

A Pilot Trial on the Effect of Levothyroxine on Proteinuria in Patients With Advanced CKD



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Introduction: Thyroid hormones can directly affect kidney function; elevated levels of thyroid-stimulating hormone (TSH) and chronic kidney disease (CKD) are associated with proteinuria, decreased estimated glomerular filtration rate (eGFR), and progression to end-stage renal disease. Our hypothesis is that in patients with CKD and TSH at levels considered to be in the low subclinical hypothyroidism (SCH) range, lowering TSH with levothyroxine (LVX) improves the clinical parameters of renal function.

Methods: This was a double-blind, randomized, pilot clinical trial in patients with proteinuric CKD (eGFR <60 ml/min per 1.73 m² and proteinuria >150 mg/d) performed at the Hospital Civil de Guadalajara, with the intention of lowering TSH (levels of 1.25–2.5 µIU/l) in patients with TSH (levels of 2.6–9.9 µIU/ml with FT4 in the range of 0.7–1.8 ng/dl). Patients were randomized 1:1 to receive LVX or placebo for 12 weeks. The primary objective was to evaluate absolute levels of proteinuria at the beginning compared to the end of the study and, as a secondary objective, the changes in serum creatinine (sCr), eGFR, cholesterol, triglycerides, low-density lipoprotein (LDL), and blood pressure, and to assess the tolerability and safety of LVX.

Results: Between March and November 2018, a total of 163 patients were assessed for eligibility; 119 patients did not meet the inclusion criteria or were excluded, and 32 patients were randomized. The demographic and clinical characteristics of the 2 study groups were essentially not different. Subjects were 66.87 (SD 12.19) years of age, 62.5% were female, 75% were diabetes mellitus, eGFR was 23.55 (±12.91) ml/min per 1.73 m², TSH was 5.37 ± 2.13 µIU/ml, proteinuria in 24-hour urine collection was 1.52 ± 1.12, and all of them were taking angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). Proteinuria at 12 weeks in the LVX group was 0.89 SD ± 1.28 g/d, and in the placebo group it was 1.35 SD ± 0.85 g/d; when compared to placebo, LVX showed a significant decrease in proteinuria of 1.1 g/d (*P* = 0.0011). The eGFR in the LVX group showed an improvement of 4 ml/min/1.73 m² (*P* = 0.049); in the placebo group, there was a decrease of 1.98 ml/min per 1.73 m². The sCr, cholesterol, triglycerides, low-density lipoprotein, systolic blood pressure, and diastolic blood pressure were not different between groups. Adverse events were reported in the LVX group in 7.14% of patients and in 11.11% of patients in the placebo group; none left the study because of adverse effects, and there were no serious adverse events.

Conclusion: This single-center, randomized, double-blind, placebo-controlled pilot clinical trial in patients with advanced proteinuric CKD who already used ACEIs or ARBs demonstrated that administering LVX to obtain a TSH range close to 2.5 µIU/ml decreased proteinuria and improved eGFR. Future research is needed to confirm our results and to determine whether our findings generalize to patient groups not explicitly enrolled in this small pilot trial.

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KEYWORDS: chronic kidney disease; levothyroxine; TSH

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Chronic noncommunicable diseases such as obesity, diabetes mellitus, hypertension, and chronic kidney disease (CKD) have become a major public health problem in the Mexican population.^{1,2} Between 1990

and 2013, the CKD burden rapidly climbed, with age-standardized years of life lost (YLL) and disability-adjusted life-year (DALY) rates increasing more than 130%, the second highest DALY due to CKD in the world.³ The incidence of end-stage renal disease has increased dramatically in parallel with these risk factors.⁴

Thyroid hormones can directly affect kidney function, and impaired renal function can also contribute to thyroid disorders.^{5–9} The prevalence of primary overt, subclinical hypothyroidism (SCH) and low T3 syndrome increases with the progression of CKD.^{10,11}

The prevalence of SCH in patients with an estimated glomerular filtration rate (eGFR) >60 ml/min per 1.73 m² is 7% and is up to 17.9% in those with an eGFR <60 ml/min per 1.73 m².¹¹ Thyroid hormone affects the kidney by multiple mechanisms; local hemodynamic changes, decreased renal blood flow, decreased cardiac output, circulating volume, and decreased atrial natriuretic factor contribute to a decrease in renal perfusion with a concomitant reduction in eGFR,^{5–7,11–13} affecting the renin–angiotensin–aldosterone system, glomerular basement membrane, and renal tubular function, and leading to the development of proteinuria through direct effects on megalin and podocytes.^{8,9}

The frequency of proteinuria in patients with normal thyroid function (euthyroid), SCH, and hypothyroidism is 1.29%, 2.2%, and 2.97%, respectively.¹⁴ In addition, it has been reported that the progression to end-stage renal disease is more accelerated in patients with SCH than in euthyroid patients,^{14,15–18} and there is evidence that high (>3 µIU/ml) and low (<0.5 µIU/ml) thyroid-stimulating hormone (TSH) are associated with higher mortality rates in patients with CKD.¹⁹ There is also an association of mortality in patients with CKD and thyroid functional disease due to increased cardiovascular risk,²⁰ particularly in patients on hemodialysis,^{21–23} as well as peritoneal dialysis²⁴ and thyroid function disease.

