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Original article

Sucroferric oxyhydroxide, vitamin D, and inflammation in hemodialysis: A proof-of-concept study

Oxihidróxido sucroférrico, vitamina D e inflamación en hemodiálisis: un estudio de prueba de concepto

Fernando Henríquez-Palop [a,b], Carmen Mora-Fernández [c,d,e], Javier Donate-Correa [c,d,e], Ernesto Martín-Núñez [d,f,*], Juan F. Navarro-González [c,d,e,g,h,i,*]

[a] *Centros de Diálisis Avericum, Las Palmas de Gran Canaria, Spain*
[b] *Escuela de Doctorado y Estudios de Posgrado, Universidad de La Laguna, Tenerife, Spain*
[c] *Unidad de Investigación, Hospital Universitario Nuestra Señora de Candelaria, Carretera del Rosario 145, 38010 Santa Cruz de Tenerife, Spain*
[d] *GEENDIAB (Grupo Español para el Estudio de la Nefropatía Diabética), Sociedad Española de Nefrología, Santander, Spain*
[e] *RICORS2040 (RD21/0005/0013 y RD24/0004/0022), Instituto de Salud Carlos III, Madrid, Spain*
[f] *Investigación Traslacional Cardiovascular, Navarrabiomed – IdISNA (Instituto de Investigación Sanitaria de Navarra), Avenida del Príncipe de Viana 33–35, 31008 Pamplona, Spain*
[g] *Servicio de Nefrología, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain*
[h] *Instituto de Tecnologías Biomédicas, Universidad de La Laguna, Tenerife, Spain*
[i] *Facultad de Ciencias de la Salud, Universidad Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain*

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ABSTRACT

Introduction: Hyperphosphatemia, vitamin D deficiency, and chronic inflammation contribute to cardiovascular risk in hemodialysis patients. Sucroferric oxyhydroxide (SFO) effectively lowers serum phosphate, but its effects on inflammation, vitamin D status, and Klotho (KL) expression remain unclear.
Methods: This prospective observational study included 42 hemodialysis patients switched to SFO after a two-week washout from previous phosphate binders and followed for six months. An exploratory subgroup (n = 18) underwent extended assessment of cytokines and leukocyte KL gene expression. Biochemical markers, inflammatory indices, cytokines, and gene expression were measured at baseline and six months.
Results: SFO significantly reduced serum phosphate (−27.5%) and intact parathyroid hormone (−38.3%), while increasing 25(OH)D_3 concentrations by 42.7%. Hematologic inflammatory indices improved (neutrophil-to-lymphocyte ratio −44.5%; platelet-to-lymphocyte ratio −18.9%), whereas C-reactive protein and cytokine levels remained unchanged. Leukocyte KL expression declined despite biochemical improvement. Higher 25(OH)D_3 concentrations were independently associated with lower inflammatory indices.
Conclusions: SFO improves phosphate control, vitamin D status, and hematologic inflammatory indices in hemodialysis patients, although persistent KL suppression indicates ongoing molecular dysregulation. Integrative strategies addressing phosphate, vitamin D, and Klotho pathways warrant further investigation.

Palabras clave:
Hiperfosfatemia
Quelantes de fosfato
Hemodiálisis
Klotho
Enfermedad renal crónica
Metabolismo mineral

RESUMEN

Introducción: La hiperfosfatemia, la deficiencia de vitamina D y la inflamación crónica son frecuentes en los pacientes en hemodiálisis y contribuyen al aumento del riesgo cardiovascular.
Métodos: El oxihidróxido sucroférrico (SFO), un quelante de fósforo a base de hierro, reduce eficazmente los niveles séricos de fosfato; sin embargo, sus efectos más amplios sobre la inflamación, el estado de vitamina D y la expresión de Klotho (KL) aún no están claros. Este estudio prospectivo y observacional incluyó a 42 pacientes en hemodiálisis con hiperfosfatemia persistente que fueron cambiados a SFO tras un periodo de lavado de dos semanas sin sus quelantes previos y seguidos durante seis meses. Un subgrupo exploratorio

* Corresponding author.
E-mail addresses: emarnu87@gmail.com (E. Martín-Núñez), jnavgon@gobiernodecanarias.org (J.F. Navarro-González).

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Vitamina D
Inflamación

(n = 18) se sometió a una evaluación ampliada de marcadores inflamatorios, citocinas y expresión génica de KL en leucocitos, basándose exclusivamente en la disponibilidad de muestras biológicas adecuadas (tubos PAXgene y paneles completos de citocinas), sin criterios clínicos adicionales de selección.
Resultados: El tratamiento con SFO produjo reducciones significativas en fosfato sérico (−27,5%), hormona paratiroidea intacta (−38,3%) y en el producto calcio-fósforo, acompañadas de un aumento del 42,7% en los niveles séricos de 25(OH)D_3. Los índices hematológicos inflamatorios mejoraron (relación neutrófilos/linfocitos −44,5%; relación plaquetas/linfocitos −18,9%), mientras que la proteína C reactiva y las citocinas no mostraron cambios significativos. La expresión de KL en leucocitos disminuyó a pesar de la mejoría bioquímica. Niveles más altos de 25(OH)D_3 se asociaron de forma independiente con índices inflamatorios más bajos.
Conclusiones: Estos hallazgos sugieren que el SFO mejora el metabolismo mineral, el estado de vitamina D y los marcadores hematológicos de inflamación en pacientes en hemodiálisis, aunque la persistente disminución de KL indica una disfunción molecular subyacente. Las estrategias integradoras para el manejo del trastorno mineral y óseo de la enfermedad renal crónica que combinen control del fosfato, optimización de vitamina D y modulación de Klotho requieren investigaciones adicionales.

