting the activation of nuclear factor-kappa beta, IL-6, IL-12, interferon-alpha, and TNF-alpha, while increasing anti-inflammatory cytokine IL-10 [90]. Through vitamin D receptors (VDRs), calcitriol inhibits T effector cell proliferation, reduces IL-2 and IFN-γ production, decreases cytotoxicity, and lowers the synthesis of IL-17 and IL-23 [45].

The relationship between vitamin D and natriuretic peptide levels has been explored in several studies [92–94]. In the LURIC Study, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels were significantly and inversely correlated with 25-OHD ($p < 0.001$) and calcitriol ($p < 0.001$) levels in patients undergoing coronary angiography [93]. Ma et al. [52] also found that 25(OH)D was inversely correlated with NT-proBNP, a marker associated with ventricular dysfunction and greater disease severity. Among vitamin D's cardioprotective effects, Patel and Rizvil [53] observed a reduction in the expression of myocardial hypertrophy markers, such as atrial natriuretic peptide and growth factors promoting cardiomyocyte proliferation.

In a study involving intravenous calcitriol administration for treating hyperparathyroidism in chronic kidney disease patients on dialysis, Kim et al. [95] reported a reduction in LV hypertrophy and QT interval dispersion. Calcium also plays a role in cardiomyocyte proliferation and activation of the AKT protein kinase, which is implicated in myocardial hypertrophy. Increased cytoplasmic calcium prompts mitochondria to buffer excess levels, but in pathological conditions—such as ischemia and reperfusion—this mechanism fails, leading to cellular toxicity. Elevated calcium activates AKT, contributing to cardiac hypertrophy development. In conditions like heart failure and chronic kidney disease, AKT activation is abnormally high, resulting in heart dilation, elevated

Table 4b
Distribution of laboratory cardiovascular risk factors in factors in study groups at baseline assessment and after the intervention, Recife, 2025. Conclusion

Assessment	Variable	Group				
		Supplementation n (%)	Placebo n (%)	Total Group n (%)	p-value	OR (95 % CI)
After intervention	Hyperthyroidis m or hypothyroidism - Thyroid function (TSH)				$p^{(1)} < 0.001$*	
	Altered	6 (5.5)	43 (40.2)	49 (22.6)		1.0
	Normal	104 (94.5)	64 (59.8)	168 (77.4)		11.6 (4.7 to28.9)
	TOTAL	110 (100.0)	107 (100.0)	217 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 1.000$	$p^{(2)} < 0.001$*		
Baseline assessment	Hyperparathyroidism				$p^{(1)} = 0.960$	
	Altered	39 (35.1)	39 (35.5)	78 (35.3)		1.0 (0.6 to 1.7)
	Normal	72 (64.9)	71 (64.5)	143 (64.7)		1.0
	TOTAL	111 (100.0)	110 (100.0)	221 (100.0)		
After intervention	Hyperparathyroi dism				$p^{(1)} < 0.001$*	
	Altered	3 (2.7)	56 (51.4)	59 (26.9)		**
	Normal	107 (97.3)	53 (48.6)	160 (73.1)		
	TOTAL	110 (100.0)	109 (100.0)	219 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 0.001$*	$p^{(2)} = 0.040$*		
Baseline assessment	Chronic kidney disease: Albuminuria				$p^{(1)} = 0.613$	
	Altered	26 (23.4)	29 (26.4)	55 (24.9)		1.0
	Normal	85 (76.6)	81 (73.6)	166 (75.1)		1.2 (0.6 to 2.2)
	TOTAL	111 (100.0)	110 (100.0)	221 (100.0)		
After intervention	Chronic kidney disease: Albuminuria				$p^{(1)} < 0.001$*	
	Altered	6 (5.5)	36 (33.3)	42 (19.3)		1.0
	Normal	104 (94.5)	72 (66.7)	176 (80.7)		8.7 (3.5 to 21.6)
	TOTAL	110 (100.0)	108 (100.0)	218 (100.0)		
p-value		$p^{(2)} < 0.001$*	$p^{(2)} = 0.008$*	$p^{(2)} = 0.036$*		
Baseline assessment	High sensitivity C-reactive protein				$p^{(1)} = 0.591$	
	Altered	105 (93.8)	102 (91.9)	207 (92.8)		1.3 (0.5 to 3.7)
	Normal	7 (6.3)	9 (8.1)	16 (7.2)		1.0
	TOTAL	112 (100.0)	111 (100.0)	223 (100.0)		
After intervention	High sensitivity C-reactive protein				$p^{(1)} = 0.002$*	
	Altered	100 (89.3)	111 (99.1)	211 (94.2)		**
	Normal	12 (10.7)	1 (0.9)	13 (5.8)		
	TOTAL	112 (100.0)	112 (100.0)	224 (100.0)		
p-value		$p^{(2)} = 0.180$	$p^{(2)} = 0.021$*	$p^{(2)} = 0.648$		

* Significant difference at 5.0 % level.
** Not determined due to occurrence of very low frequencies and very broad confidence interval.
[1] Pearson's chi-squared test.
[2] McNemar's test.

angiotensin II, and volume overload [54,55].