The American Thyroid Guidelines, the American Association of Endocrinology,²⁵ and European Guidelines and Clinical Practice Guidelines²⁶ recommend beginning LVX doses of 0.25 µg and not going above 0.50 µg in patients with high cardiovascular risk,^{27,28} as patients with CKD have been considered.²⁹

Levothyroxine is usually well tolerated in the general population at standard doses (1.6–18.8 µg/kg). In patients with SCH, overdose symptoms were reported in 10% to 21% of cases, and a Cochrane meta-analysis of thyroid hormone replacement for SCH found no significant adverse events.³⁰

However, many patients with CKD will experience renal progression, despite antiproteinuric treatment.^{31,32} These observations led to the examination of alternative pathways to delay CKD, with disappointing results so far. The most commonly used antiproteinuric^{33,34} drugs are angiotensin-converting enzyme inhibitors,³⁵ angiotensin receptor blockers,³⁶ aldosterone antagonists,^{37–40} and, although they are less effective, statins,^{41,42} allopurinol,⁴³ and vitamin D activators.^{43–48}

Treatment of SCH with LVX in the general population improves the lipid profile and cardiac function,^{49–51} and patients with CKD show improvement in eGFR and serum creatinine (sCr),^{14,51} but there are no clinical trials in this field in patients with CKD.

Our hypothesis is that in patients with CKD and TSH at levels considered to be in the SCH range, the normalization of TSH with LVX improves the clinical parameters of renal function.

MATERIALS AND METHODS

We conducted a pilot randomized, single-center, double-blind, placebo-controlled, parallel group, dose-adjusting trial of levothyroxine (LVX) 25 µg administered orally once daily to patients with proteinuric CKD conducted at the Hospital Civil de Guadalajara from March 2018 to 31 January 2019. The study objectives were to evaluate the efficacy and safety of normalizing TSH levels with LVX and to explore the clinical effect of LVX compared with placebo.

The measurement of TSH and FT4 was carried out with the UniCel DxI 800 (Beckman Coulter Inc., Indianapolis, IN) access Immunoassay system by chemiluminescence, with the serum FT4 (assay type 2-step competitive) reportable range of 0.25 to 6 ng/dl (3.2–77.2 pmol/l), analytical sensitivity 0.25 ng/dl (3.2 pmol/l), and serum TSH (assay type 1-step sandwich) reportable range of 0.03 to 100 µIU/ml, which incorporates functionality for the lower limit of detection, analytical sensitivity 0.01 µIU/ml, and 0.03 uIU/ml functional, and all samples were analyzed in a single laboratory.

Patients with CKD (eGFR <60 ml/min per 1.73 m² by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) were eligible if they were >18 years of age or if they had proteinuria >150 mg/24 h. With TSH levels between 2.5 and 10.0 µIU/ml, we chose TSH >2.5 µIU/ml, as there is evidence that there was an association of a decrease in eGFR^{10,52} with proteinuria,¹⁰ and TSH <10.0 µIU/ml excludes clinical hypothyroidism. All patients treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II

receptor blockers (ARBs) and without renal replacement therapy who attended the Renal Health Clinic were considered for participation in this pilot clinical trial.

We excluded patients with the following: primary hypothyroidism or preexisting thyroid disease; previous ischemic heart disease within a period of <6 months; arrhythmia; pregnancy; use of drugs that interact with the synthesis of thyroid hormones (Supplementary Table S1); those who did not provide informed consent; those with a serum TSH level <2.5 $\mu\text{IU/ml}$ or >10 $\mu\text{IU/ml}$; those with a free serum T4 value between 0.6 and 1.8 ng/dl; those with positive anti-thyroid antibodies; and patients weighing <50 kg or >90 kg, because within this weight, all patients will maintain a dosage of 0.3–0.5 $\mu\text{g/kg}$ per day, so it will be easy to prescribe the LVX dose with a narrow error window.

Approval was obtained from the participating site's Research and Ethics Committee (Hospital CG 034/18 March 2018). Patients provided written informed consent before enrollment in accordance with local and national laws. Conduct and reporting are consistent with the 2010 Consolidated Standards of Reporting Trials (CONSORT) extension for pilot trials.⁵³ The trial was registered in the Clinical Trials Registry (NCT03898622).

