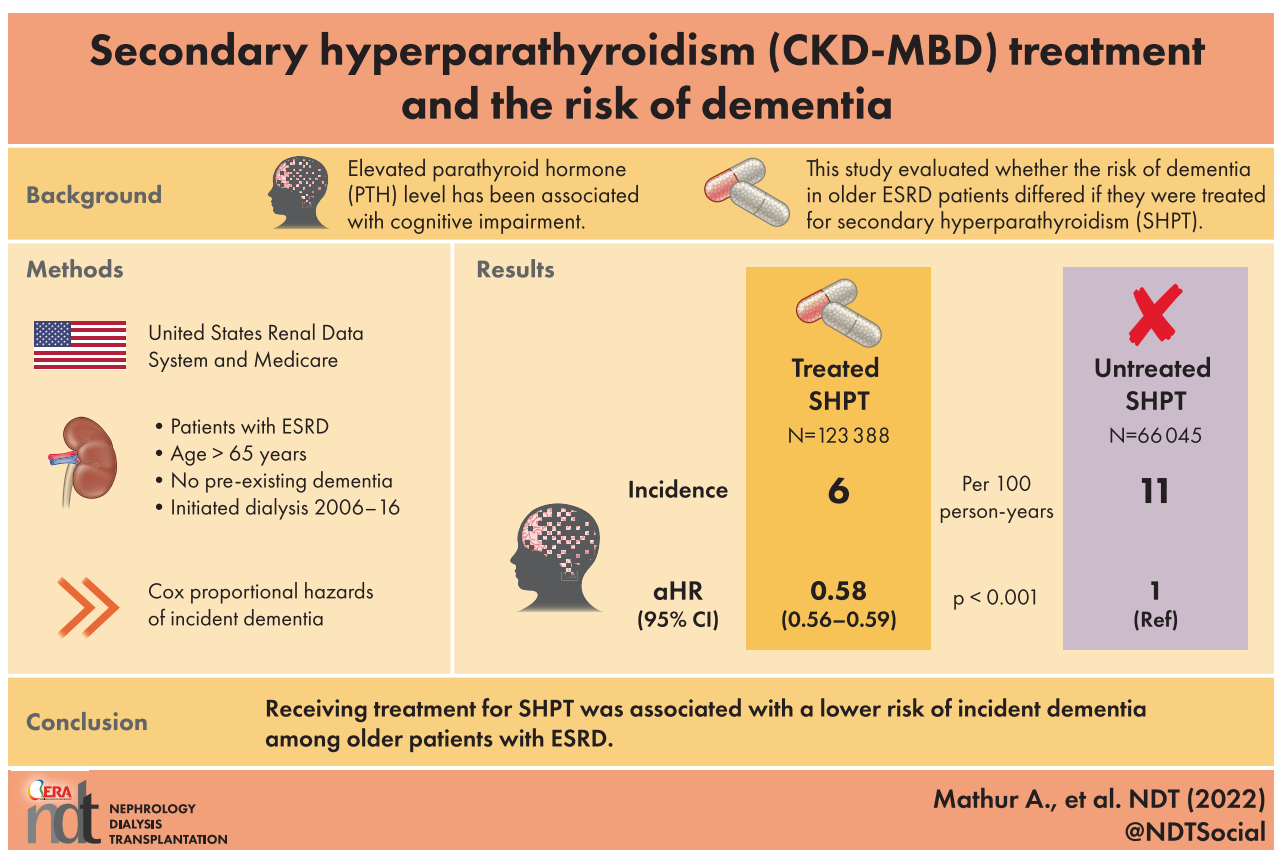# Secondary hyperparathyroidism (CKD-MBD) treatment and the risk of dementia

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GRAPHICAL ABSTRACT

Secondary hyperparathyroidism (CKD-MBD) treatment and the risk of dementia

Background
Elevated parathyroid hormone (PTH) level has been associated with cognitive impairment.

This study evaluated whether the risk of dementia in older ESRD patients differed if they were treated for secondary hyperparathyroidism (SHPT).

Methods
United States Renal Data System and Medicare

- Patients with ESRD
- Age > 65 years
- No pre-existing dementia
- Initiated dialysis 2006–16

Cox proportional hazards of incident dementia

Results

	Treated SHPT N=123 388		Untreated SHPT N=66 045
Incidence	6	Per 100 person-years	11
aHR (95% CI)	0.58 (0.56–0.59)	p < 0.001	1 (Ref)

Conclusion
Receiving treatment for SHPT was associated with a lower risk of incident dementia among older patients with ESRD.