Introduction

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is characterized by disturbances in phosphate and calcium homeostasis, secondary hyperparathyroidism, and vitamin D deficiency. These abnormalities not only impair bone metabolism but also drive vascular calcification and chronic inflammation, thereby increasing cardiovascular morbidity and mortality among patients undergoing hemodialysis (HD).[1,2]

Hyperphosphatemia, a hallmark of CKD-MBD, promotes endothelial dysfunction and immune activation through nuclear factor-κB signaling, leading to elevated pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α.[3] Concurrently, vitamin D deficiency, which is highly prevalent in end-stage kidney disease, exacerbates immune dysregulation and has been associated with cardiovascular complications, infections, and neurocognitive decline.[4,5]

Sucroferric oxyhydroxide (SFO) is a non-calcium, iron-based phosphate binder with minimal systemic absorption and well-documented efficacy in controlling serum phosphate.[6] Beyond phosphate reduction, emerging data indicate that SFO may reduce circulating calciprotein particles – pro-inflammatory complexes implicated in vascular calcification – and potentially modulate inflammation and nutritional status in dialysis populations.[7,8]

However, the interplay between phosphate control, vitamin D status, inflammation, and α-Klotho (KL) – a vasculoprotective protein frequently downregulated in CKD – remains insufficiently understood. Persistent KL suppression despite biochemical improvement may reflect unresolved cellular stress or epigenetic repression.[9] In addition, the potential interplay between phosphate control, vitamin D status, and systemic inflammation remains incompletely understood, particularly in the context of iron-based phosphate binders such as sucroferric oxyhydroxide.

The present study evaluated the effects of six months of SFO therapy on phosphate control, vitamin D status, systemic inflammation, and KL gene expression in patients undergoing maintenance HD with persistent hyperphosphatemia. We hypothesized that enhanced phosphate control would be accompanied by increased serum 25(OH)D_3 concentrations and reduced inflammatory indices, while KL expression might remain suppressed.

Materials and methods

Study design

This was a prospective, observational, single-center study conducted between January and July 2023 at Dialysis Center Avericum SL (Las Palmas de Gran Canaria, Spain). All patients had previously received phosphate binders. After a standardized 2-week washout period, patients were switched to sucroferric oxyhydroxide (SFO) due to persistent hyperphosphatemia despite prior therapy, with the goal of achieving guideline-recommended serum phosphate targets. The study followed the STROBE guidelines for reporting observational studies.[10]

The protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Hospital Universitario de Gran Canaria Dr. Negrín (Approval Code: 2021-414-1). Written informed consent was obtained from all participants.

Patients

Fifty-three adult patients undergoing maintenance HD three times per week for more than three months were screened. Inclusion criteria were: age ≥18 years; serum phosphate >5.0 mg/dL despite use of conventional phosphate binders (both calcium-based and non-calcium-based agents other than SFO); and a clinical indication to initiate SFO following binder washout. Thus, all patients had prior exposure to phosphate binders but remained hyperphosphatemic.

Exclusion criteria included active infection, malignancy, autoimmune disease, recent hospitalization (<3 months), life expectancy <6 months, or ongoing treatment with systemic corticosteroids or other immunosuppressive agents. Regarding mineral metabolism therapies, patients were excluded only if they had initiated or undergone dose adjustments of calcimimetics or pharmacologic doses of vitamin D analogues within the preceding three months, while those on stable chronic maintenance regimens were permitted to participate.

Intervention and clinical monitoring

Eligibility for switching to SFO was established at screening based on documented, persistent hyperphosphatemia under previous phosphate binders. The 2-week washout period was performed exclusively to avoid pharmacologic carryover and to establish a clean biochemical baseline, following methodological standards used in phosphate-binder studies. After the washout, SFO was initiated at 500–1500 mg/day with meals and titrated to achieve serum phosphate levels below 4.5 mg/dL, in accordance with guideline-based clinical practice and previous evidence on SFO effectiveness.[11–13] All patients received standard dietary counseling. Clinical and laboratory parameters were assessed at baseline and after six months. Treatment adherence and adverse events were recorded prospectively.

Vitamin D therapy was recorded and maintained stable throughout the study period. Treatment included nutritional vitamin D supplementation (cholecalciferol) and active vitamin D receptor activators (calcitriol and/or paricalcitol), prescribed according to routine clinical practice. No systematic initiation or dose escalation of vitamin D analogues occurred during follow-up unless clinically indicated.

Biochemical and inflammatory assessments

Fasting blood samples were collected pre-dialysis at baseline and at six months using BD SST™ serum tubes and PAXgene™ Blood RNA tubes (PreAnalytiX, Switzerland). The PAXgene system preserves RNA integrity for accurate gene expression analysis.[14]

Routine biochemical measurements included serum calcium, phosphate, intact parathyroid hormone (iPTH), magnesium, 25-hydroxyvitamin D_3 [25(OH)D_3], hemoglobin, hematocrit, transferrin saturation (TSAT), ferritin, albumin, and bicarbonate. C-reactive protein (CRP), cytokines (TNF-α, IL-6, IL-10), and fibroblast growth factor-23 (FGF-23) were measured by enzyme-linked immunosorbent assay (ELISA) using commercial kits (R&D Systems and Millipore).

Erythropoiesis-stimulating agent (ESA) therapy was recorded throughout the study, and weekly epoetin-equivalent doses were collected. ESA hyporesponsiveness was assessed clinically, based on the absence of adequate hemoglobin response despite stable or increasing ESA requirements, as well as the need for high ESA doses to maintain target hemoglobin levels.

Vitamin D deficiency was defined as 25(OH)D_3 <20 ng/mL,[15] and persistent inflammation as CRP >5 mg/L at six months.[16] Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated from absolute leukocyte counts.[17] For extended analyses (cytokines and leukocyte KL expression), an exploratory subgroup was formed based on feasibility, specifically the availability of appropriately collected PAXgene RNA tubes and complete cytokine panels. All 42 patients completed the 6-month clinical follow-up and were included in the primary endpoints. The reasons for missing extended molecular data in the remaining 24 patients (such as poor tolerance or lack of adherence) refer strictly to non-compliance with the specific blood-sampling protocol required for molecular processing, without affecting their participation or follow-up in the main clinical cohort. Reasons for missing molecular data in the remaining patients are summarized in Fig. 1.