Measures of renal function included the eGFR calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.⁵⁴ Proteinuria was measured by means of 24-hour urine collection, expressed in grams per day, at the beginning and end of the study. Serum creatinine, serum electrolytes, hemoglobin, albumin, cholesterol, TSH, FT4, and triglycerides were measured at the beginning of the study and every 4 weeks for 4 months.

Using a Web-based randomization system, we randomly assigned participants in a 1:1 ratio. Standard care was defined pragmatically; in both the study intervention and the standard care group, the nephrologist determined all aspects of clinical care, based on standard practice and individual patient needs, independent of the study intervention.

The study consisted of 3 phases. The first phase, with a duration of 8 to 12 weeks, consisted of enrolling patients and collecting demographic and clinical baseline measurements (proteinuria, lipid profile, serum electrolytes, arterial pressure, weight, TSH level, hemoglobin, and serum albumin). The second phase consisted of both groups being treated according to the allocation arm, and the third phase consisted of comparing the variables studied and the data analysis. The dose of LVX has previously been shown to be safe and efficient in adult patients with CKD.^{14,51}

Table 1. Dose adjustment of levothyroxine

TSH range	Dose adjustment
TSH < 0.5 $\mu\text{IU/ml}$	Suspend the pill
TSH (0.5–1 $\mu\text{IU/ml}$)	Suspend the pill if it is at minimum dose
TSH (1.2–2.4 $\mu\text{IU/ml}$)	Suspend the pill if it is at minimum dose
TSH (2.5–4.3 $\mu\text{IU/ml}$)	Dose 25 $\mu\text{g/d}$
TSH (4.4–6.1 $\mu\text{IU/ml}$)	Keep dose if 50 $\mu\text{g/d}$ or increase if taking 25 $\mu\text{g/d}$
TSH (6.2–8 $\mu\text{IU/ml}$)	Keep dose if 50 $\mu\text{g/d}$ or increase if taking 25 $\mu\text{g/d}$
TSH (8.1–9.9 $\mu\text{IU/ml}$)	Keep dose if 50 $\mu\text{g/d}$ or increase if taking 25 $\mu\text{g/d}$

TSH, thyroid-stimulating hormone.

All vials (placebo or levothyroxine) presented drugs in one-quarter tablet = 25 μg the first month. In addition, the following months were adjusted according to the TSH range.

Our primary objective was to evaluate the effect of lowering TSH with the use of LVX or placebo to assess absolute levels at the beginning compared to the end of the study, when proteinuria was measured in urine collected for 24 hours. The secondary objectives were to evaluate the changes in sCr and eGFR and to assess the tolerability and safety of LVX and changes in cholesterol, triglycerides, LDL and blood pressure.

Interventions

The treating nephrologist and the patients were blinded to the study intervention.

If randomized to the intervention arm, the intervention consisted of treatment with oral levothyroxine (LVX) between 0.25 and 0.50 μg according to a dose of 0.3 to 0.5 $\mu\text{g/kg}$ per day during fasting (in the case of taking a drug that interacts with the absorption, use of it was changed according to the hours specified). The dose adjustment was every 4 weeks. Levothyroxine or placebo was adjusted to 25 or 50 μg according to TSH levels (Table 1).

Participants allocated to placebo took 1 pill per day, with the same bottle characteristics as patients in the intervention arm, for >12 weeks.

The preparation and packaging of LVX and placebo were carried out by a pharmacist who was not involved in the development of the present study. All patients were followed up every 4 weeks for usual renal health consultation. In addition, the specific aspects of the protocol consisted of monitoring thyroid function for the adjustment of LVX or placebo dose according to the previous dosage adjustment.

To ascertain compliance and adherence to treatment, a record sheet was created with all drug supplied and returned. During the course of the study, the investigator was responsible for providing additional instructions to retrain any subjects who did not comply with the administration of the study drug or with attendance at the required clinical visits.

Adverse events were recorded during the follow-up, which included thyroid profile control tests every 4 weeks. Previously specified adverse effects