Zittermann and Koefer [56] showed that calcitriol acts via cytosolic VDRs in most body cells, including cardiomyocytes, vascular endothelial cells, and smooth muscle cells. Vitamin D regulates actin–myosin interactions and intracellular calcium homeostasis, influencing myocardial contractility [46,57].

Animal studies highlight the importance of VDRs in controlling myocardial hypertrophy [47,48]. Through VDRs, calcitriol regulates cardiomyocyte proliferation, morphology, and growth; increases the expression of cardiac muscle proteins and myotrophin; reduces atrial natriuretic factor expression; and enhances both expression and nuclear localization of VDRs in these cells [48,56]. Vitamin D reduces fibrosis in multipotent mesenchymal cells by promoting VDR expression and nuclear translocation, thereby decreasing profibrotic factors (TGF-β1 and plasminogen activator inhibitor) and collagen isoforms, while increasing anti-fibrotic factors.

VDR gene polymorphisms (FokI and BsmI) are recognized markers of altered vitamin D signaling pathways and are linked to left ventricular hypertrophy, a strong cardiovascular risk factor in end-stage kidney disease. One study found a significant association between the BsmI Bb genotype and LV hypertrophy [49].

Another key mechanism in heart failure is extracellular matrix degradation by matrix metalloproteinases (MMPs), which release matrix-binding growth factors and matrikines—peptides that regulate connective tissue cell activity. These changes alter collagen fiber type, arrangement, and cross-links, fostering fibrosis. Collagen degradation by MMPs (elevated in heart failure) produces structurally weaker fibers, contributing to ventricular dilation. MMPs participate in angiogenesis, tissue repair, morphogenesis, stem cell mobilization, and wound healing, but also in inflammation and post-ischemic cardiac remodeling. A proper balance with tissue inhibitors of metalloproteinases (TIMPs) is critical, as TIMPs suppress MMP activity. Vitamin D deficiency can suppress TIMPs, accelerating ventricular remodeling, dilation, and heart failure [46].

MMP-2 and MMP-9, members of the gelatinase subgroup, degrade collagen IV and gelatin and are found in the myocardium, capable of breaking down all extracellular matrix components between cardiomyocytes [46]. After ischemia, MMP-2 and MMP-9 are inversely correlated with LV contractility and positively correlated with ischemia duration. These enzymes also modulate inflammation by cleaving immune proteins as well as actin and myosin filaments [58,59].

A large prospective study by Pandit et al. [60] found associations between vitamin D levels and interventricular septum thickness and LV mass index, independent of age, hypertension, and vitamin D therapy, emphasizing its role in ventricular remodeling. Ford et al. [61], analyzing the RECORD Study along with systematic reviews and meta-analyses, concluded that vitamin D may protect older adults from heart failure by preventing onset and slowing progression.

In an experimental study, Hlaing et al. [50] examined calcitriol's role in cardiomyocyte proliferation, apoptosis, phenotype, cell cycle progression, and differentiation. Calcitriol inhibited proliferation without inducing apoptosis, downregulated proliferating cell nuclear antigen (PCNA), and reduced cyclin-dependent kinases CDK2, CDK4, and Chek1. It promoted cardiomyotube formation, induced casein kinase-1-

Table 5a
Vitamin D statistics, depression score, current suicide risk score and cardiovascular risk factors according to group and assessment Recife, 2025.