Leukocyte gene expression

Total RNA was extracted from whole blood using the PAXgene Blood RNA Kit, following the manufacturer's instructions. Complementary DNA (cDNA) was synthesized using the High-Capacity RNA-to-cDNA Kit (Applied Biosystems). Quantitative real-time polymerase chain reaction (qRT-PCR) was performed with PerfeCTa FastMix II (QuantaBio) on a QuantStudio 5 platform.

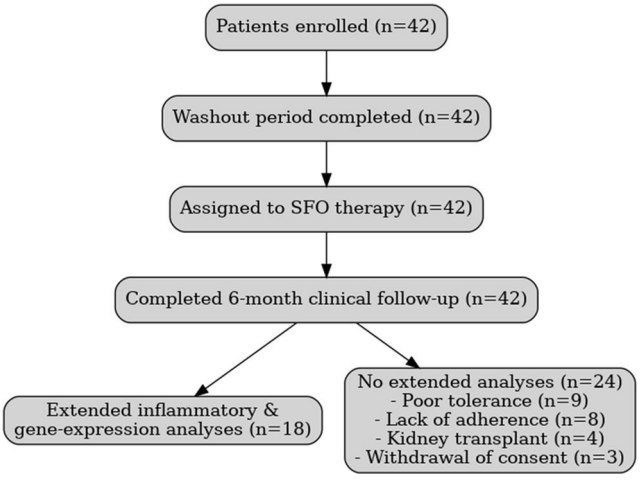

Fig. 1. Study flowchart. All 42 patients completed the 6-month clinical follow-up under sucroferric oxyhydroxide (SFO) therapy. Extended inflammatory and leukocyte gene-expression analyses were feasible in 18 patients. In the remaining 24, these assessments could not be performed due to poor tolerance (n = 9), lack of adherence (n = 8), kidney transplant (n = 4), or withdrawal of consent (n = 3).

KL, TNF-α, IL6, IL10, and GAPDH expression were quantified using TaqMan Gene Expression Assays: Hs00183100_m1 (KL), Hs00174128_m1 (TNF), Hs00174131_m1 (IL6), Hs00961622_m1 (IL10), and Hs99999905_m1 (GAPDH). Relative expression was normalized to GAPDH and calculated using the $2-\Delta\Delta Ct$ method.[18] All samples were run in triplicate, and RNA quality was verified spectrophotometrically.

Statistical analysis

Continuous variables were expressed as mean ± SD or median [IQR], as appropriate. Normality was evaluated using the Shapiro–Wilk test. Paired *t*-tests or Wilcoxon signed-rank tests were applied for pre–post comparisons. Linear regression assessed associations between changes in 25(OH)D_3 and inflammatory indices (ΔNLR, ΔPLR).

Persistent inflammation (CRP >5 mg/L) was modeled using logistic regression. Because of the limited number of events, Firth's penalized likelihood estimation was used, with exact logistic regression as sensitivity analysis. Event-per-variable ratios were calculated to minimize overfitting, and results are reported as odds ratios (OR) with 95% confidence intervals (CI).

The primary endpoint was the change in serum phosphate at six months. Secondary endpoints included changes in iPTH, 25(OH)D_3, NLR, PLR, cytokines, and KL expression.[19] No formal sample size calculation was performed given the exploratory design. A post hoc power analysis indicated $>80\%$ power to detect the observed changes in phosphate, 25(OH)D_3, NLR, and PLR. Statistical analyses were conducted using SPSS version 26.0 (IBM, Armonk, NY), and significance was defined as $p < 0.05$ (two-sided).

Results

Patient characteristics

Forty-two patients (mean age 63.4 ± 12.7 years; 56.3% [n = 24/42] men) were enrolled (Fig. 1). The median dialysis vintage was 47 [28-82] months. Diabetes mellitus was present in 64.3% (n = 27/42) of participants, and 100% (n = 42/42) had hypertension (Table 1).

Regarding CKD etiology, the relatively high proportion of glomerular disease and autosomal dominant polycystic kidney disease likely reflects the referral pattern and case-mix of our center, as well as the specific clinical profile of patients selected for phosphate binder switch due to persistent hyperphosphatemia. Therefore, this etiologic distribution may introduce selection bias and should be interpreted with caution when extrapolating our findings to broader HD populations.

Changes in mineral metabolism

After six months of treatment with SFO, serum phosphate significantly decreased from 6.12 ± 0.81 to 4.44 ± 0.67 mg/dL (−27.5%, $p < 0.001$). Intact parathyroid hormone (iPTH) declined from 478 [325–639] to 295 [208–431] pg/mL (−38.3%, $p < 0.001$). The calcium–phosphorus product also improved markedly. Serum calcium levels remained stable throughout the study (9.1 ± 0.4 vs. 9.2 ± 0.3 mg/dL; $p = 0.44$) (Fig. 2).

Serum 25-hydroxyvitamin D_3 [25(OH)D_3] concentrations increased significantly, from 17.6 ± 7.8 to 25.1 ± 8.4 ng/mL (+42.7%, $p < 0.001$). Vitamin D deficiency (<20 ng/mL) decreased from 69% to 31% of participants. Magnesium, ferritin, and transferrin saturation remained within reference ranges.[11–13]*Inflammatory markers*

Hematologic inflammatory indices improved following SFO therapy. The NLR decreased from 4.4 [3.1–6.9] to 2.5 [1.8–3.8] (−44.5%, $p < 0.001$), and the PLR declined from 167 [132–216] to

Table 1
Baseline characteristics of the overall study population ($n = 42$).

