HHS Public Access

Author manuscript

Hemodial Int. Author manuscript; available in PMC 2020 September 10.

Published in final edited form as:

Hemodial Int. 2017 October ; 21(4): 534–541. doi:10.1111/hdi.12527.

Thyroid Function in End Stage Renal Disease and Effects of Frequent Hemodialysis

Joan C. Lo, MD[1], **Gerald J. Beck, PhD**[2], **George A. Kaysen, MD, PhD**[3], **Christopher T. Chan, MD**[4], **Alan S. Kliger, MD**[5], **Michael V. Rocco, MD**[6], **Minwei Li, MS**[2], **Glenn M. Chertow, MD MPH**[7], **FHN Study**

[1]Division of Research, Kaiser Permanente Northern California; Oakland CA

[2]Department of Quantitative Health Sciences, Cleveland Clinic; Cleveland OH

[3]Division of Nephrology, Department of Medicine, University of California Davis; Davis CA

[4]Division of Nephrology, University Health Network, University of Toronto; Toronto ON, Canada

[5]Division of Nephrology, Department of Medicine, Yale School of Medicine and Yale New Haven Health System; New Haven CT

[6]Section on Nephrology, Department of Internal Medicine, Wake Forest School of Medicine; Winston-Salem NC

[7]Division of Nephrology, Department of Medicine, Stanford University School of Medicine; Palo Alto CA

Abstract

INTRODUCTION: End-stage renal disease (ESRD) is associated with perturbations in thyroid hormone concentrations and an increased prevalence of hypothyroidism. Few studies have examined the effects of hemodialysis dose or frequency on endogenous thyroid function.

METHODS: Within the Frequent Hemodialysis Network (FHN) Trials, we examined the prevalence of hypothyroidism in patients with ESRD. Among those with endogenous thyroid function (without overt hyper/hypothyroidism or thyroid hormone supplementation), we examined the association of thyroid hormone concentration with multiple parameters of self-reported health status, and physical and cognitive performance, and the effects of hemodialysis frequency on serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and free tri-iodothyronine (FT3) levels. Conventional thrice-weekly hemodialysis was compared to in-center (6 days/week) hemodialysis (Daily Trial) and nocturnal (6 nights/week) home hemodialysis (Nocturnal Trial) over 12 months.

FINDINGS: Among 226 FHN Trial participants, the prevalence of hypothyroidism was 11% based on thyroid hormone treatment and/or serum TSH ≥8 mIU/mL. Among the remaining 195 participants (147 Daily, 48 Nocturnal) with endogenous thyroid function, TSH concentrations

CORRESPONDENCE: Joan C. Lo MD, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612, 510-891-3492 office, 510-891-3508 fax, Joan.C.Lo@kp.org.

CONFLICT OF INTEREST: None

were modestly (directly) correlated with age (r=0.16, p=0.03) but not dialysis vintage. Circulating thyroid hormone levels were not associated with parameters of health status or physical and cognitive performance. Furthermore, frequent in-center and nocturnal hemodialysis did not significantly change (baseline to month 12) TSH, FT4 or FT3 concentrations in patients with endogenous thyroid function.

DISCUSSION: Among patients receiving hemodialysis without overt hyper/hypothyroidism or thyroid hormone treatment, thyroid indices were not associated with multiple measures of health status and were not significantly altered with increased dialysis frequency.

Keywords

end stage renal disease; daily dialysis; nocturnal dialysis; thyroid; hypothyroidism

INTRODUCTION

Despite considerable overlap in the symptoms related to hypothyroidism and end-stage renal disease (ESRD), there are limited data pertaining to thyroid function in patients with ESRD. Increased thyroid gland volume[1] and an increased prevalence of goiter[2,3] have been observed, potentially related to altered iodine metabolism, autoimmune and uremic factors.[4] Existing data suggest that primary hypothyroidism is more common in patients with ESRD compared with the general population.[3,5] Cases of reversible primary hypothyroidism with iodine restriction have been reported in patients with mild to severe renal dysfunction and those receiving maintenance hemodialysis, suggesting that impaired renal excretion of iodine may contribute to the observed association between hypothyroidism and chronic kidney disease (CKD).[6,7] These observations are of interest, given that two large observational studies reported an inverse graded relation between kidney function and risk of prevalent clinical or subclinical hypothyroidism within the general population[8,9] and among patients with moderate to severe CKD.[10] However, the mechanisms underlying the association of kidney function and thyroid disease, including the potential effects of dialysis on free thyroid hormone concentrations, have not been clearly elucidated.