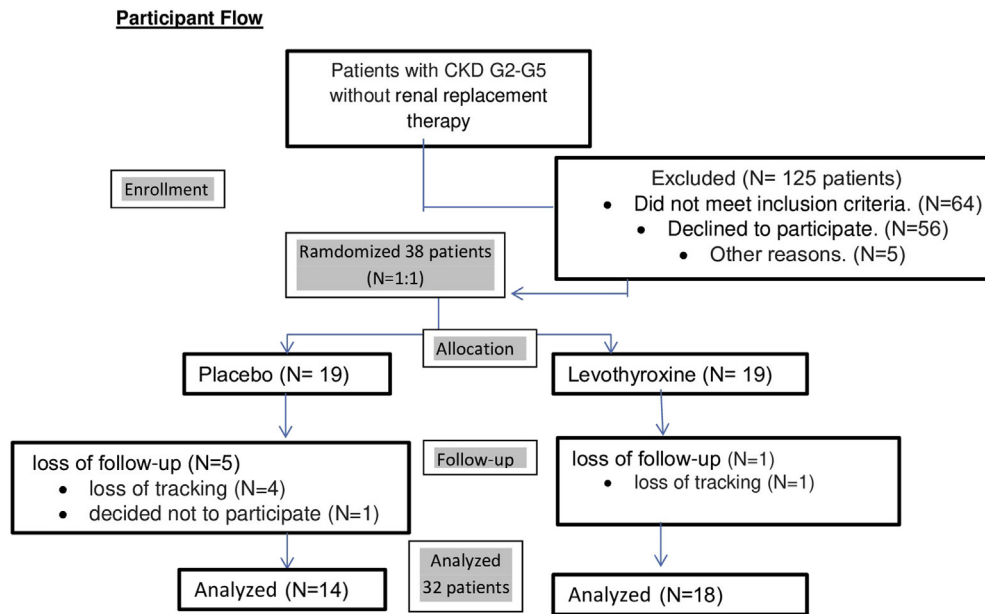


Figure 1. Flowchart during the study period.

were reported and followed up, and were rated in intensity according to the Common Terminology Criteria for Adverse Events (CTC) v. 3.0 (1–5), along with the start date and end date, as well as the treatment received.

This protocol was not sponsored or financed by any pharmaceutical company, nor are there any conflicts of interest on the part of the authors.

Statistical Analyses

The sample calculation was at will. The reason for this pilot trial was to investigate areas of uncertainty regarding future definitive randomized clinical trials on the effects of thyroid hormone reduction with levothyroxine on proteinuria in patients with advanced chronic kidney disease based on eGFR and proteinuria. This was a small-scale study conducted to test the plan and method of a research study; this pilot study addresses treatment safety assessments, determination of dose levels and response, and estimation of the effect of treatment and its variance.

The methodology for a clinical trial of superiority was carried out. Parametric continuous variables are given as the mean and SD, and nonparametric continuous variables are reported as medians. Comparisons were made using the Student *t* test or the Mann–Whitney test. Categorical variables are presented as percentages and were compared using the χ^2 test or Fisher exact test. The prespecified threshold for significance was a *P* value <0.05. All statistical analyses were performed using the statistical programs SPSS version 20 (SPSS IBM Corporation, Armonk, NY) and GraphPad 7 (GraphPad Software, San Diego, CA).

RESULTS

From March to November 2018, a total of 163 patients attended the Renal Health Clinic and were considered for participation. Of the patients, 125 were excluded because 64 did not meet the inclusion criteria, 56 patients decided not to participate, and another 5 did not meet the other specifications. Only 38 patients provided consent to participate. Of these, 6 patients were lost during follow-up, leaving a total of 32 patients (77.2%) to be analyzed. Of those, 14 patients (43.75%) were randomized to the placebo group and 18 (56.25%) to the LVX group (Figure 1).

Baseline clinical and demographic characteristics are shown in Table 2. Both groups had similar characteristics with respect to sex, age, number of comorbidities, CKD grade, weight, albumin, eGFR, hemoglobin, systolic blood pressure (SBP), diastolic blood pressure (DBP), lipid profile, and proteinuria, except for the statistically higher TSH, sCr and LDL levels in the LVX group. At baseline, the mean (SD) levels of LDL cholesterol were significantly lower in the placebo group than in the LVX group (75.5 ± 19 mg/dl and 102.38 ± 31 –42 ng/dl, respectively, *P* = 0.01). The TSH levels in the placebo group were significantly lower than those in the LVX group (4.46 ± 1.68 μ IU/ml and 5.93 ± 2.2 μ IU/ml, respectively; *P* = 0.02). The sCr levels of the placebo group were significantly higher than those of the LVX group (3.05 SD ± 1.65 mg/dl and 2.46 SD ± 1.13 mg/dl, respectively, *P* = 0.05).

The primary objective, measured at 3 months of randomization, is presented in Table 3 and Figure 2. A total of 32 patients were analyzed, 14 in the placebo