Variable	Value
Age (years)	63.4 ± 12.7
Male (%)	56.3
Comorbidities (%)	Diabetes 64.3
	Hypertension 100
	Dyslipidemia 95.2
	Ischemic heart disease 21.4
	Chronic heart failure 52.4
	Peripheral arterial disease 54.8
CKD etiology (%)	Glomerulonephritis 38.1
	Diabetic nephropathy 19.0
	CKD of uncertain etiology 42.9
	Autosomal dominant polycystic kidney disease 26.2
Time on HD (months)	65.1 ± 48.7
Dialysis modality (%)	Standard HD 78.6; online HDF 21.4
Biochemistry	Urea – 142 ± 39.7 mg/dL
	Creatinine – 7.91 ± 2.27 mg/dL
	Na – 137 ± 2.7 mEq/L
	K – 5.31 ± 0.82 mEq/L
	Ca – 8.94 ± 0.53 mg/dL
	Pi – 6.16 ± 0.94 mg/dL
	Ca × P – 55.1 ± 8.5 mg^2/dL^2
	iPTH – 614 ± 498 pg/mL
	25(OH)VitD – 17.4 ± 7.7 ng/mL
	Albumin – 3.64 ± 0.27 g/dL
	CRP – 6.41 ± 3.52 mg/L
Medication use (%)	Statins 88.1; iron 92.9; vitamin D analogues 59.5; calcimimetics 38.1

Percentages for chronic kidney disease (CKD) etiologies may sum to more than 100% because contributing etiologies were not mutually exclusive in patients presenting multiple baseline renal pathologies (e.g., concurrent diabetic and hypertensive nephropathy).
Values are expressed as mean ± SD or percentage, as appropriate. *Abbreviations*: IHD, ischemic heart disease; CHF, chronic heart failure; PAD, peripheral arterial disease; CKD, chronic kidney disease; GN, glomerulonephritis; DN, diabetic nephropathy; CKDu, chronic kidney disease of uncertain etiology; ADPKD, autosomal dominant polycystic kidney disease; HD, hemodialysis; HDF, hemodiafiltration; Na, sodium; K, potassium; Ca, calcium; Pi, phosphate; Ca × P, calcium–phosphorus product; iPTH, intact parathyroid hormone; CRP, C-reactive protein.

136 [118–188] (−18.9%, $p = 0.02$). In contrast, C-reactive protein (CRP) levels and cytokines (IL-6, TNF-α, IL-10) did not show significant changes ($p > 0.05$ for all) (Table 2).

Persistent inflammation, defined as CRP >5 mg/L, was observed in 33% of patients at baseline and 28% after six months ($p = 0.47$).[16,17] Fibroblast growth factor-23 (FGF-23) levels remained stable.

ESA requirements remained stable over the 6-month follow-up. No patient fulfilled clinical criteria for ESA hyporesponsiveness, and no sustained increase in ESA requirements was observed during the study period.

Leukocyte KL expression

Despite improvements in biochemical and hematologic parameters, leukocyte Klotho (KL) gene expression significantly decreased after six months (median fold change −0.39 [IQR −0.65 to −0.14]; $p = 0.01$). This reduction was consistent across subgroups stratified by baseline phosphate or vitamin D status.

Correlations and regression analyses

In exploratory logistic regression models, higher baseline 25(OH) D3 concentrations demonstrated a significant protective effect against persistent inflammation in unadjusted assessments (OR [95% CI]). However, due to the limited sample size and low event-per-variable ratio, this predictive value did not reach consistent statistical significance across all fully adjusted multivariate models. These findings emphasize the exploratory nature of our regression data. No associations were observed between serum phosphate or iPTH changes and inflammatory indices (Fig. 3). Logistic regression identified no predictors of persistent inflammation at six months.

Regarding the primary endpoint, 86% of participants showed a reduction in serum phosphate concentration. Secondary endpoints (iPTH, vitamin D, and hematologic indices) also showed significant