In the absence of overt hypothyroidism, reduced levels of triiodothyronine (T3) and thyroxine (T4) levels have been reported in patients with ESRD,[3,11–14] possibly a consequence of chronic nonthyroidal illness (euthyroid sick syndrome), unresolved uremia and/or protein malnutrition.[11] End-stage renal disease has also been associated with symptoms of depression, asthenia and reduced energy, potentially related to the accumulation of nitrogenous waste products, although these symptoms are similar to those associated with perturbations in thyroid function.[15,16] Furthermore, low levels of thyroid hormone have been associated with cardiac dysfunction[17,18] and increased mortality risk[14,19–21] in patients with ESRD, independent of other risk factors.

The Frequent Hemodialysis Network (FHN) trials provide a unique opportunity to characterize thyroid status and associated health status in a community dwelling population of patients receiving hemodialysis and to examine the effects of hemodialysis frequency on indices of thyroid function. These trials were designed in light of physiologic and observational studies suggesting benefits of more frequent hemodialysis.[22] The FHN Daily

and Nocturnal Trials randomized patients receiving conventional thrice weekly hemodialysis to either daily in-center hemodialysis or nocturnal home hemodialysis, aiming to determine the effects of hemodialysis frequency on multiple intermediate outcomes, including cardiac structure and function, physical health and performance, mental health, cognitive function, hypertension, nutritional status, anemia, bone and mineral metabolism, and general health-related quality of life. This ancillary study to the FHN trials examined the prevalence of thyroid function abnormalities in ESRD, the associations of indices of thyroid function with multiple intermediate outcomes, and the effects of hemodialysis frequency on circulating thyroid hormone concentrations. We hypothesized that frequent hemodialysis would increase levels of free tri-iodothyronine (FT3) and thyroxine (FT4) and that improvement in thyroid function associated with frequent hemodialysis would be observed in parallel with improvements in multiple measures of health status.

METHODS

Study Population

The FHN trials compared the effects of conventional thrice weekly hemodialysis with in-center daily hemodialysis (6 days per week) and nocturnal home hemodialysis (6 nights per week) over a 12-month treatment interval, with examination of two co-primary outcomes: death or change in left ventricular mass by cardiac magnetic resonance imaging and death or change in self-reported physical health (the Physical Health Composite score from the RAND SF-36 health survey). Secondary outcomes in multiple domains were examined at baseline and over 12 months. For the Daily Trial, a total of 245 patients were randomized to 3 (N=120) or 6 (N = 125) times per week hemodialysis; for the Nocturnal Trial, a total of 87 patients were randomized to 3 (N=42) or 6 (N = 45) times per week hemodialysis, both with follow-up to 12 months.

The FHN Daily and Nocturnal Trials were approved by the Institutional Review Board at each participating site, with biosamples stored at the NIDDK Repository obtained by informed consent for future biomarker analyses. This ancillary study, using stored biosamples and clinical data from the FHN Trials was also approved by the Institutional Review Board at Kaiser Permanente Northern California.

Measurements

Thyroid hormone laboratory measurements were conducted at the University of California Davis (Biomedical Sciences Laboratory) using stored serum frozen at −70C obtained from the NIDDK Biorepository. Samples were taken at baseline and month 12 (or if not available then, used the month closest to month 12, ranging from 10–15 months). Serum thyroid stimulating hormone (TSH) was measured in duplicate by enzyme-linked immunoassay (Alpco Diagnostics, Salem NH) with an intra- and inter-assay CV of 2.5–5.7% and 5.7–8.9%, respectively; manufacturer observed TSH values ranged between 0.3–8.1 uIU/mL for normal individuals, with suggested age-specific TSH values of 0.4–4.2 (age 21–54 years) and 0.5–8.9 (age 55–87 years) uIU/mL from external reference guides. Serum free thyroxine (FT4) was measured in duplicate by enzyme-linked immunoassay (Alpco Diagnostics, Salem NH) with an intra- and inter-assay CV of 3.3–11.0% and 6.0–10.8%, respectively, and

a reported normal reference range of 0.8–2.2 ng/dL. Serum free triiodothyronine (FT3) was measured in duplicate by enzyme-linked immunoassay (Alpco Diagnostics, Salem NH) with an intra- and inter-assay CV of 3.1–4.9% and 7.9–13.2%, respectively, and reported normal reference range of 1.4–4.2 pg/mL. All assays were completed with no more than one freeze thaw cycle occurring at the NIDDK Biorepository for specimen aliquoting.

