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Vitamin D and nutritional support in patients with heart failure: effect on circulating cytokines

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Abstract

Background: heart failure (HF) is recognized as a highly state of inflammation. Increased circulating levels of cytokines have been previously reported and generally associated with worse clinical outcomes. In this context, the modulation of inflammation-related parameters seems to be a reasonable therapeutic option for improving the clinical course of the disease.

Aim: to compare changes in circulating cytokines and clinical progression of patients with HF when calcifediol supplementation is administered along with Mediterranean diet alone or with Mediterranean diet and 2 hypercaloric, hyperproteic oral nutritional supplements (ONS) enriched with eicosapentaenoic acid (EPA) docosahexaenoic acid (DHA) fatty acids.

Patients and methods: 25-hydoxi-vitamin D (25OHvitD) and circulating cytokines (IL-6, IL-8, IL-10, IP-10, MCP-1) were determined at baseline and after 24 weeks of nutritional support in a cohort of 38 patients previously included in an open label, controlled clinical tiral; briefly patients were randomized to receive calcifediol plus Mediterranean Diet (control group) vs calcifediol plus Mediterranean Diet and ONS (intervention group). Epidemiological, clinical, anthropometric, and biochemical evaluation was also performed.

Results: 25OHVitD insufficiency was observed in 58.3 % of patients. Patients from the intervention group exhibited higher increase in serum 25OHVitD, higher decrease in ferritin, C-reactive protein (C-RP), IL-8, IL-6 and IP-10; although 25OHVitD levels positively correlated at baseline with body cell mass and the phase angle ($p < 0.05$) they did not correlate with serum ferritin, C-RP or the circulating evaluated interleukins. Any associations were observed between serum 25OHVitD and left ventricular ejection fraction (LVEF) or the N-terminal pro-brain natriuretic peptide (NT-proBNP). An age-, sex- and 25OHvitD adjusted multivariate analysis showed that the only cytokine associated with increased mortality in patients with HF was MCP-1 (OR 1.01, 95 %CI, 1.01-1.02), which was not modulated in the intervention or the control group after 24-weeks of treatment.

Conclusion: although the combination of calcifediol, Mediterranean diet and hypercaloric, hyperproteic, EPA and DHA enriched ONS with decreased serum levels of inflammation related parameters (C-RP) and ferritin, as well as circulating cytokines, 25OHvitD levels were not correlated with these inflammation markers or the clinical progression of patients (mortality and new hospital admissions).

Keywords:
Oral supplements. Calcifediol. Heart failure. Cytokines. Mortality. Outcomes.

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INTRODUCTION

Vitamin D deficiency (VDD) is increasingly recognized as a significant factor in cardiovascular health, with associations identified in both coronary heart disease (CHD) and heart failure (HF) (1). Specifically, VDD, defined as 25-hydroxyvitamin D (25-OH-Vit D) levels < 20 ng/mL, has been associated with risk factors for cardiovascular disease and adverse outcomes (2) including all-cause mortality, cardiovascular mortality, and major adverse cardiovascular events (MACE) (1). Similarly, in patients with HF, multiple studies have revealed a striking correlation between VDD and worse prognosis (3). Furthermore, VDD in HF patients has been associated with reduced left ventricular ejection fraction (LVEF), increased natriuretic peptides, and increased mortality (4). Prospective studies have even indicated that the risk of developing HF is higher in patients with VDD (5). These associations highlight the potential role of vitamin D in the pathogenesis and progression of HF. Despite the strong epidemiological evidence implicating VDD in adverse cardiovascular outcomes, clinical trials involving vitamin D supplementation have largely failed to demonstrate consistent improvements in CVD outcomes; this discrepancy suggests that the relationship between vitamin D and cardiovascular disease is complex and may involve intermediary factors or specific patient subgroups that could benefit from intervention (1).

VDD has been involved in and may promote greater risk through inflammation; individuals with both VDD and elevated high-sensitivity C-reactive protein (hsCRP) levels exhibit an approximately 3-fold greater hazard of cardiovascular mortality vs those with normal vitamin D levels and low hsCRP (1). Similar findings have been observed for all-cause mortality and MACE, suggesting a synergistic detrimental effect of VDD and inflammation in cardiac heart disease (1).