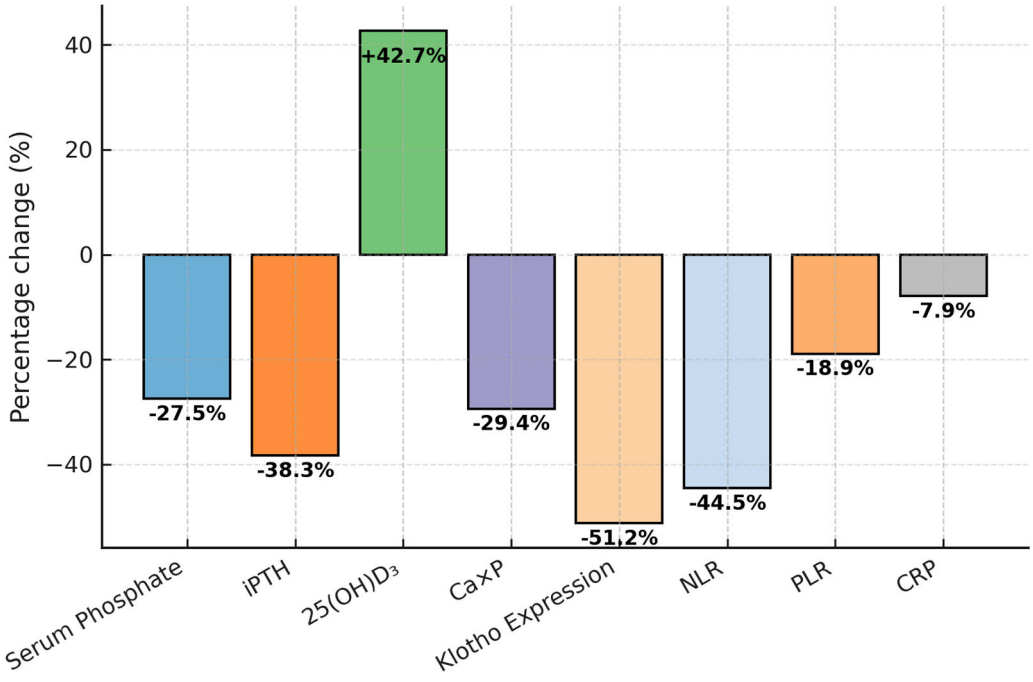

Fig. 2. Percentage changes after 6 months of SFO therapy. Data are presented as mean percentage change relative to baseline values. Mineral metabolism: phosphate, iPTH, and Ca × P decreased; $25(OH)D_3$ increased. Inflammation: NLR and PLR decreased, whereas CRP showed a modest, non-significant decline. Gene expression: KL expression declined markedly. iPTH, intact parathyroid hormone; Ca × P, calcium–phosphorus product; 25(OH)D3, 25-hydroxyvitamin D3; KL, Klotho; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; SFO, sucroferric oxyhydroxide.

Table 2
Evolution of mineral metabolism, biochemical, and inflammatory parameters ($n = 18$).

Parameter	Baseline	6 months	*p*-Value	Test
Mineral metabolism				
P (mg/dL)	6.18 ± 1.07	4.48 ± 0.61	<0.001	(3)
iPTH (pg/mL)	798.3 ± 672.4	492.6 ± 468.9	<0.001	(2)
25(OH)VitD (ng/mL)	16.2 ± 8.5	23.2 ± 8.1	<0.001	(1)
FGF-23 (pg/mL)	2234.8 ± 2214.1	2056.9 ± 2508.0	0.382	(2)
KL PBMCs (a.u.)	1.70 ± 1.48	0.83 ± 0.43	0.001	(2)
Ca (mg/dL)	9.02 ± 0.56	8.81 ± 0.59	0.237	(1)
Ca × P (mg^2/dL^2)	55.8 ± 10.3	39.4 ± 5.0	<0.001	(2)
Mg (mg/dL)	2.22 ± 0.50	2.27 ± 0.33	0.227	(3)
Biochemical parameters				
Hemoglobin (g/dL)	11.0 ± 1.2	11.8 ± 1.1	0.084	(1)
Hematocrit (%)	32.8 ± 3.5	35.8 ± 3.9	0.016	(1)
HCO_3 (mEq/L)	21.0 ± 2.3	21.3 ± 2.4	0.652	(1)
Iron (μg/dL)	45.3 ± 11.3	51.2 ± 12.1	0.105	(1)
Ferritin (ng/mL)	385.2 ± 284.5	391.1 ± 159.5	0.865	(3)
Transferrin (mg/dL)	193.6 ± 28.2	183.2 ± 38.1	0.241	(1)
TSAT (%)	0.18 ± 0.04	0.22 ± 0.03	<0.001	(1)
Inflammation				
Uric acid (mg/dL)	5.6 ± 1.5	5.3 ± 1.0	0.019	(1)
NLR (a.u.)	3.41 ± 1.17	1.89 ± 0.54	<0.001	(1)
PLR (a.u.)	139.5 ± 47.2	113.0 ± 25.7	0.014	(1)
CRP (mg/L)	6.41 ± 3.52	5.90 ± 2.34	0.087	(1)
TNF PBMCs (a.u.)	0.68 ± 0.55	0.38 ± 0.22	0.150	(2)
IL-6 PBMCs (a.u.)	1.39 ± 0.74	1.63 ± 1.56	0.774	(2)
IL-10 PBMCs (a.u.)	1.76 ± 1.30	1.80 ± 1.21	0.661	(2)
TNF-α (pg/mL)	2.12 ± 0.73	1.86 ± 0.72	0.204	(2)
IL-6 (pg/mL)	5.90 ± 2.21	8.95 ± 6.50	0.327	(2)
IL-10 (pg/mL)	8.87 ± 11.7	15.8 ± 21.7	0.924	(2)

Note: Data are presented as mean ± SD. Statistical tests: (1) paired Student's *t*-test; (2) paired *t*-test on log-transformed data; (3) Wilcoxon signed-rank test. *Abbreviations*: a.u., arbitrary units; Ca × P, calcium–phosphorus product; CRP, C-reactive protein; FGF-23, fibroblast growth factor-23; HCO_3, bicarbonate; IL, interleukin; iPTH, intact parathyroid hormone; KL, Klotho; Mg, magnesium; NLR, neutrophil-to-lymphocyte ratio; PBMCs, peripheral blood mononuclear cells; P, phosphate; PLR, platelet-to-lymphocyte ratio; TSAT, transferrin saturation; TNF, tumor necrosis factor; 25(OH)VitD, 25-hydroxyvitamin D_3.

improvements, while cytokine and KL results indicated complex regulation beyond mineral metabolism.

Discussion

This study demonstrates that treatment with SFO for six months effectively improves phosphate control and vitamin D status in patients undergoing maintenance HD with persistent hyperphosphatemia, while concurrently reducing hematologic markers of inflammation. These findings extend previous evidence on SFO efficacy in mineral metabolism and suggest potential ancillary benefits related to systemic inflammation and vitamin D repletion.[6–8]

Mineral metabolism and vitamin D status

The observed reduction in serum phosphate (−27.5%) and intact parathyroid hormone (−38.3%) confirms that SFO is an effective non-calcium phosphate binder in routine clinical use, consistent with results from randomized and real-world studies.[11–13,19–21] The parallel 42.7% increase in serum 25(OH)D_3 represents an important and novel finding. Improvement in vitamin D status may reflect decreased intestinal phosphate burden and improved nutritional intake, as previously reported in patients treated with iron-based binders.[22–24] In contrast to calcium-based agents, SFO minimizes the risk of hypercalcemia, which may preserve endogenous vitamin D metabolism.[24,25]

Beyond improved phosphate control, several complementary mechanisms may contribute to the observed increase in serum 25(OH)D_3 following SFO therapy. Sustained reduction of intestinal phosphate burden may alleviate FGF-23-mediated suppression of vitamin D metabolism, thereby favoring higher circulating 25(OH)D_3 concentrations. In addition, iron-based phosphate binders such as SFO have been associated with improved gastrointestinal tolerance and nutritional status, which could indirectly enhance dietary vitamin D intake and absorption. Finally, avoidance of calcium overload may preserve endogenous vitamin D hydroxylation pathways. Importantly, these mechanisms remain speculative, and this observational study was not designed to establish mechanistic causality. These interpretations should be considered hypothesis-generating and require confirmation in controlled mechanistic studies.