We examined the following parameters of health status at baseline and during follow-up. The RAND SF-36 item health survey[23] was used to derive physical and mental health composite (PHC and MHC) scores where higher scores reflect better physical or mental health status, along with a general health scale (0 to 100, where 100 indicates perfect health); the Beck Depression Inventory,[24,25] a 21-item survey designed to measure the presence and severity of depressive symptoms; the Health Utilities Index (HUI-3) scored to a final result from 0 to 1 as a measure of overall health utility, with function derived from community preferences for various health attributes;[26] the Feeling Thermometer, a visual analog scale (0 to 100, where 100 indicates perfect health); and the time to recover (in minutes) after a dialysis session. The short physical performance battery consists of three lower extremity mobility tests pertaining to standing balance, timed chair stand and timed walk was used to calculate a physical performance score (0–12). The Trail Making Test B, which measures the ability to visually search, sustain attention and perform cognitive shifting during completion of an activity and the Modified Mini Mental Status exam were conducted as measures of global cognitive function.

Statistical Analyses

We compared groups by treatment status using standard descriptive statistics, including Students t-test for continuous variables and chi-squared or Fisher's exact test for categorical variables. We examined the association between free thyroid hormone concentrations and continuous measures of health status using Pearson correlations and partial correlations were used to adjust for demographic and clinical factors that might affect health status and/or thyroid levels. To examine the effect of dialysis frequency on changes in thyroid function measures, and to include all observations, even in those subjects with no 12-month measurements (e.g. due to missing end of study visit and/or missing sample), we employed a mixed-effects model with an unstructured covariance matrix, with adjustment for clinical center in the Daily Trial. Secondarily, as a sensitivity analysis, we conducted these analyses with inclusion of FHN Trial participants receiving thyroid hormone supplementation (excluding two with TSH > 8 μIU/mL). All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute, Cary, NC) with a p-value criterion of <0.05 as the threshold for statistical significance.

RESULTS

Thyroid function studies with TSH measured were available in 167 Daily and 59 Nocturnal FHN Trial participants, including 22 participants receiving thyroid hormone supplementation (all with TSH <5 μIU/mL except three with TSH of 7.0–7.9 μIU/mL and two with TSH >10 μIU/mL) and three with TSH level >8 μIU/mL in the absence of thyroid hormone supplementation. These 25 (11% of 226) individuals were collectively classified as

hypothyroid and initially excluded from primary analyses examining the relation among thyroid function, measures of health status and hemodialysis frequency, due to the effects of underlying hypothyroidism and/or treatment on thyroid hormone indices. An additional six participants were excluded due to missing baseline TSH in whom thyroid status could not be confirmed, TSH ≤0.01 μIU/mL, treatment with propylthiouracil, or lack of both FT3 and FT4 measures. The primary analytic cohort included 195 individuals with TSH values between 0.2 and 8.0 uIU/mL classified as having endogenous thyroid function, including 14 individuals with TSH levels of 5.0–7.9 μIU/mL (6.2% of the source cohort).

Table 1 shows the clinical characteristics of the FHN Trial participants with endogenous thyroid function at baseline, including 147 Daily (33% female) and 48 Nocturnal (38% female) participants. In the Daily Trial, 59% were under age 55 and 13% were age 65 years and older at study entry; only three were over age 80 years. The majority (68%) had received maintenance hemodialysis for at least two years and 42% had diabetes mellitus. In the Nocturnal Trial, 52% were under age 55 and 27% were age 65–79; none were age 80 years or older. The majority had received hemodialysis for less than two years and more than half (56%) had diabetes mellitus. Mean (± SD) baseline TSH concentrations were 2.33 ± 1.39 (Daily Trial) and 2.18 ± 1.44 (Nocturnal Trial). As expected, baseline TSH was modestly correlated with age ($r = 0.16$, $p = 0.028$). There was no association between TSH concentration and dialysis vintage.