	Group			
Variable	Assessment	Supplementation	Placebo	*P* value
		Mean ± DP (CV) Median (P25; P75)	Mean ± DP (CV) Median (P25; P75)	
Vitamin D	Before	23,51 ± 7,16 (30,46) 22,50 (19,00; 27,00)	23,41 ± 6,32 (27,00) 23,00 (19,00; 28,00)	p[(1)] = 0,919
	After	58,41 ± 10,50 (17,98) 57,00 (53,00; 63,00)	21,12 ± 5,31 (25,14) 21,00 (17,25; 25,00)	p[(1)] < 0,001*
	P value	p[(3)] < 0,001*	p[(3)] < 0,001*	
MADRS (Depression)	Before	27,16 ± 6,30 (23,20) 26,00 (24,00; 30,00)	25,07 ± 6,20 (24,73) 24,00 (20,00; 28,00)	p[(1)] = 0,015*
	After	7,73 ± 2,72 (35,19) 8,00 (6,00; 10,00)	22,48 ± 6,62 (29,45) 22,00 (18,00; 28,00)	p[(1)] < 0,001*
	P value	p[(3)] < 0,001*	p[(3)] < 0,001*	
Suicide risk	Before	10,51 ± 9,80 (93,24) 7,00 (1,00; 17,00)	7,88 ± 8,40 (106,60) 7,00 (1,00; 15,25)	p[(1)] = 0,072
	After	1,43 ± 2,08 (145,45) 0,00 (0,00; 4,00)	7,79 ± 7,23 (92,81) 7,00 (1,00; 11,00)	p[(1)] < 0,001*
TC	Before	226,60 ± 41,05 (18,12) 227,00 (192,00; 256,00)	225,92 ± 42,78 (18,94) 227,00 (197,50; 254,00)	p[(2)] = 0,671
	After	193,09 ± 24,78 (12,83) 196,50 (177,75; 210,00)	238,81 ± 39,61 (16,59) 246,00 (210,00; 263,00)	p[(1)] < 0,001*
	P value	p[(3)] < 0,001*	p[(3)] < 0,001*	
HDL	Before	41,06 ± 11,13 (27,11) 38,00 (34,00; 45,00)	41,34 ± 9,58 (23,17) 38,00 (35,00; 46,50)	p[(1)] = 0,526
	After	47,90 ± 8,85 (18,48) 45,00 (41,00; 52,00)	39,72 ± 8,82 (22,21) 38,00 (32,00; 45,00)	p[(1)] < 0,001*
	P value	p[(3)] < 0,001*	p[(3)] < 0,001*	
TG	Before	182,11 ± 66,26 (36,38) 180,00 (161,00; 198,00)	172,44 ± 68,91 (39,96) 170,50 (130,00; 195,00)	p [(1)] = 0,124
	After	138,57 ± 35,37 (25,53) 42,00 (126,00; 148,00)	181,69 ± 42,24 (23,25) 178,00 (158,00; 201,00)	p[(1)] < 0,001*
	P value	p[(3)] < 0,001*	p[(3)] < 0,001*	

* Significant difference at 5,0 % level.
[1] Mann-Whitney's test.
[2] t-Student test with equal variances.
[3] Paired Wilcoxon's test.

Table 5b
Vitamin D statistics, depression score, current suicide risk score and cardiovascular risk factors according to group and assessment Recife, 2025.

	[(2)]Group			
Variable	Assessment	Supplementation	Placebo	P value
		Mean ± DP (CV) Median (P25; P75)	Mean ± DP (CV) Median (P25; P75)	
PTH	Before	61,68 ± 17,71 (28,71) 60,00 (50,00; 74,00)	60,98 ± 17,69 (29,01) 60,50 (51,75; 72,25)	p[(1)] = 0,847
	After	43,52 ± 9,73 (22,36) 43,00 (37,00; 51,00)	66,60 ± 16,01 (24,04) 67,00 (58,00; 78,00)	p[(1)] < 0,001*
	P value	p[(3)] < 0,001*	p[(3)] < 0,001*	
PCR-U	Before	2,25 ± 1,39 (61,78) 2,30 (1,20; 3,20)	2,06 ± 1,50 (72,82) 2,10 (0,99; 2,80)	p[(1)] = 0,187
	After	0,77 ± 0,51 (66,23) 0,80 (0,30; 1,20)	2,71 ± 1,27 (46,86) 2,50 (1,90; 3,35)	p[(1)] < 0,001*
	P value	p[(3)] < 0,001*	p[(4)] < 0,001*	

* Significant difference at 5,0 % level.
[1] Mann-Whitney's test.
[2] t-Student test with equal variances.
[3] Paired Wilcoxon's test.
[4] Paired t-Student test.

α (a negative regulator of the canonical Wnt pathway), and upregulated non-canonical Wnt, known to induce cardiac differentiation during development. The combined inhibition of canonical Wnt signaling and vitamin D's antiproliferative effects linked vitamin D to altered cardiomyocyte differentiation—a key mechanism in heart failure. These findings suggest vitamin D supplementation may prevent or improve cardiovascular disorders related to pathological remodeling and differentiation.