Inflammation and hematologic indices

Although traditional inflammatory biomarkers such as C-reactive protein and cytokines remained unchanged, both the NLR and PLR improved significantly. These hematologic indices have been validated as sensitive predictors of inflammation and cardiovascular risk in chronic kidney disease.[17,26] This apparent discrepancy is biologically plausible. Hematologic indices such as NLR and PLR can reflect early shifts in leukocyte dynamics and innate immune activation, whereas soluble inflammatory markers like CRP and cytokines show substantial intra-individual variability in hemodialysis and limited sensitivity to detect short-term changes in low-grade inflammation. In our cohort, NLR and PLR decreased markedly while IL-6 and TNF-α did not change significantly, a pattern consistent with prior reports questioning the sensitivity of CRP and cytokines and supporting the prognostic usefulness of hematologic indices in dialysis populations. The small molecular subgroup ($n = 18$) further limits the statistical power to detect changes in cytokine concentrations. The strong inverse correlation between 25(OH)D_3 and both NLR and PLR suggests that improved vitamin D status may exert anti-inflammatory effects through modulation of leukocyte activity and cytokine signaling, supporting prior translational studies linking vitamin D sufficiency to reduced systemic inflammation.[27–29] However, these findings should not be interpreted as being exclusively driven by phosphate control, as multiple factors – including vitamin D status, iron-related effects, and overall clinical context – may contribute to the observed changes in hematologic inflammatory indices.

Importantly, ESA therapy remained stable during follow-up, and no signal of ESA hyporesponsiveness was observed. This reduces the likelihood that changes in hematologic inflammatory indices were driven by variations in anemia management rather than underlying biological effects.

Klotho expression and residual molecular inflammation

Despite biochemical and hematologic improvement, leukocyte Klotho (KL) gene expression decreased after SFO therapy. This finding is consistent with previous reports describing persistent suppression of KL in dialysis patients even under optimized mineral metabolism.[9,24,30] Downregulation of KL may reflect epigenetic silencing, oxidative stress, or chronic exposure to uremic toxins that are not corrected by phosphate control alone.[31,32] The disconnect between improved clinical parameters and suppressed KL expression underscores that CKD-associated inflammation has a multifactorial origin extending beyond phosphate retention.[33,34]

Integrative interpretation

Taken together, these data suggest that SFO provides biochemical control and improvement in surrogate inflammatory indices, yet fails to normalize KL transcriptional activity. This paradox highlights the

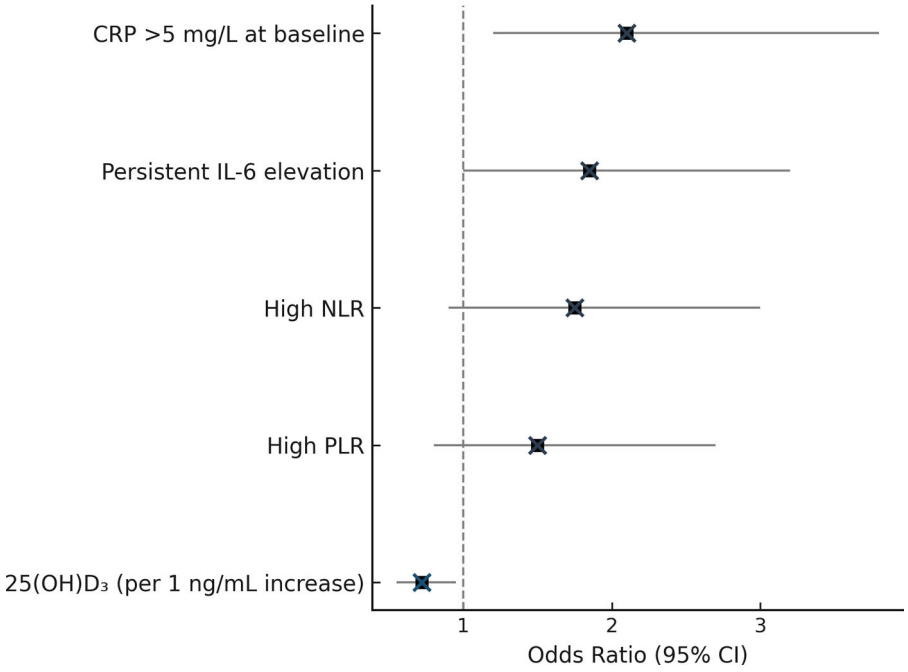

Fig. 3. Exploratory analysis of predictors of persistent inflammation at 6 months. Odds ratios (OR, 95% CI) for baseline and follow-up parameters. Only serum 25(OH)D_3 showed a protective effect, with each 1 ng/mL increase associated with lower odds of persistent inflammation. The red dashed line represents the null value (OR = 1). 25 (OH)D3, 25-hydroxyvitamin D3; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; IL-6, interleukin-6; CI, confidence interval.

complexity of CKD-mineral and bone disorder (CKD-MBD), where mineral dysregulation, oxidative stress, and vitamin D metabolism interact at molecular and cellular levels. Future studies integrating transcriptomic and metabolomic approaches could elucidate whether iron-mediated phosphate binding directly affects pathways governing KL expression and vitamin D bioactivation.[35,36]

Study strengths and limitations

The present work provides novel insight into the interrelationship between phosphate control, vitamin D status, and inflammation in a real-world dialysis cohort. Its strengths include the prospective design, homogeneous patient population, and molecular analysis of leukocyte KL expression. Limitations include the single-center design, small sample size, and absence of a control group, which may restrict external validity. In addition, inflammatory findings are based primarily on hematologic indices (NLR and PLR), which, although clinically relevant, represent indirect markers of inflammation and may be influenced by multiple factors. Nevertheless, post hoc power analysis supports adequate statistical sensitivity for the primary outcomes. The observational design also precludes causal inference, and additional mechanistic studies are warranted.