Evidence from these sources consistently points towards a significant association between VDD and adverse cardiovascular outcomes, including HF. Inflammation seems to be a crucial mediator in this relationship, with lower vitamin D levels often correlating with higher levels of pro-inflammatory markers (5). Additionally, it has been described that vitamin D may exhibit immunomodulatory properties in reducing certain inflammatory cytokines like α necrosis tumor factor (TNF-α) in patients with HF, despite this, vitamin D supplementation trials have not consistently translated these effects into improved clinical outcomes (1).

HF is recognized as a systemic pro-inflammatory state that involves the activation of both innate and adaptive immunity mechanisms. Hemodynamic stress and volume overload in HF can lead to cardiomyocyte damage, stimulating the release of pro-inflammatory cytokines such as MCP-1, and IL-6 (5). These inflammatory signals can have effects on additional organs, which contributes to skeletal muscle inflammation, adipose tissue inflammation and atherogenesis. This pro-inflammatory state deteriorates ventricular function by inducing myocardial contractile dysfunction, hypertrophy, apoptosis, and fibrosis, ultimately leading to the progression of HF due con cardiac remodeling (6). Elevated concentrations of inflammatory markers in HF patients have been associated with adverse outcomes such as reduced LVEF, increased pro-BNP, and increased mortality (5). The complex interplay between inflammation and HF suggests that targeting inflammatory pathways could be a potential therapeutic strategy (1).

Several authors suggest that vitamin D possesses immunoregulatory functions, furthermore, *in vitro* and *in vivo* models have demonstrated protective roles through mechanisms involving various inflammatory pathways (5). Despite this, there is inconsistent evidence from the clinical trials about the use of vitamin D supplementation for decreasing inflammation in these patients (7,8).

In this context, we aimed to evaluate the correlation between vitamin D and circulating cytokines levels in patients with a recent admission due to HF, their relation with nutritional parameters (combining anthropometric, instrumental and biochemical measurements) and determine their progression after 24-weeks of vitamin D supplementation along with Mediterranean diet alone or vitamin D supplementation, Mediterranean diet and nutritional support with a hypercaloric, hyperproteic, omega 3 (*n*-3)- enriched oral nutritional supplement (ONS).

MATERIAL AND METHODS

PATIENTS

This study was approved by *Hospital Universitario Reina Sofía* Ethics Committee (Cordoba, Spain; reference No. 5164 approved on October 21st, 2021 and updated on May 30th, 2023). The study was conducted in full compliance with the criteria set forth in the Declaration of Helsinki and national and international clinical practice guidelines. We conducted a prospective open-label study in which written informed consent was obtained from each participant prior to their inclusion in the study. All patients received comprehensive information about the study before consenting to participate. Only those who agreed to participate were subsequently included. This cohort was initially evaluated in an open, randomized, controlled clinical trial (ClinicalTrials.gov number: NCT05848960) (9). The trial included patients of both sexes, aged between 18 and 85 years, with a left ventricular ejection fraction (LVEF) < 50 % and who had been hospitalized due to heart failure over the past 6 months.

NUTRITIONAL SUPPORT

In the clinical trial, patients received vitamin D supplementation with calcifediol at a different dose depending on the baseline levels of 25-OH-Vit D (25-OH-Vit D > 30 ng/mL: dose 0.266 mg every 30 days; 25-OH-Vit D 20-29 ng/mL: dose of 0.266 mg calcifediol every 21 days; 25-OH-Vit D 10-19 ng/mL: dose of 0.266 mg calcifediol every 15 days; 25-OH-Vit D < 10 ng/mL: dose of 0.266 mg calcifediol every 10 days. Additionally, patients were randomized by the clinical investigator to receive either Mediterranean diet alone or Mediterranean diet plus 2 hypercaloric, hyperproteic ONS per day, with a 1:1 allocation for 24 weeks. The ONS included slow-release carbohydrates, fiber mixture and a combination of *n*-3 and *n*-6 fatty acids. ONS were kindly donated by Vegenat Healthcare®, bottles were administered every 3 weeks. A total of 19 patients were included in each arm. All patients referred an adherence > 75 % to treatment. At baseline, all patients received general education and advice about nutritional support, Mediterranean diet and physical activity.