Examination of the associations of TSH, FT4 and FT3 with measures of health status among those with endogenous thyroid function found that serum TSH concentration was modestly (inversely) correlated with lower extremity physical performance ($r = -0.21$, $p = 0.004$) and (directly) correlated with the Trail Making Test B ($r = 0.17$, $p = 0.021$), but these associations were no longer significant after adjusting for differences in age, sex, vintage, diabetes and comorbidity burden, $r = -0.13$ ($p = 0.07$) and 0.12 ($p = 0.11$), respectively. Furthermore, other indices of physical or cognitive function were not associated with TSH in these patients. No significant associations of FT4 and FT3 with measures of health status were seen among subjects with endogenous thyroid function, without or with adjustment for differences in age, sex, vintage, diabetes and comorbidity burden (all $|r| < 0.15$, $p > 0.05$).

Table 2 shows the serum concentrations of TSH, FT4 and FT3 at baseline and month 12, along with the change in thyroid indices between baseline and month 12, when restricting analyses to Daily and Nocturnal Trial participants with both baseline and month 12 measurements. Changes in thyroid indices from baseline to month 12 were not statistically significant when compared between treatment arms for each trial.

Table 3 demonstrates the effect of hemodialysis frequency on changes in serum concentrations of TSH, FT4 and FT3, examined in all 147 Daily and 48 Nocturnal participants with endogenous thyroid function using mixed-effects models to account for missing values. A positive mean change indicates that the month 12 thyroid lab value increased from baseline. The treatment effect compares the change from baseline to month 12 between the hemodialysis frequency arms. A treatment effect with a positive sign indicates a net increase comparing daily to conventional hemodialysis. A treatment effect with a negative sign indicates a net decrease comparing daily to conventional hemodialysis.

In the Daily Trial, there were no significant changes in TSH, FT4 or FT3 between conventional and daily hemodialysis treatment arms. In sensitivity analyses, these results were similar when participants receiving thyroid hormone supplementation (and with TSH <8 mIU/mL) were included in the analyses (data not shown, p>0.18). Among Nocturnal Trial participants with endogenous thyroid function, changes in thyroid indices were not significant, including increased FT3 levels associated with dialysis frequency (p=0.07), although a significant increase in FT4 concentrations was observed in sensitivity analyses that included those receiving thyroid hormone therapy (treatment effect 0.10, 95% CI 0.01–0.20, p=0.03).

DISCUSSION

Across a relatively large clinical trial population of patients receiving hemodialysis randomized to frequent *versus* conventional hemodialysis, we estimated that the prevalence of hypothyroidism was in the range of 11% (or as high as 17% if potentially subclinical cases are included, TSH 5.0–7.9 uIU/mL). Among those with evidence of endogenous thyroid function (absence of hyper or hypothyroidism or thyroid hormone supplementation), no association of free thyroid hormone concentrations (FT4 and FT3) were observed with measures of self-reported health status, and physical and cognitive performance. Frequent in-center daily hemodialysis and nocturnal home hemodialysis also did not result in significant changes in thyroid hormone levels among those with endogenous thyroid function, despite a significant effect of dialysis frequency on FT4 levels seen only in Nocturnal Trial participants when including participants receiving thyroid hormone therapy.

The etiology underlying the increased prevalence of hypothyroidism in ESRD has not been clearly elucidated, but the accumulation of inorganic iodide secondary to reduced renal excretion and accumulation of other uremic toxins with central and peripheral effects are thought to play a contributing role.[27] These mechanistic processes are supported by observations of increased prevalence of primary hypothyroidism in association with declining renal function reported from large population studies.[8–10] In a large cohort of 2715 patients receiving hemodialysis in the greater Boston area, 12.9% were classified as hypothyroid,[28] somewhat lower than findings from a large U.S. dialysis organization with 8840 patients, among whom 22% were classified as hypothyroid also using a TSH threshold of ≥5.0 mIU/L.[20] Data from our study demonstrate a prevalence of 11% with TSH ≥8 uIU/mL (17% with TSH ≥5 uIU/mL) or evidence of thyroid hormone treatment, within range of these published estimates.