Table 2. Demographic and clinical baseline characteristics

Baseline characteristics	Placebo (n = 14)	Levothyroxine (n = 18)	All (N = 32)	P value
Sex, n, % female	10 (71.42)	10 (55.55)	20 (62.5)	NA
Age, yr, SD	63.85 ± 15	69.22 ± 8.7	66.87 ± 12.19	0.41
Diabetes mellitus	11 (78.57)	13 (72.22)	24 (75)	1.00
Hypertension	12 (85.71)	16 (88.88)	28 (87.5)	1.00
Weight, kg, SD	67.90 ± 13.83	67.01 ± 11.32	67.55 ± 12.13	0.88
Obesity (BMI >30 kg/m ²)	1 (7.14)	3 (6.6)	4 (12.5)	0.61
CKD G3a (45–59 ml/min per 1.73 m ²)	0	3 (16.6)	3 (9.37)	0.23
CKD G3b (30–44 ml/min per 1.73 m ²)	2 (14.28)	4 (22.22)	6 (18.75)	0.67
CKD G4 (15–29 ml/min per 1.73 m ²)	5 (35.71)	7 (38.88)	12 (37.5)	1.00
CKD G5 (<15 ml/min per 1.73 m ²)	7 (50)	4 (22.22)	11 (34.37)	0.14
eGFR (ml/min per 1.73 m ²)	18.14 ± 9.96	27.72 ± 13.38	23.55 ± 12.91	0.078
TSH, µIU/ml	4.46 ± 1.68	6.08 ± 2.18	5.37 ± 2.13	0.02
T4L, ng/dl	0.93 ± 0.12	0.99 ± 0.14	0.96 ± 0.13	0.65
Proteinuria grams/d urine collection	1.28 ± 1.28	1.71 ± 1.20	1.52 ± 1.12	0.14
sCr, mg/dl	3.65 ± 1.65	2.46 ± 1.13	2.98 ± 1.51	0.05
Albumin, mg/dl	3.99 ± 0.41	3.8 ± 0.41	3.88 ± 0.42	0.24
Triglycerides, mg/dl	194 ± 75.3	144.66 ± 91.76	172.5 ± 87.71	0.09
Cholesterol, mg/dl	170.57 ± 45.96	165.5 ± 59.67	167.71 ± 54.16	0.67
LDL, mg/dl	75.5 ± 19	102.38 ± 31.42	90.62 ± 29.86	0.01
Hemoglobin, g/dl	11.37 ± 1.21	11.95 ± 1.61	11.72 ± 1.48	0.17
SBP, mm Hg	148.14 ± 27.7	160 ± 19.4	154.81 ± 24.14	0.17
DBP, mm Hg	79 ± 11.72	81.83 ± 8.2	80.59 ± 10	0.60
ACEI or ARB	14 (100)	18 (100)	32 (100)	1.00
Allopurinol	14 (100)	18 (100)	32 (100)	1.00
Statin	14 (100)	18 (100)	32 (100)	1.00

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensinogen receptor blockers; BMI, body mass index; DBP, diastolic blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; G, grade; kg, kilograms; LDL, low-density cholesterol; NA, not available; SBP, systolic blood pressure; sCr, serum creatinine. Data are n (%) or ±SD, unless otherwise noted.

group and 18 in the LVX group, whereas 6 were lost during follow-up. The mean (SD) proteinuria at 3 months in the LVX group was 0.89 ± 1.28 g/d, and in the placebo group 1.35 ± 0.85 g/d. When compared to placebo, LVX showed a significant decrease in proteinuria of 1.1 g/d ($P = 0.0011$).

The comparative secondary objectives are presented in Table 3 and Figure 3. For the eGFR, the LVX group showed an improvement of 4.04 ml/min per 1.73 m² ($P = 0.049$); in the placebo group, there was a decrease of 1.96 ml/min per 1.73 m². The placebo group showed a decrease in TSH of 0.4 µIU/ml, and the LVX group

Table 3. Clinical and laboratory variable changes at the end of the study period (12 weeks), according to the placebo or levothyroxine group

Primary objective	Placebo	Levothyroxine	P value
Proteinuria, g/d	+0.2 (−0.4 to 2.1) (1.35 ± 0.85)	−1.1 (−4.1 to 0.9) (0.89 ± 1.28)	0.0011
Secondary objectives			
Changes in eGFR, ml/min per 1.73 m ²	−1.96 (−5 to 3) (16.18 ± 8.37)	4.04 (9.8 to −2) (31.76 ± 11.9)	0.049
sCr, mg/dl	0.05 (−0.5 to 1.49) (3.71 ± 1.55)	−0.2 (−0.7 to 0.5) (2.36 ± 1.27)	0.32
Cholesterol, mg/dl	−28.46 (107 to 26) (142.11 ± 44.05)	−18 (−57 to 37) (147.5 ± 30.8)	0.18
Triglycerides, mg/dl	−21 (−94 to 108) (173.2 ± 51.46)	−14.6 (−286 to 66) (130 ± 41.79)	0.71
SBP, mm Hg	−2.5 (−57 to 35) (145.64 ± 18.58)	−5.5 (−75 to 57) (154.5 ± 26.38)	0.33
DBP, mm Hg	−6.43 (−17 to 14) (72.57 ± 9.78)	−9.06 (−20 to 10) (72.77 ± 11.51)	0.33
TSH, µIU/ml	−0.4 (−3.09 to 1.87) (3.97 ± 1.77)	−3.2 (−6.8 to 1.6) (3.2 ± 1.5)	0.0032
T4L, ng/dl	−0.1 (−0.18 to 0.12) 0.92 ± 0.24	0.05 (−0.38 to 0.4) 1.04 ± 0.21	0.77
Weight, kg	1.63 (−3.5 to 5.5) (68.96 ± 14.65)	−1.05 (−3.5 to 2.1) (65.86 ± 11.65)	0.20

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; sCr, serum creatinine; TSH, thyroid-stimulating hormone.