NEPHROLOGY DIALYSIS TRANSPLANTATION

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ABSTRACT

Background. Elevated parathyroid hormone (PTH) levels have been reported as a potential risk factor for cognitive impairment. Compared with the general population, older adults with end-stage renal disease (ESRD) who are frequently affected by secondary hyperparathyroidism (SHPT) are at increased risk of developing dementia. The main objective of our study was to evaluate if the risk of dementia in older (age ≥66 years) ESRD patients differed if they were treated for SHPT.

Methods. Using the United States Renal Data System and Medicare claims, we identified 189 433 older adults without a diagnosis of dementia, who initiated dialysis between 2006 and 2016. SHPT treatment was defined as the use of vitamin D analogs, phosphate binders, calcimimetics or

KEY LEARNING POINTS

What is already known about this subject?

- Secondary hyperparathyroidism (SHPT), characterized by elevated parathyroid hormone levels (PTH), is prevalent among dialysis patients.

What this study adds?

- Elevated PTH has been associated with cognitive impairment.

What impact this may have on practice or policy?

- Our study demonstrates that treatment of SHPT lowers dementia risk, highlighting the additional burden of SHPT, and provides additional support for treatment of SHPT.

parathyroidectomy. We quantified the association between treated SHPT and incident dementia during dialysis using a multivariable Cox proportional hazards model with inverse probability weighting, considering SHPT treatment as a time-varying exposure.

Results. Of 189 433 older ESRD adults, 92% had a claims diagnosis code of SHPT and 123 388 (65%) were treated for SHPT. The rate of incident dementia was 6 cases per 100 person-years among SHPT treated patients compared with 11 cases per 100 person-years among untreated patients. Compared with untreated SHPT patients, the risk of dementia was 42% lower [adjusted hazard ratio (aHR) = 0.58, 95% confidence interval (CI): 0.56–0.59] among SHPT treated patients. The magnitude of the beneficial effect of SHPT treatment differed by sex ($P_{interaction}$ = .02) and race ($P_{interaction} \leq$ .01), with females (aHR = 0.56, 95% CI: 0.54–0.58) and those of Asian (aHR = 0.51, 95% CI: 0.46–0.57) or Black race (aHR = 0.51, 95% CI: 0.48–0.53) having a greatest reduction in dementia risk.

Conclusion. Receiving treatment for SHPT was associated with a lower risk of incident dementia among older patients with ESRD. This work provides additional support for the treatment of SHPT in older ESRD patients.

Keywords: dialysis, elderly, ESRD, hyperparathyroidism, mineral metabolism

INTRODUCTION

Up to 70% of older (age >65 years) patients with end-stage renal disease (ESRD) suffer from cognitive impairment [2–4]. Furthermore, the incidence of dementia and Alzheimer's disease, the most commonly diagnosed types of dementia, begins to rise soon after dialysis initiation and is 10 times higher than the incidence in community-dwelling older adults [5]. Older ESRD patients who develop dementia are at a 1.5-fold higher risk of disability, 2-fold increased risk of hospitalization and a 2-fold higher risk of subsequent mortality [5]. Age, race, sex, diabetes, hemodialysis vintage, prior history of stroke and race have been identified as risk factors for cognitive impairment and dementia among ESRD patients, however, these are difficult to modify [6, 7]. Therefore, the identification of modifiable risk factors for cognitive decline and dementia in older ESRD patients is critical.

Secondary hyperparathyroidism (SHPT), characterized by severely elevated parathyroid hormone levels (PTH), arises from the metabolic abnormalities of ESRD affecting the majority of ESRD patients and represents one such potentially modifiable dementia risk factor. PTH can cross the blood–brain barrier binding to receptors in the brain thereby affecting cognition [8–10]. In patients without ESRD, elevated PTH levels are associated with impaired cognitive function and dementia [11–15].

Further, several single-institution studies have demonstrated improvement in specific cognitive domains after treatment of SHPT [16–18]; such treatments for SHPT include medications like phosphate binders, vitamin D analogs and calcimimetics or surgical parathyroidectomy. Yet, despite the existence of SHPT treatment guidelines, it remains untreated in up to 30%–60% of patients, representing a potential missed opportunity to address one of the central complications of ESRD: cognitive decline and dementia [1, 19, 20]. Furthermore, SHPT disease severity, management and outcomes vary by race [21–23].