Conclusions

In maintenance hemodialysis patients with persistent hyperphosphatemia, sucroferric oxyhydroxide therapy was associated with effective phosphate reduction, improved vitamin D status, and favorable changes in hematologic inflammatory indices. These changes in inflammatory indices should be interpreted cautiously, as they may reflect multifactorial influences beyond phosphate control alone. However, persistent suppression of leukocyte Klotho (KL) expression despite biochemical improvement highlights residual molecular dysregulation and the limits of conventional therapy. These findings suggest that addressing mineral imbalance alone may be insufficient to restore vascular-protective and immunometabolic homeostasis in advanced CKD. Integrative approaches – including phosphate control, vitamin D optimization, and Klotho-targeted interventions – warrant further investigation. Larger, controlled studies are needed to validate these exploratory associations and guide precision therapies in CKD-MBD.

Authors' contributions

Fernando Henríquez-Palop: conceptualization, methodology, data analysis, writing. Carmen Mora-González: data analysis and review. Ernesto Martín-Núñez: data analysis, writing, review, and editing. Juan F. Navarro-González: conceptualization, supervision, writing, review, and editing.

Ethical approval

The study was approved by the Ethics Committee of the Dr. Negrín University Hospital of Gran Canaria (Approval Code: 2021-414-1) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability

The data generated and analyzed during the study are available upon reasonable request to the corresponding author.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.nefro.2026.501573.