Few studies have examined the effect of dialysis treatment on thyroid hormone levels. In a pilot study of 40 patients with ESRD where free thyroxine (FT4) and tri-iodothyronine (FT3) were measured before and after hemodialysis, levels of both FT4 and FT3 increased post-dialysis, although no change in thyroid stimulating hormone (TSH) level was observed.[29] Others have found that immediate dialysis-related changes in thyroid indices are not sustained, and potentially relate to hemoconcentration or transient effects of hemodialysis on thyroid hormone binding.[30,31] Low FT3 is also evident in the setting of protein malnutrition and chronic illness, and may increase as a reflection of improvement in these health parameters rather than thyroid function per se. Given the association of thyroid function,

mortality and cardiovascular outcomes, and particularly the association of low triiodothyronine and thyroxine with increased mortality risk,[14,27,32] the extent to which increased frequency of hemodialysis affects endogenous thyroid function and circulating thyroid indices, independent of nutrition, illness severity and other related health outcomes, may have important implications for long term outcomes. In our study we observed a nonsignificant increase in FT3 level associated with increased dialysis frequency in the Nocturnal Trial and a significant increase in FT4 when including the broader subset of patients receiving thyroid hormone therapy. The implication of these findings is unclear.

This study has several limitations to consider. First, because we did not have detailed information pertaining to prior thyroid history, dosage and change in dosage for participants receiving thyroid replacement therapy, we were unable to examine the effects of more frequent hemodialysis in the subgroup of patients with overt thyroid dysfunction. Second, we did not have measures pertaining to the effects of dialysis frequency on iodine clearance. Third, these analyses were conducted using data from participants enrolled in two randomized trials, somewhat limited by modest sample size within each trial arm among those with evidence of endogenous thyroid function, especially the Nocturnal Trial. Thus, findings may not be generalizable to the broader population of patients with ESRD. Finally, we cannot exclude the potential limitations of conventional FT4 and FT3 assays, including assay precision characteristics as well as performance in the setting of uremia, other disease states or medication use, where protein-hormone binding may be altered. The strengths of this study include use of data reported from a carefully characterized diverse multicenter population of patients receiving chronic hemodialysis in whom longitudinal measures of thyroid function were obtained.

In summary, the estimated prevalence of hypothyroidism was in the range of 11% or higher among patients receiving hemodialysis. Among ESRD patients with endogenous thyroid function, baseline indices of thyroid function were unassociated with a variety of measures of health status; in addition, more frequent hemodialysis had no significant effect on thyroid hormone levels. Further studies should be conducted in larger clinical populations and those receiving nocturnal hemodialysis to additionally characterize whether there are short or long-term effects of hemodialysis frequency on thyroid hormone levels in this vulnerable population, including those with thyroid dysfunction.

ACKNOWLEDGEMENTS

The Frequent Hemodialysis Network Trials (registered at ClinicalTrials.gov NCT00264758 and NCT00271999) were supported by grants from the National Institutes of Health (U01 DK066579, U01 DK066597, U01 DK066480, U01 DK066481) and the Centers for Medicare and Medicaid Services and the National Institutes of Health Research Foundation (with contributions from Amgen, Baxter, DaVita, Dialysis Clinics, Inc., Fresenius Medical Care North America, Renal Research Institute and Satellite Healthcare). This Frequent Hemodialysis Network Trial ancillary study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (R01 DK076165).

REFERENCES

1. Hegedus L, Andersen JR, Poulsen LR, et al. Thyroid gland volume and serum concentrations of thyroid hormones in chronic renal failure. Nephron 1985;40:171–4. [PubMed: 2860573]

2. Lim VS, Fang VS, Katz AI, Refetoff S. Thyroid dysfunction in chronic renal failure. A study of the pituitary-thyroid axis and peripheral turnover kinetics of thyroxine and triiodothyronine. J Clin Invest 1977;60:522–34. [PubMed: 408377]

3. Kaptein EM, Quion-Verde H, Chooljian CJ, et al. The thyroid in end-stage renal disease. Medicine (Baltimore) 1988;67:187–97. [PubMed: 3259281]

4. Amato AA, Santos GM, Neves Fde A. Thyroid hormone action in chronic kidney disease. Curr Opin Endocrinol Diabetes Obes 2008;15:459–65. [PubMed: 18769220]

5. Prevalence Paudel K. and clinical characteristics of hypothyroidism in a population undergoing maintenance hemodialysis. J Clin Diagn Res 2014;8:MC01–4.