Given that PTH impacts cognitive function, we hypothesized that the incidence of dementia would differ between older ESRD patients who were and were not treated for SHPT. Therefore, we sought to: (i) investigate whether SHPT treatment was associated with dementia risk and specifically Alzheimer's disease risk; and (ii) identify subgroups of SHPT patients who would benefit the most from SHPT treatment.

MATERIALS AND METHODS

Study population

Using the United States Renal Data System (USRDS), we identified 597 003 older (aged ≥66 years) ESRD patients who initiated dialysis between 2006 and 2016. We included patients on either hemodialysis or peritoneal dialysis. We restricted the study population to those with Medicare as a primary payer during 1-year pre-ESRD and Medicare Part A, B and D at the time of dialysis initiation (n = 217 444). Among older ESRD patients with Medicare, we further excluded those with a claim for dementia prior to dialysis (n = 23 459) and those without data from CMS-2728 (n = 4552). The final study population included 189 433 patients, assuming all dialysis patients had SHPT because PTH levels begin to rise in stage 3 chronic kidney disease [24–26] (Fig. 1). Although adynamic bone disease (ABD) is increasing in prevalence and unlike SHPT is associated with suppressed PTH, it may represent a
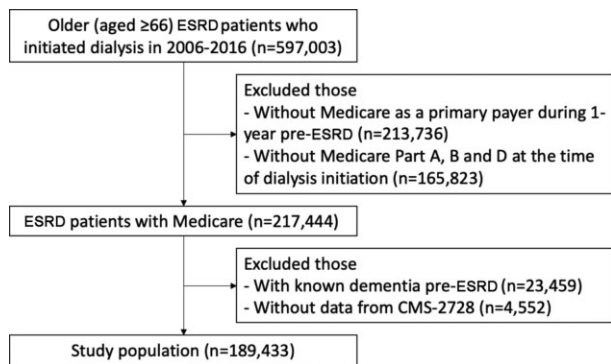
FIGURE 1: Study population was defined to examine the association of secondary hyperparathyroidism treatment during dialysis with incident dementia among older end-stage renal disease patients.

small percentage of our population. We followed the study population until the date of transplantation, end of Medicare coverage, death or administrative censoring (31 December 2016), whichever came first.

SHPT treatment

Treated SHPT was defined as receiving medications including vitamin D analogs (calcitriol, doxercalciferol, paricalcitol, ergocalciferol), phosphate binders (calcium acetate, calcium carbonate sevelamer, lanthanum carbonate, aluminum hydroxide) or cinacalcet, or undergoing surgical parathyroidectomy. These were chosen as treatments because low vitamin D levels and elevated phosphate levels both independently stimulate PTH and can independently lead to hyperparathyroidism even in non-dialysis patients [27, 28]. We did not include additional chronic kidney disease-mineral and bone disorder (CKD-MBD) treatments such as treatment of bone abnormalities. Medication use was obtained using Medicare Part D. Parathyroidectomy was ascertained using International Classification of Diseases 9th Revision (ICD-9), International Classification of Diseases 10th Revision (ICD-10) and Current Procedural Terminology (CPT) codes (Supplementary data, Table S1). We allowed a 30-day gap between the last day of a previous prescription and the first day of a current prescription. For example, a patient who had been prescribed cinacalcet for 30 days on 1 April 2015 and again for 30 days on 30 May 2015 was considered as treated between 1 April 2015 and 29 June 2016. Patients who underwent parathyroidectomy were considered treated since the operation day.

Dementia and Alzheimer's disease diagnoses

Incident dementia and Alzheimer's disease, the most common types of dementia, were defined as diagnosed via claims. Diagnoses were ascertained using a validated ICD-9 and ICD-10 codes using the previously published definitions (Supplementary data, Table S1) [5, 29–32]. Incident dementia and Alzheimer's disease were defined as having at least one inpatient or two outpatient claims during a 1-year period and the earliest date was used as the date of first diagnosis of dementia or Alzheimer's disease [29, 31].