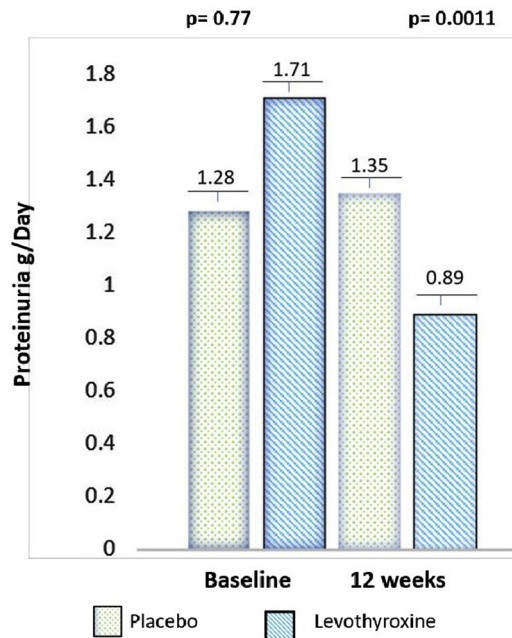


Figure 2. Proteinuria (in grams per day) at the end of the study period (12 weeks) in the placebo and levothyroxine groups.

showed a decrease in TSH of $3.2 \mu\text{IU/ml}$ ($P = 0.0032$). When comparing the weight reduction, the LVX arm showed a reduction in weight of $-1.05 \pm 3.72 \text{ kg}$, whereas the placebo group showed an increase in weight of $1.63 \text{ SD} \pm 5.59 \text{ kg}$ ($P = 0.20$). For sCr, cholesterol, triglycerides, LDL, SBP, and DBP, there were no differences between the groups at 3 months (Figure 3). Adverse effects are shown in Table 4. Urinary tract infection presented in 1 patient in the placebo group (7.14%) and nervousness in 2 patients in the LVX group (11.11%) (relative risk 1.55 95% confidence interval 0.15–15.47, $P = 1.0$). No patients left the study because of adverse effects. Adverse events were not severe according to the severity scale.

DISCUSSION

This pilot randomized, single-center, double-blind study in patients with advanced proteinuric CKD demonstrated that administering LVX to obtain a normal TSH range decreased proteinuria and improved eGFR, with few adverse events.

The management of proteinuria in CKD is mainly due to the effects of blocking the renin–angiotensin–aldosterone system (RAAS), such as with ACEIs and ARBs,^{35,36} and other drugs to a lesser magnitude, such as allopurinol,⁵⁵ aldosterone antagonists,^{37–40} statins,^{41,42} and calcitriol^{44–47}; however, despite these treatments, there is still residual proteinuria that contributes to the deterioration of renal function and cardiovascular risk.² Proteinuria in hypothyroid human beings and rats has been related to

RAAS activity,⁹ blood pressure, and oxidative stress, although it may be a reflection of glomerular hypertension and decreased glomerular filtration rate,⁵ changes in the management of tubular proteins, or changes in the structure of the glomerular barrier, specifically at the podocyte and megalin.^{8,9} In our study, the significant decrease in proteinuria of 1.1 g/d in the LVX group could be explained by the normalization of the TSH range. In addition, the antiproteinuric benefit observed with LVX could be explained by the alteration of glomerular pressure due to the negative inotropic effect on the heart, reduction in the circulating intravascular volume, and increase in peripheral resistance, with renal vasoconstriction adding a counterregulatory effect of RAAS, as well as changes at the level of the glomerular, tubular, and podocyte basal membrane.^{5,10} Higher baseline ranges were observed for TSH, LDL, and sCr in the LVX group, which could explain why the higher the TSH, the greater the effect on proteinuria.^{14,50,51} It is very important to consider the administration of LVX in patients with CKD and alterations in TSH for a greater benefit in decreasing proteinuria, thus adding the correlation that thyroid hormone in endothelial damage and in cardiovascular risk could also decrease mortality and decrease eGFR.^{14,19,50,52}