6. Sanai T, Inoue T, Okamura K, et al. Reversible primary hypothyroidism in Japanese patients undergoing maintenance hemodialysis. Clin Nephrol 2008;69:107–13. [PubMed: 18218304]

7. Sato K, Okamura K, Yoshinari M, et al. Reversible primary hypothyroidism and elevated serum iodine level in patients with renal dysfunction. Acta Endocrinol (Copenh) 1992;126:253–9. [PubMed: 1574955]

8. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G. Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. Clin J Am Soc Nephrol 2008;3:1296–300. [PubMed: 18550654]

9. Lo JC, Chertow GM, Go AS, Hsu CY. Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. Kidney Int 2005;67:1047–52. [PubMed: 15698444]

10. Rhee CM, Kalantar-Zadeh K, Streja E, et al. The relationship between thyroid function and estimated glomerular filtration rate in patients with chronic kidney disease. Nephrol Dial Transplant 2015;30:282–7. [PubMed: 25246335]

11. Lim VS. Thyroid function in patients with chronic renal failure. Am J Kidney Dis 2001;38:S80–4. [PubMed: 11576928]

12. Hardy MJ, Ragbeer SS, Nascimento L. Pituitary-thyroid function in chronic renal failure assessed by a highly sensitive thyrotropin assay. J Clin Endocrinol Metab 1988;66:233–6. [PubMed: 3121662]

13. Ramirez G, O'Neill W, Jr., Jubiz W, Bloomer HA. Thyroid dysfunction in uremia: evidence for thyroid and hypophyseal abnormalities. Ann Intern Med 1976;84:672–6. [PubMed: 937878]

14. Rhee CM, Brent GA, Kovesdy CP, et al. Thyroid functional disease: an under-recognized cardiovascular risk factor in kidney disease patients. Nephrol Dial Transplant 2015; 30:724–737. [PubMed: 24574542]

15. Molitch ME, Hou SH. Neuroendocrine alterations in systemic disease. Clin Endocrinol Metab 1983;12:825–851. [PubMed: 6323068]

16. Hochstetler LA, Flanigan MJ, Lim VS. Abnormal endocrine tests in a hemodialysis patient. J Am Soc Nephrol 1994;4:1754–9. [PubMed: 8068873]

17. Monzani F, Di Bello V, Caraccio N, et al. Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. J Clin Endocrinol Metab 2001;86:1110–5. [PubMed: 11238494]

18. Zoccali C, Benedetto F, Mallamaci F, et al. Low triiodothyronine and cardiomyopathy in patients with end-stage renal disease. J Hypertens 2006;24:2039–46. [PubMed: 16957565]

19. Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P. Low triiodothyronine and survival in end-stage renal disease. Kidney Int 2006;70:523–8. [PubMed: 16775599]

20. Rhee CM, Kim S, Gillen DL, et al. Association of thyroid functional disease with mortality in a national cohort of incident hemodialysis patients. The Journal of clinical endocrinology and metabolism 2015;100:1386–95. [PubMed: 25632971]

21. Xu H, Brusselaers N, Lindholm B, Zoccali C, Carrero JJ. Thyroid Function Test Derangements and Mortality in Dialysis Patients: A Systematic Review and Meta-analysis. American journal of kidney diseases : the official journal of the National Kidney Foundation 2016; 68:923–932. [PubMed: 27596516]

22. Suri RS, Garg AX, Chertow GM, et al. Frequent Hemodialysis Network (FHN) randomized trials: study design. Kidney Int 2007;71:349–59. [PubMed: 17164834]

23. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med 2001;33:350–7. [PubMed: 11491194]

24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71. [PubMed: 13688369]

25. Craven JL, Rodin GM, Johnson L, Kennedy SH. The diagnosis of major depression in renal dialysis patients. Psychosom Med 1987;49:482–92. [PubMed: 3671637]

26. Furlong WJ, Feeny DH, Torrance GW, Barr RD. The Health Utilities Index (HUI) system for assessing health-related quality of life in clinical studies. Ann Med 2001;33:375–84. [PubMed: 11491197]

27. Zoccali C, Mallamaci F. Thyroid function and clinical outcomes in kidney failure. Clin J Am Soc Nephrol 2012;7:12–4. [PubMed: 22173863]

28. Rhee CM, Alexander EK, Bhan I, Brunelli SM. Hypothyroidism and mortality among dialysis patients. Clin J Am Soc Nephrol 2013;8:593–601. [PubMed: 23258793]