NUTRITIONAL EVALUATION

A morphofunctional nutritional evaluation was performed as previously described (10-12). Briefly, physical examination included body composition analysis (bioelectrical bioimpedance, abdominal, arm and calf circumferences), functional tests (up and go test and handgrip strength) and nutritional ultrasound of abdominal adipose tissue and rectus-femoris (RF) muscle of the quadriceps. Biochemical nutritional analysis was also performed (hemoglobin, lymphocytes, total cholesterol, total, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, transferrin, albumin, prealbumin), heart-related markers (N-terminal pro-brain natriuretic peptide (NT-proBNP)) and inflammation markers (C-reactive protein (C-RP) and ferritin) were included. Left ventricular ejection fraction (LVEF) measured using transthoracic ultrasound was also evaluated.

CYTOKINE MEASUREMENT

Serum cytokines were quantified by Cytometry Bead Array (CBA, BD Cytometric Bead Array Human Soluble Protein Master, ref. 558264/558265; Becton Dickinson and Company, San Jose, CA, USA). The following cytokines were analysed based on the manufacturer´s instructions for use: IL-6 (ref. 558276), IL-8 (CXCL8, ref. 558277), IL-10 (ref. 558274), MCP-1 (CCL2, ref. 558287) and IP-10 (CXCL10, ref. 558280). For sample acquisition, a FACS Canto II was used, and a minimum of 300 events were recorded per each cytokine. Median Fluorescence Intensity (MFI) data was transformed in concentration (pg/mL) using a calibration curve as a reference.

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov test was used to assess the data normal distribution. For the descriptive statistics, the mean and standard deviation of the continuous variables and the frequencies and percentages of the discrete variables were calculated. To assess differences across continuous variables, the Mann-Whitney U test was used (nonparametric data). Paired analysis was performed by Wilcoxon test (nonparametric data). For differences between the discrete variables, Pearson´s test was used. Statistical analyses were performed using SPSS statistical software version 20, and Graph Pad Prism version 6. Significance was defined as a *p*-value of < 0.05.

RESULTS

BASELINE CHARACTERISTICS OF THE GROUPS

A total of 38 patients were included in the study, 28.9 % were women, 42.1 % had type 2 diabetes mellitus and 34.2 % had ischemic cardiomyopathy; the median ejection fraction was 33 % and baseline NT-proBNP was 4225 pg/mL. A total of 73.7 %exhibited overweight or obesity. There were no differences in patients that underwent Mediterranean diet alone (control group) and those who received additional nutritional support (intervention group) (Table I). Median 25-OHvitD at baseline was 18 (11-26) ng/dL, 58.3 % of patients had 25OHvitD < 20 ng/dL. Specific baseline characteristics are shown in table I.

After 6 months of nutritional intervention, 25-OHvitD increased to 22 (16-31) ng/dL, this increase was higher in the intervention group [from 17 (9-29) to 25 (19-38), $p = 0.08$] than the control group [form 15 (11-21) to 17 (9-29)]. In parallel, serum ferritin and C-RP significantly decreased in the intervention group ($p < 0.01$) but not in the control group ($p>0.05$); additionally, also NT-proBNP levels significantly decreased in patients that received nutritional support with ONS (Table II).

CLINICAL ASSOCIATIONS AND CORRELATIONS BETWEEN SERUM 25-OHvitD AND NUTRITIONAL PARAMETERS

In this cohort, 25OHvitD at baseline was correlated with body cell mass (BCM) $r = 0.612$ ($p < 0,01$) and the phase angle (PA) $r = 0.349$ ($p < 0.05$). Baseline 25OHvitD < 20 ng/dL was associated with increased BMI (29.9 kg/m2 (IQR 5.55) vs 26.4 kg/m2 (IQR 7.9), any other association with anthropometric or biochemical parameters, including LVEF and NT-proBNP was observed.