In our study, eGFR increased in the LVX group by $4 \text{ ml/min per } 1.73 \text{ m}^2$, compared to that in the placebo group, in which eGFR decreased by $2 \text{ ml/min per } 1.73 \text{ m}^2$. Van Welsem *et al.*⁹ reported that the normalization of hypothyroidism after treatment with LVX led to a significant improvement in renal function in a patient with CKD.⁵ In addition, Shin *et al.* demonstrated that reaching a TSH goal of 1 to $4.5 \mu\text{IU/ml}$ with LVX at a dose of 25 to $50 \mu\text{g/d}$ improved the eGFR $+4.31 \pm 0.5 \text{ ml/min per } 1.73 \text{ m}^2$.⁵¹ Chang *et al.* used a TSH goal of $1.16\text{--}2.86 \mu\text{IU/ml}$ with a dose of LVX $25 \mu\text{g/d}$ and obtained an improvement in eGFR $+5.77 \text{ ml/min per } 1.73 \text{ m}^2$ ($P = 0.015$).¹⁴

Although previous studies have shown that LVX improves cardiac function, renal function, and dyslipidemia and delays progression of CKD that is already established in patients with SCH, there is still a lack of consensus in the current guidelines on whether to treat SCH in patients with CKD. In particular, little is known about the effect of thyroid hormone replacement on changes in eGFR.^{21–24} Some studies exist comparing CKD and thyroid disorders in which normal TSH ranges were maintained and an improvement in the progression of CKD, decreased proteinuria,^{5,9,13,17} improved lipid profile,³⁷ and lower cardiovascular risk were observed.²⁰ Rhee *et al.* found, in more than 220,000 patients, that at TSH levels $>3 \mu\text{IU/ml}$ and TSH $<0.5 \mu\text{IU/ml}$, there is a higher mortality rate in patients with CKD G3.¹⁹