29. Alsaran K, Sabry A, Alshahhat H, Babgy E, Alzahrani F. Free thyroxine, free triiodothyronine and thyroid-stimulating hormone before and after hemodialysis in Saudi patients with end-stage renal disease: is there any difference? Saudi J Kidney Dis Transpl 2011;22:917–21. [PubMed: 21912019]

30. van Leusen R, Meinders AE. Cyclical changes in serum thyroid hormone concentrations related to hemodialysis: movement of hormone into and out of the extravascular space as a possible mechanism. Clin Nephrol 1982;18:193–9. [PubMed: 7140033]

31. Sakurai S, Hara Y, Miura S, et al. Thyroid functions before and after maintenance hemodialysis in patients with chronic renal failure. Endocrinol Jpn 1988;35:865–76. [PubMed: 3250862]

32. Meuwese CL, Dekker FW, Lindholm B, et al. Baseline levels and trimestral variation of triiodothyronine and thyroxine and their association with mortality in maintenance hemodialysis patients. Clin J Am Soc Nephrol 2012;7:131–8. [PubMed: 22246282]

Table 1.

Baseline characteristics of subjects with end stage renal disease receiving chronic hemodialysis with endogenous thyroid function.

	FHN Daily Trial		FHN Nocturnal Trial	
	3x/week (N=72)	6x/week (N=75)	3x/week (N=25)	6x/week (N=23)
Age Group, N (%)				
< 55	41 (56.9%)	46 (61.3%)	11 (44.0%)	14 (60.9%)
55–64	19 (26.4%)	22 (29.3%)	7 (28.0%)	3 (13.0%)
≥ 65	12 (16.7%)	7 (9.3%)	7 (28.0%)	6 (26.1%)
Race/Ethnicity, N (%)				
Non-Hispanic White	11 (15.3%)	12 (16.0%)	13 (52.0%)	12 (52.2%)
Black (Hispanic/Non-Hispanic)	36 (50.0%)	33 (44.0%)	10 (40.0%)	11 (47.8%)
All Others	25 (34.7%)	30 (40.0%)	2 (8.0%)	0
Years since ESRD, N (%)				
< 2 years	24 (33.3%)	23 (30.7%)	19 (76.0%)	12 (52.2%)
≥ 2 years	48 (66.7%)	52 (69.3%)	6 (24.0%)	11 (47.8%)
Charlson Comorbidity Index, N (%)				
0	29 (40.3%)	28 (37.3%)	7 (28.0%)	7 (30.4%)
1–2	20 (27.8%)	25 (33.3%)	8 (32.0%)	8 (34.8%)
≥ 3	23 (31.9%)	22 (29.3%)	10 (40.0%)	8 (34.8%)
Diabetes mellitus	31 (43.1%)	31 (41.3%)	13 (52.0%)	14 (60.9%)
Hemoglobin (g/dL)	12.1 ± 1.12	12.0 ± 1.21	12.0 ± 1.17	11.9 ± 0.91
Serum albumin (g/dL)	4.00 ± 0.45	4.00 ± 0.39	4.07 ± 0.46	4.03 ± 0.47
Serum prealbumin (mg/dL)	33.1 ± 8.73	34.8 ± 9.08	32.1 ± 8.38	31.8 ± 8.82

Unless otherwise indicated, numbers represent mean ± standard deviation

Differences between treatment arms within the Daily and Nocturnal Trials were not significant

Table 2.

Baseline and month 12 thyroid indices in FHN participants with endogenous thyroid function

Daily Trial	**3x/week**				**6x/week**			
	N	**Baseline**	**Month 12**	**Change**	**N**	**Baseline**	**Month 12**	**Change**
TSH (uIU/mL)	43	2.01 ± 1.33	2.33 ± 1.44	0.32 ± 1.29 (0.25)	49	2.06 ± 1.16	2.02 ± 1.22	−0.04 ± 0.89 (0)
Free T4 (ng/dL)	44	0.86 ± 0.23	0.90 ± 0.27	0.04 ± 0.15 (0)	50	0.84 ± 0.21	0.91 ± 0.30	0.07 ± 0.26 (0.02)
Free T3 (pg/mL)	36	2.46 ± 0.75	2.59 ± 0.74	0.12 ± 0.43 (0.16)	44	2.57 ± 0.88	2.81 ± 0.95	0.24 ± 0.64 (0.26)
Nocturnal Trial	**3x/week**				**6x/week**			
	N	**Baseline**	**Month 12**	**Change**		**Baseline**	**Month 12**	**Change**
TSH (uIU/mL)	16	1.71 ± 0.75	1.86 ± 0.89	0.15 ± 1.06 (0.07)	12	1.93 ± 1.00	1.87 ± 0.97	−0.06 ± 0.68 (0.10)
Free T4 (ng/dL)	16	0.96 ± 0.11	0.93 ± 0.14	−0.04 ± 0.14 (−0.07)	12	1.02 ± 0.18	1.04 ± 0.18	0.02 ± 0.11 (0)
Free T3 (pg/mL)	16	3.27 ± 1.42	2.97 ± 1.20	−0.30 ± 0.55 (−0.36)	10	2.83 ± 0.38	3.17 ± 0.99	0.34 ± 1.00 (−0.12)