Table I. Baseline clinical characteristics of the patients. Inter-group comparison based on nutritional intervention

Characteristics	Total (*n* = 38)	Calcidefiol plus Mediterranean diet (*n* = 19)	Calcidefiol plus Mediterranean diet and ONS (*n* = 19)	*p*
Sex (♂/♀)	71.1 %/28.9 % (11/27)	31.6/68.4 (6/13)	73.7/26.3 (14/5)	0.50
Age (years)	67.5 (61-78)	72 (64.5-80)	65 (56-72)	0.06
Tobacco exposure (%)				
No	57.9 (22/38)	42.1 (8/19)	73.7 (14/19)	
Active	18.4 (7/38)	15.8 (3/19)	21.1 (4/19)	
Previous exposure	23.7 (9/38)	42.1 (8/19)	5.3 (1/19)	
Type 2 diabetes *mellitus*	42.1 (16/38)	36.8 (7/19)	47.4 (9/19)	0.38
Previous ischemic cardiomyopathy	34.2 (13/38)	36.8 (7/19)	31.6 (6/19)	0.50
Ejection fraction (%)	33 (25-49.5)	40 (32.5-54)	38 (23-35)	0.46
NT-proBNP (pg/mL)	4225 (2001-7289)	3678 (1966-7203)	4412 (2177-7255)	0.59
Current weight (kg)	78 ± (70.3-89.5)	81 (75-90)	76 (70-85)	0.17
Overweight/obesity (%)	73.7 (28/38)	57.1 (16/19)	42.9 (12/19)	0.14
Mortality (%)	13.2 (5/38)	21.1 (4/19)	5.3 (1/19)	0.17

Categorical data are expressed as percentages and absolute number in brackets. Continuous variables are expressed as median with interquartile range n brackets. ONS: oral nutritional supplement.

Table II. Biochemical analysis at baseline and 6 months after nutritional support

	Total			Mediterranean diet			Mediterranean diet and OS		
Characteristics	Baseline (*n* = 38)	6 months (*n* = 33)	*p*1	Baseline (*n* = 19)	6 months (*n* = 15)	*p*2	Baseline (*n* = 19)	6 months (*n* = 18)	*p*3
Biochemical parameters									
Ferritin (mg/dL)	106 (35-176)	73 (32 - 111)	0.003	74 (32 - 171)	80 (37 - 113)	0.46	130 (104 - 169)	80 (37 - 113)	< 0.01
C-RP (mg/L)	2.1 (0.5-6.9)	1.0 (0.5-2.6)	0.02	2.2 (0.5-15)	2.1 (0.5-5.6)	0.79	1.4 (0.7-5.8)	0.7 (0.5-1.5)	< 0.01
NT-proBNP (pg/mL)	1855 (1080-4364)	741 (393-1992)	<0.01	1757 (557-6027)	489 (178-1676)	0.17	1952 (1179-3307)	1303 (741-2111)	0.02
Vitamin D (ng/dL)	18 (11-26)	22 (16-31)	0.08	15 (11-21)	17 (9-29)	0.51	17 (9-29)	25 (19-38)	0.08
Interleukin levels									
IL-6	0.8 (0-11)	0	0.001	2.4 (0 -14.97)	0	0.07	0 (0 - 7.55)	0	0.01
IL-8	116 (26-311)	8.84 (2.8-14.9)	< 0.0001	190 (38.1-621.7)	10.27 (2.41-14.56)	0.001	53.1 (20-160.5)	7.83 (5.63-20.65)	0.001
IP-10	314.5 (226-409)	196 (94-328)	0.002	288 (229-492)	208 (120-419)	0.25	319 (219-391)	193 (70-318)	0.002
IL-10	0	0		0	0		0	0	
MCP-1	154 (85-234)	163 (84-220)	0.30	173 (148-244)	163 (89-206)	0.18	126 (51- 205)	162 (83-277)	0.93

p1 refers to the comparison between all patients at baseline and after 24 weeks; p2 indicates the comparison between patients of the control group (Mediterranean diet) at baseline and after 24 weeks; p3 indicates the comparison between patients of the intervention group (Mediterranean diet plus oral nutritional supplementation) at baseline and after 24 weeks.

After 24-weeks of intervention, 25-OHvitD < 20 ng/mL was associated with higher serum ferritin ($p < 0.05$) and remarkably, 25-OHvitD > 30 ng/mL were associated with lower body cell mass (BCME), extracellular cell mass (ECME), lean mass, water and bone mass (Fig. 1).

CORRELATIONS AMONG 25OHvitD, BODY COMPOSITION AND CIRCULATING CYTOKINE LEVELS

Although, at baseline, 25OHvitD positively correlated with phase angle ($r = 0.428$; $p = 0.01$) and negatively with C-reactive protein serum levels (C-RP; $r = -0,378$; $p = 0.02$) serum 25OHvitD levels did not significantly correlate with circulating levels of IL6, IL8, IL10, MCP1 and IP10. After 24-weeks of intervention, serum 25OHvitD negatively correlated with extracellular mass ($r = -0.375$; $p = 0.03$) and IL6 levels $r = -0.390$ ($p < 0.05$).