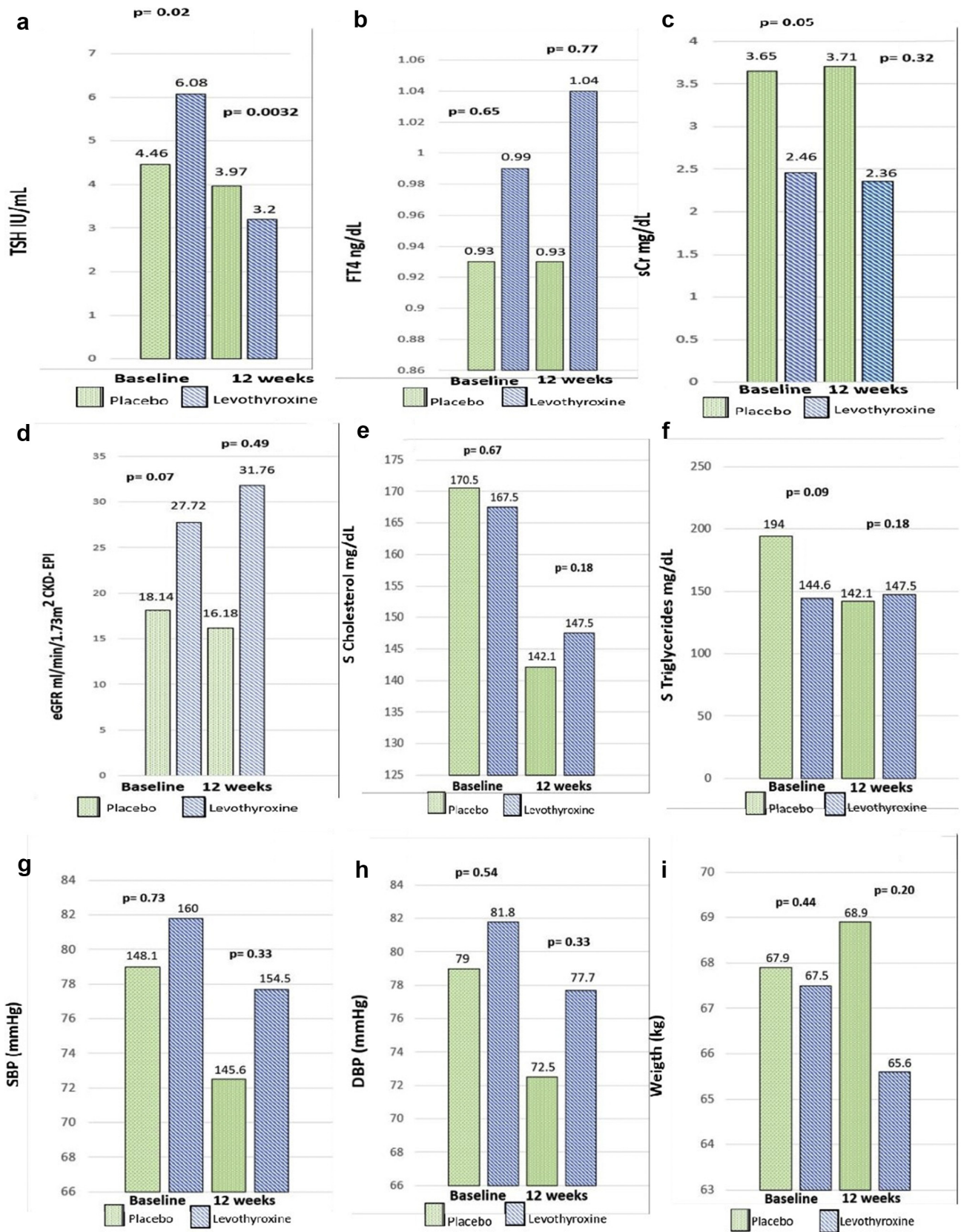


Figure 3. Clinical and laboratory variable changes at the end of the study period (12 weeks), according to placebo or levothyroxine group. (a) Serum thyroid-stimulating hormone (TSH); (b) serum FT4; (c) serum creatinine (sCr); (d) estimated glomerular filtration rate (eGFR); (e) serum cholesterol; (f) serum triglycerides; (g) systolic blood pressure (SBP); (h) diastolic blood pressure (DBP); (i) Weight loss (in kilograms). CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Table 4. Adverse events during the study period

Group	n (%)	Outcome
LVX group	1 (7.14)	Urinary tract infection ^a
Placebo group	2 (11.11)	Anxiety ^b

CI, confidence interval; LVX, levothyroxine; RR, relative risk.

^aUrinary tract infection: duration of 5 days, without complications.

^bAnxiety: duration of 3 days, without complications.

RR = 1.55, 95% CI 0.15–15.47, *P* = 1.0.

There are already studies in which the elevation of TSH is associated with the progression of CKD.^{14,15} In patients already undergoing renal replacement therapy, such as hemodialysis with elevated TSH, it was associated with mortality,^{21–23} similar to peritoneal dialysis.²⁴

We sought to reinforce these benefits of maintaining a range of TSH (<4.5 μ IU/ml, considering previous studies in which mortality was associated with TSH >2.5 μ IU/ml).^{19,29} In addition, some authors have reported a greater progression to terminal CKD and mortality in patients with SCH versus euthyroid hypothyroidism.^{19,20} The American²⁵ and European guidelines²⁷ do not mention the potential benefit of the use of LVX and its impact in patients with CKD and SCH.

Another possibility of improving proteinuria and eGFR is that by decreasing TSH, an increase in catabolism and weight reduction was achieved, eliminating hyperfiltration and proteinuria. It should be mentioned that at the beginning of the study, only 4 patients had a BMI >30 kg/m², 1 patient from the placebo group and 3 patients from the LVX group (*P* = 0.61), and the differences in weight loss (in kilograms) at the end of the study were higher in the LVX group than in the placebo group, with an average of $-1.05 \text{ SD} \pm 3.72 \text{ kg}$ and $1.63 \text{ SD} \pm 5.59 \text{ kg}$, respectively, but the differences were not significant (*P* = 0.20). Among the other variables relevant to this study, there were no significant changes in BP or HR.

Regarding tolerance, the use of LVX was safe, there were no severe adverse events, and no patient had to discontinue the study drug. However, more patients in the LVX dose adjustment were required (relative risk = 1.55, 95% confidence interval = 0.15–15.47, *P* = 1.0). In previous studies, no serious adverse effects have been reported when giving LVX to patients with CKD, considering that they are patients with cardiovascular risk.^{25,26} This information can be interpreted as showing that LVX is a useful treatment in hypothyroidism and that the risk is minimal.^{28,29}

Several limitations need to be acknowledged. This paper presents the results of a small, single-center, randomized controlled pilot clinical trial. As such, estimates of treatment effects may be overoptimistic and/or unique to the population studied. The main analyses did not impute missing data, which, in both the

placebo and LVX groups, were assumed to be missing at random. Other limitations of our study include the racial homogeneity of the study population and the short treatment duration (12 weeks). The sustainability of these effects over a longer time period needs to be confirmed in longer-term studies. However, the results demonstrate that the study intervention is feasible and has promising effects on multiple measures of renal function. Another limitation is that TSH levels were different at the time of randomization, although we believe that this had no impact on the final result, as both groups were in ranges of abnormality. Furthermore, there is no objective evidence to suggest that the study population is unique. However, as with all pilot projects, our findings remain exploratory and hypothesis generating.

In conclusion, this single-center, randomized, double-blind, placebo-controlled pilot clinical study in patients with advanced proteinuric CKD who already used ACEIs or ARBs demonstrated that administering LVX to obtain a TSH range close to 2.5 μ IU/ml decreased proteinuria and improved eGFR. These findings could encourage the performance of a clinical trial with sufficient statistical power to demonstrate the benefit of normalizing TSH with LVX in patients with CKD.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Table S1. Drugs that interact with levothyroxine.

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