These data include participants with both baseline and month 12 measurements and give mean ± SD. For changes, value in parentheses gives the median.

Changes in TSH, FT4 and FT3 were not significant comparing 3x and 6x weekly hemodialysis treatment arms for the Daily and Nocturnal FHN Trials (p=0.15, 0.58, 0.71 for the Daily Trial and p=0.84, 0.12, 0.07 for the Nocturnal Trial for TSH, FT4 and FT3, respectively).

Table 3.

The effect* of dialysis frequency on thyroid indices in FHN Trial participants with endogenous thyroid function

DAILY TRIAL						
Thyroid Indices	**Treatment Arm**	**Baseline Median (n) (interquartile range)**	**Month 12 Median (n) (interquartile range)**	**Adjusted Mean Change from Baseline* (95% CI)**	**Treatment Effect* (95% CI)**	**P-Value**
TSH (uIU/mL)	3x/week	2.22 (72) (1.17, 3.41)	2.07 (43) (1.22, 2.78)	0.37 (−0.01 to 0.75)	−0.35 (−0.76 to 0.07)	0.10
	6x/week	1.88 (75) (1.31, 3.01)	1.83 (49) (1.03, 2.52)	0.02 (−0.35 to 0.39)		
FT4 (ng/dL)	3x/week	0.88 (72) (0.73, 1.05)	0.89 (44) (0.70, 1.06)	0.02 (−0.05 to 0.10)	0.03 (−0.05 to 0.12)	0.42
	6x/week	0.88 (75) (0.71, 1.00)	0.88 (50) (0.67, 1.09)	0.06 (−0.02 to 0.13)		
FT3 (pg/mL)	3x/week	2.37 (67) (2.05, 2.73)	2.49 (39) (2.24, 2.79)	0.10 (−0.11 to 0.32)	0.14 (−0.10 to 0.38)	0.25
	6x/week	2.59 (72) (2.14, 3.03)	2.78 (45) (2.26, 3.33)	0.24 (0.04 to 0.45)		
NOCTURNAL TRIAL						
Thyroid Indices	**Treatment Arm**	**Baseline Median (n) (interquartile range)**	**Month 12 Median (n) (interquartile range)**	**Adjusted Mean Change from Baseline* (95% CI)**	**Treatment Effect (95% CI)**	**P-Value**
TSH (uIU/mL)	3x/week	1.83 (25) (1.43, 2.42)	1.63 (16) (1.36, 2.28)	−0.08 (−0.53 to 0.38)	−0.10 (−0.73 to 0.53)	0.75
	6x/week	2.06 (23) (1.43, 2.81)	1.86 (12) (1.01, 2.53)	−0.18 (−0.69 to 0.34)		
FT4 (ng/dL)	3x/week	0.98 (25) (0.90, 1.01)	0.92 (16) (0.83, 1.07)	−0.03 (−0.09 to 0.04)	0.08 (−0.02 to 0.17)	0.11
	6x/week	0.94 (23) (0.73, 1.07)	1.04 (12) (0.91, 1.19)	0.05 (−0.02 to 0.12)		
FT3 (pg/mL)	3x/week	2.60 (25) (2.24, 3.09)	2.76 (16) (2.27, 3.13)	−0.16 (−0.52 to 0.20)	0.53 (−0.04 to 1.10)	0.07
	6x/week	2.59 (23) (2.09, 3.07)	2.76 (10) (2.56, 3.26)	0.37 (−0.08 to 0.82)		

*Mixed models for the Daily Trial were adjusted for clinical center.

†CI = confidence interval