CLINICAL ASSOCIATION BETWEEN HF-RELATED OUTCOMES AND CIRCULATING INTERLEUKINS

At the 24-week follow-up, 27.3 % of patients ($n = 9$) experienced at least 1 hospital readmission due to HF. Most (6/9) had a single readmission, while the remaining 3 patients had 2 or more. Among those readmitted, 55.6 % ($n = 5$) belonged to the control group and 44.4 % ($n = 4$) to the intervention group ($p = 0.3$). Despite mortality rate was higher in the control group (21.1 %) vs the intervention group (5.3 %), this difference was not statistically significant. An age-, sex- and 25OHvitD adjusted multivariate analysis showed that the only cytokine associated with increased mortality in patients with HF was MCP-1 (OR 1.01, 95 %CI, 1.01-1.02). In contrast, no circulating cytokine was associated with new hospital admissions due to HF at the 24-week follow-up.

DISCUSSION

Given the conflicting evidence on the anti-inflammatory effects of vitamin D supplementation in specific contexts, we evaluated the clinical impact of its combination with oral nutritional supplements (ONS) in patients recently hospitalized for HF. In this cohort, we observed that patients from the intervention group resulted in clinical improvements including lean mass gain, cell mass gain, decreased levels of serum ferritin and C-RP, and a more significant improvement in functionality, quality of life, LVEF and decrease in NT-proBNP serum levels after 24 weeks of intervention. In parallel, we observed that Mediterranean diet and vitamin D supplementation with calcifediol resulted in decreased IL-8 circulating levels in these patients, while its combination with an ONS (with slow-release carbohydrates, fiber mixture and enriched with EPA and DHA) resulted in an additional significant decrease in serum IL-6 and IP-10 (13). Clinically, as expected, lower 25OHvitD levels

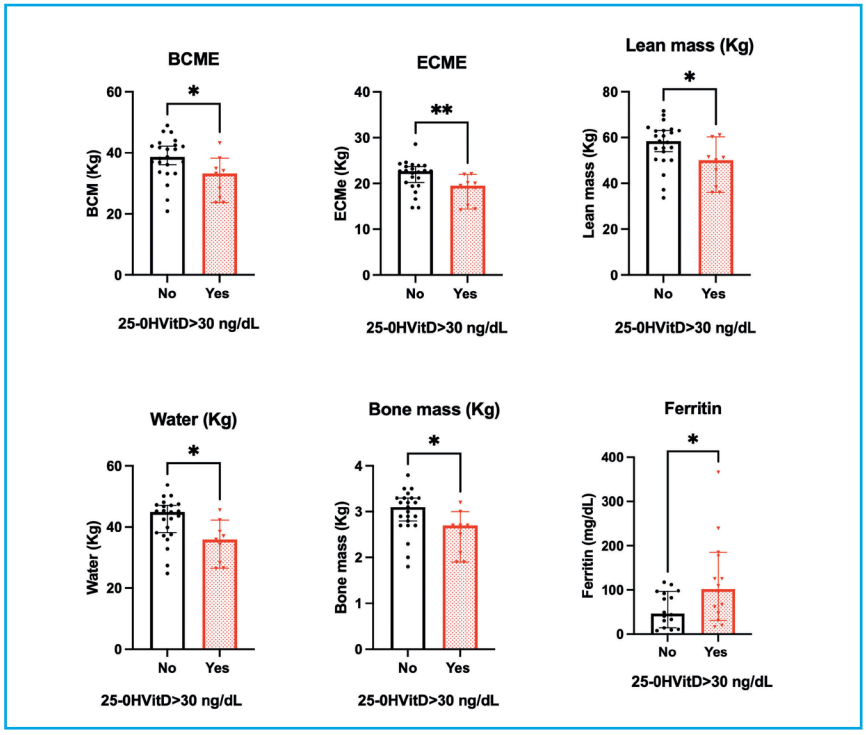

Figure 1. Clinical associations between 25OHvitD, clinical and biochemical parameters after 24-weeks of nutritional support and vitamin D supplementation. Serum 25-OHvitD levels tended to correlate with transferrin ($p = 0.05$). Additionally, serum25-OHvitD negatively correlated with body weight $r = -0.380$ ($p < 0.05$), BMI $r = -0.359$ ($p < 0.05$) and adipose tissue in the rectus femoris $r = -0.375$ ($p < 0.05$). Both, at baseline and at the end of the study, 25-OHvitD levels were not associated with circulating interleukins.