References

1. Nitta K, Hanafusa N, Akiyama K, Kawaguchi Y, Tsuchiya K. Chronic kidney disease-mineral and bone disorder (CKD-MBD), from bench to bedside. Kidney Dial. 2023;3:46–55, http://doi.org/10.3390/kidneydial3010004
2. Ketteler M, Evenepoel P, Holden RM, Isakova T, Jørgensen HS, Komaba H, et al. Chronic kidney disease-mineral and bone disorder: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2025;107:405–23, http://doi.org/10.1016/j.kint.2024.11.013
3. Salera D, Merkel N, Bellasi A, de Borst MH. Pathophysiology of chronic kidney disease-mineral bone disorder (CKD-MBD): from adaptive to maladaptive mineral homeostasis. Clin Kidney J. 2025;18 Suppl 1:i3–14, http://doi.org/10.1093/ckj/sfae431
4. Ishtawi D, Alrabadi N, Khatib I. Prevalence of vitamin D deficiency in end-stage kidney disease hemodialysis patients: a real-world cohort. Sci Rep. 2023;13:10214, http://doi.org/10.1038/s41598-023-37215-9
5. Chen IW, Wang WT, Lai YC, Chang YJ, Lin YT, Hung KC. Association between vitamin D deficiency and major depression in patients with chronic kidney disease: a cohort study. Front Nutr. 2025;12(1540633), http://doi.org/10.3389/fnut.2025.1540633
6. Floege J, Covic AC, Ketteler M, Mann JF, Rastogi A, Spinowitz B, et al. Long-term effects of the iron-based phosphate binder, sucroferric oxyhydroxide, in dialysis patients. Nephrol Dial Transplant. 2015;30:1037–46, http://doi.org/10.1093/ndt/gfv006
7. Thiem U, Hewitson TD, Toussaint ND, Holt SG, Haller MC, Pasch A, et al. Effect of the phosphate binder sucroferric oxyhydroxide in dialysis patients on endogenous calciprotein particles, inflammation, and vascular cells. Nephrol Dial Transplant. 2023;38:1282–96, http://doi.org/10.1093/ndt/gfac271
8. Kalantar-Zadeh K, Ficociello LH, Zhou M. Management of serum phosphorus over a 1-year follow-up in patients on peritoneal dialysis prescribed sucroferric oxyhydroxide as part of routine care: a retrospective analysis. BMC Nephrol. 2024;25, http://doi.org/10.1186/s12882-024-03633-8
9. Donate-Correa J, Martín-Núñez E, Mora-Fernández C, Navarro-González JF. Klotho expression inversely correlates with inflammation and vascular damage in chronic kidney disease. Antioxidants (Basel). 2023;12, http://doi.org/10.3390/antiox12020325
10. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS Med. 2007;4:e296, http://doi.org/10.1371/journal.pmed.0040296
11. Sprague SM, Ketteler M, Covic AC, Floege J, Rakov V, Walpen S, et al. Long-term efficacy and safety of sucroferric oxyhydroxide in African American dialysis patients. Hemodial Int. 2018;22:480–91, http://doi.org/10.1111/hdi.12663
12. Vervloet MG, Boletis IN, de Francisco ALM, Kalra PA, Ketteler M, Messa P, et al. Real-world safety and effectiveness of sucroferric oxyhydroxide for treatment of hyperphosphataemia in dialysis patients: a prospective observational study. Clin Kidney J. 2021;14:1770–9, http://doi.org/10.1093/ckj/sfaa211
13. Wyatt CM, Leonard MB. Current Clinical Trials in CKD-MBD. Clin J Am Soc Nephrol. 2022;17:1652–61, http://doi.org/10.2215/CJN.11210822
14. Anckaert J, Avila Cobos F, Decock A, Decruyenaere P, Deleu J, De Preter K. Blood collection tube and RNA purification method recommendations for extracellular RNA transcriptome profiling. Nat Commun. 2025;16:4513, http://doi.org/10.1038/s41467-025-58607-7
15. Holick MF, Binkley NC, Bischoff-Ferrari HA. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–30, http://doi.org/10.1210/jc.2011-0385
16. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207, http://doi.org/10.1056/NEJMoa0807646
17. Turkmen K, Guney I, Yerlikaya FH, Tonbul HZ. The relationship between neutrophil-to-lymphocyte ratio and inflammation in end-stage renal disease patients. Ren Fail. 2012;34:155–9, http://doi.org/10.3109/0886022X.2011.641514
18. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the $2-\Delta\Delta CT$ method. Methods. 2001;25:402–8, http://doi.org/10.1006/meth.2001.1262
19. Fuller DS, Dluzniewski PJ, Cooper K, Bradbury BD, Robinson BM, Tentori F. Combinations of mineral and bone disorder markers and risk of death and hospitalizations in the international Dialysis Outcomes and Practice Patterns Study. Clin Kidney J. 2019;13:1056–62, http://doi.org/10.1093/ckj/sfz112
20. United States Renal Data System. 2023 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2023.
21. Zhao WM, Tao SM, Liu GL. Neutrophil-to-lymphocyte ratio in relation to the risk of all-cause mortality and cardiovascular events in patients with chronic kidney disease: a systematic review and meta-analysis. Renal Failure. 2020;42:1059–66, http://doi.org/10.1080/0886022X.2020.1832521
22. Pradeep U, Chiwhane A, Acharya S, Daiya V, Kasat PR, Sachani P, et al. A comprehensive review of advanced biomarkers for chronic kidney disease in older adults: current insights and future directions. Cureus. 2024;16:e70413.
23. Granata S, Masola V, Zoratti E, Scupoli MT, Baruzzi A, Messa M, et al. NLRP3 inflammasome activation in dialyzed chronic kidney disease patients. PLoS ONE. 2015;10:e0122272, http://doi.org/10.1371/journal.pone.0122272
24. Donate-Correa J, Martín-Carro B, Cannata-Andía JB, Mora-Fernández C, Navarro-González JF. Klotho, Oxidative Stress, and Mitochondrial Damage in Kidney Disease. Antioxidants (Basel). 2023;12, http://doi.org/10.3390/antiox12020239
25. Disthabanchong S. Phosphate and cardiovascular disease beyond chronic kidney disease and vascular calcification. Int J Nephrol. 2018;2018(4967406), http://doi.org/10.1155/2018/4967406
26. Ashman N, Brown C, Dattani I. A randomized controlled trial of different serum phosphate ranges in subjects on hemodialysis (SPIRIT). Nephrol Dial Transplant. 2019;34:1152–62, http://doi.org/10.1093/ndt/gfy127
27. Sun CY, Chang SC, Wu MS. Suppression of Klotho expression by protein-bound uremic toxins is associated with increased DNA methyltransferase expression and DNA hypermethylation. Kidney Int. 2012;81:640–50, http://doi.org/10.1038/ki.2011.445
28. Ribeiro M, Carvalho KSC, Moraes MR. Hemodialysis intensifies NLRP3 inflammasome expression and oxidative stress in patients with chronic kidney disease. Int J Mol Sci. 2025;26, http://doi.org/10.3390/ijms26146933
29. Wang H, Yuan T, Wu W, Ou S. Vitamin D and chronic kidney disease: mechanisms, clinical implications, and future perspectives. Front Med (Lausanne). 2025;12(1643415), http://doi.org/10.3389/fmed.2025.1643415
30. Wang Y, Zhou H, Li J. Klotho suppresses NF-□B activation and NLRP3 inflammasome: implications for CKD inflammation. Front Immunol. 2024;15(1394872), http://doi.org/10.3389/fimmu.2024.1394872
31. Waitupu A, Pratiwi L, Sutanto H, Santoso D, Hertanto DM. Molecular pathophysiology of chronic kidney disease–mineral and bone disorder: focus on the fibroblast growth factor 23-Klotho axis and bone turnover dynamics. Exp Physiol. 2025;110:e70001, http://doi.org/10.1113/EP092401
32. Razzaque MS, Mohammadi M. Can targeting the FGF23-αKlotho signaling system delay phosphate-driven organ damage? Expert Opinion on Therapeutic Targets. 2025;29:93–100, http://doi.org/10.1080/14728222.2025.2482552
33. Scialla JJ, Kendrick J, Uribarri J, Kovesdy CP, Gutiérrez OM, Jimenez EY. State-of-the-art management of hyperphosphatemia in patients with CKD: An NKF-KDOQI controversies perspective. Am J Kidney Dis. 2021;77:132–41, http://doi.org/10.1053/j.ajkd.2020.05.025
34. Poursistany H, Tabibi Azar S, Tabibi Azar M, Raeisi S. The current and emerging Klotho-enhancement strategies. Biochem Biophys Res Commun. 2024;693:149357, http://doi.org/10.1016/j.bbrc.2023.149357
35. Novillo-Sarmiento C, García-Sáez RM, Rivas-Domínguez A, Torralba-Duque A, Rodelo-Haad C, Rodríguez-Ortiz ME, et al. Phosphate and Inflammation in Health and Kidney Disease. Int J Mol Sci. 2025;27:408, http://doi.org/10.3390/ijms27010408
36. Alakwaa FM, Das V, Majumdar A, Nair V, Fermin D, Dey AB, et al. Leveraging complementary multi-omics data integration methods for mechanistic insights in kidney diseases. JCI Insight. 2025;10:e186070, http://doi.org/10.1172/jci.insight.186070