Chronic heart failure (CHF) involves multiple physiological systems, including immune activation and inflammatory cascades in which T regulatory (Treg) and TH17 cells play important roles [62–65]. Calcitriol promotes Treg cell differentiation directly and indirectly via antigen-presenting cells, suppressing inflammation [66]. A pioneering study found that lower Treg and higher Th17 cell counts correlated with CHF severity, with a reduced Treg/Th17 ratio in advanced stages. This imbalance was linked to lower Foxp3 and TGF-β expression and higher RORγt and IL-17 levels. Vitamin D deficiency was associated with this imbalance, while calcitriol improved CD4+ CD45RA+ T cell immunomodulation via VDRs. The authors suggest vitamin D supplementation as a non-pharmacological strategy to prevent CHF progression through immune regulation [51].

Another study showed reduced VDR expression in CD4+ CD45RA+ Treg cells in CHF patients compared to controls. Calcitriol treatment restored VDR expression and exerted immunosuppressive effects on T cells. These results provide strong evidence that vitamin D supplementation may help prevent and treat CHF by modulating immune function [53].

Vitamin D exerts cardioprotective effects by improving vascular compliance, regulating the renin–angiotensin–aldosterone system, reducing inflammation, and modulating immune function. In the present trial, supplementation normalized left ventricular ejection fraction and reduced hypertrophy in patients with depression. Mechanisms include suppression of pro-inflammatory cytokines (IL-6, IL-8, TNF-α), upregulation of anti-inflammatory IL-10, inhibition of myocardial remodeling via matrix metalloproteinase regulation, and improved intracellular calcium homeostasis in cardiomyocytes.

Experimental and clinical studies show inverse correlations between vitamin D status and natriuretic peptides, markers of hypertrophy, and ventricular dysfunction. Vitamin D receptor activation in cardiac tissue modulates proliferation, morphology, and fibrosis, while certain VDR polymorphisms are linked to greater hypertrophy risk. Calcitriol influences cardiomyocyte differentiation through Wnt signaling pathways and enhances regulatory T-cell function, restoring the Treg/Th17

balance in chronic heart failure.

These findings support vitamin D supplementation as a potential non-pharmacological strategy to prevent or attenuate pathological cardiac remodeling, hypertrophy, and heart failure progression.

4.3. Strengths

This is one of the few clinical trials assessing the effects of vitamin D supplementation on both cardiac remodeling and vascular parameters in patients with depression, a population at elevated cardiovascular risk. The prospective design with longitudinal follow-up allows for a better assessment of causal relationships between vitamin D supplementation and cardiovascular outcomes. Furthermore, the study incorporated a comprehensive evaluation, including echocardiographic parameters, vascular function assessments, and inflammatory biomarkers, providing a multidimensional perspective on vitamin D's effects. The inclusion of mechanistic biomarkers—such as natriuretic peptides, cytokine profiles, and MMP activity—strengthens the biological plausibility of the observed effects. Also, the study took place in a region of Northeast Brazil that is sunlit throughout the whole year, which minimizes the potential impact of seasonality on vitamin D production from sunlight.

4.4. Limitations

The relatively small sample size may limit statistical power and the generalizability of the findings to broader populations. Being conducted in a single center may introduce selection bias and restrict external validity.

The lack of a dose–response analysis limits the ability to determine the optimal supplementation regimen for cardiovascular benefits.

5. Conclusion

In the present study, vitamin D exerted important effects on depressive disorder, suicide risk and cardiovascular risk without any clinically significant adverse events.

This study demonstrated that a weekly oral dose of 50,000 IU of vitamin D for six months was effective and promising among patients with depression, with a reduction in inflammation and improvement in the metabolic profile, contributing to the control of depressive symptoms and proving effective for cardiovascular management.

Despite these results, further studies are needed to determine whether therapy with vitamin D is effective at reducing mortality through the reduction in cardiovascular risk factors.

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CRediT authorship contribution statement

Catarina Porto: Methodology, Data curation, Conceptualization. **Katia Petribu:** Supervision, Conceptualization. **Nathalia Barbosa:** Writing – original draft, Methodology, Formal analysis. **Rayana Magalhães:** Writing – original draft. **Cecília Lira:** Writing – original draft, Methodology. **Ana Beatriz Porto:** Writing – original draft. **Brivaldo Markman-Filho:** Writing – original draft. **Andrea Lordsleem:** Conceptualization. **Eveline Calado:** Conceptualization. **José Magalhães:** Methodology. **Everton Sougey:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Tatiana Silva:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Aluísio Junio:** Conceptualization. **Francisco Bandeira:** Methodology. **Rita Leão:** Methodology.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Does not apply.

Data availability

Qualified researchers can request access to additional data from the corresponding author.

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