were observed in patients with increased C-RP and decreased phase angle as previously described in different cohorts of patients (14), suggesting decreased muscle quality and functionality in patients with decreased serum 25OHvitD levels (15). Despite this findings, serum 25OHvitD levels were not associated with mortality or additional hospital admissions due to HF. Furthermore, it did not correlate with circulating interleukin levels and only after 24-weeks of intervention it negatively correlated with IL-6 serum levels.

As in our cohort, former studies have reported a high prevalence of VDD in HF patients; however, in contrast to our study, they observed a significant inverse correlation between serum 25OHvitD levels and several pro-inflammatory cytokines, including IL1β, TNF-α, IL6, IL8, and IL17A (5). In line with our study, a few meta-analyses of randomized controlled trials have shown no significant differences in inflammation-related markers including C-RP (4, 16). In contrast, another metanalysis suggested a potential, anti-inflammatory effect of vitamin D supplementation on TNF-α (17), however, it is unknown whether this reduction in TNF-α turns into a significant improvement in the clinical evolution for HF (18).

Another area of interest is the clinical relationship between 25-hydroxyvitamin D (25OHvitD) and body composition parameters. In this regard, we observed positive clinical correlations with BCM and the phase angle, indicating that in HF patients, higher levels of 25OHvitD are associated with better clinical conditions (19,20).

This study has some limitations. First the number of participants; furthermore, we cannot determine a specific relation between the combination of the supplementation with calcifediol and ONS and the clinical benefit. Finally, underlying molecular mechanisms were not evaluated.

Overall, our results reveal a close relation between 25OHvitD, circulating cytokines and body composition parameters in patients with HF, but no specific relations between circulating cytokines and VDD have been observed at baseline. Remarkably, the combination of nutritional support with ONS and calcifediol produced significant decrease in serum IL-6 and IP-10, suggesting that nutritional interventions can affect the clinical evolution of the heart function patients with previous admissions due to HF. Our results do not allow to differentiate whether this effect was improved by the vitamin D supplementation or the composition of the ONS itself. Importantly, MCP-1 was the only parameter independently associated with mortality and it does not change after nutritional and calcifediol supplementation.

Importantly, according to former studies, the synergistic combination of vitamin D with hypercaloric/hyperproteic ONS demonstrates clinically significant benefits in specific populations, primarily through enhanced muscle protein synthesis and metabolic optimization (9,11,21). In this context, it is hypothesized that vitamin D potentiates the effect of the nutritional support downregulating myostatin, which is a muscle growth inhibitor and enhancing leptin sensitivity (redirecting calories toward muscle synthesis) (22).

This data suggests that the role of vitamin D as an anti-inflammatory drug in cardiovascular disease is complex, maybe some factors can mask the real effect, including the origin and evolution of the HF, the severity of the deficiency, the type and dosage of supplementation, and the presence of other comorbidities (4). Large-scale, well-designed clinical trials focusing on VDD individuals with HF and assessing both inflammatory markers and long-term clinical endpoints, are necessary to fully elucidate the therapeutic potential of vitamin D supplementation in these patients since it would help to develop effective strategies for improving clinical outcomes in these patients.

CORRESPONDING AUTHORS

Aura D. Herrera-Martínez, María José Molina Puertas, and Aurora Jurado Roger are the corresponding authors of this article.

AUTHORS´ CONTRIBUTIONS

Conceptualization: A. D. H. M., C. M. J., M. J. M.P., and A. J. R.; funding acquisition: A. D. H. M.; practical performance: S. C. P., A. S. S., J. L. A., A. D. H. M., G. M. G., C. M. J., and M. A. G. M.; formal and data analysis: A. D. H. M.; preparation manuscript: A. D. H. M., M. J. M. P., and C. M. J.; critical review of manuscript: A. D. H. M., M. J. M. P., and A. J. R. Final review of the manuscript: all authors.

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