Risk of dementia comparing treated with untreated SHPT patients

To quantify the association between SHPT treatment and incident dementia after dialysis initiation, we used a Cox proportional hazards model which treated the SHPT treatments as time-varying. We assessed the proportional-hazard assumption by using a log-log plot. We adjusted confounding using a propensity score method, designed to deal with confounding by indication in many pharmacoepidemiological studies [33]. First, we used a logistic model to estimate the propensity scores, probabilities of being treated for SHPT conditional on age as a categorical variable (66–69, 70–79, 80+ years), sex, race/ethnicity, employment status, geographic regions, the primary cause of ESRD, dialysis modality, body mass index (BMI) and comorbidities (hypertension, diabetes mellitus, cerebrovascular disease, atherosclerotic heart disease, heart failure, peripheral vascular disease, cancer, functional impairment, alcohol dependence and smoking). Also, a time-varying covariate defined as days of previous medication prescriptions was included in the model to account for the severity of SHPT. Then, in the Cox model, we used weights defined as the inverse of the probability being treated for SHPT for the treated patients and the inverse of the probability of being untreated for SHPT for the untreated patients.

Risk of dementia by type of treatment and in subgroups

We used Cox proportional hazards model to compare the association of incident dementia by type of treatment (medication, parathyroidectomy and no treatment). To estimate the propensity scores, we used a multinomial logistic model including the same covariates included in the model above. Additionally, we performed stratified analyses by age (66–69, 70–79, and 80+ years), sex (female versus male), race (White, Black, Asian and other) and diabetes. We chose to perform these analyses among patients at high risk for cognitive impairment or more severe hyperparathyroidism.

Sensitivity analysis

As the PTH level is not available in the data, we assessed a minimum strength of association of unmeasured confounding by the severity of SHPT. The associations with both the SHPT treatment and incident dementia were calculated on the risk ratio scale conditional on the measured covariates to cancel out the observed association by estimating E-value as follows: $\frac{1}{HR} + sqrt\{\frac{1}{HR} \times (\frac{1}{HR} - 1)\}$ [34, 35]. We additionally performed two sensitivity analyses. We limited our study population to patients who had a diagnosis code of SHPT. We performed another analysis in which we were limited to patients only treated with calcimimetics or parathyroidectomy.

Table 1. Characteristics of older (aged ≥66 years) end-stage renal disease patients by secondary hyperparathyroidism treatment status (n = 189 433)

	Overall	Patients without SHPT treatment (n = 66 045)	Patients with SHPT treatment (n = 123 388)	P-value
Age at diagnosis (years)				<.001
66–69, n (%)	22.4	18.3	24.5	
70–79, n (%)	48.8	46.5	50.1	
80 or older, n (%)	28.8	35.2	25.4	
Female, n (%)	51.0	48.9	52.1	<.001
Race				<.001
White, n (%)	75.2	77.9	73.7	
Black, n (%)	18.8	17.3	19.5	
Asian, n (%)	4.4	3.4	5.0	
Other, n (%)	1.6	1.3	1.8	
Currently employed, n (%)	2.0	1.6	2.3	<.001
Geographic regions				<.001
Northeast, n (%)	18.6	18.1	18.9	
South, n (%)	37.4	37.2	37.6	
Midwest, n (%)	25.7	27.5	24.7	
West, n (%)	18.3	17.2	18.8	
BMI (kg/m^2)				<.001
<25, n (%)	36.0	38.9	34.5	
25–29.9, n (%)	29.8	29.2	30.1	
≥30, n (%)	34.2	31.9	35.4	
Modality—hemodialysis, n (%)	94.2	95.7	93.4	<.001
Primary cause of ESRD				<.001
Diabetes mellitus, n (%)	43.9	40.1	46.0	
Hypertension, n (%)	35.2	35.5	35.0	
Glomerulonephritis, n (%)	5.0	4.3	5.3	
Others, n (%)	15.9	20.1	13.7	
Comorbidity				
Hypertension, n (%)	87.6	85.4	88.8	<.001
Diabetes mellitus, n (%)	55.5	53.1	56.7	<.001
Cerebrovascular disease, n (%)	10.9	12.2	10.2	<.001
Atherosclerotic heart disease, n (%)	25.3	26.1	24.8	<.001
Heart failure, n (%)	39.9	43.5	37.9	<.001
Peripheral vascular disease, n (%)	15.6	16.9	15.0	<.001
Cancer, n (%)	10.5	12.0	9.8	<.001
Functional impairment, n (%)	19.6	25.8	16.2	<.001
Alcohol dependence, n (%)	0.7	1.0	0.6	<.001
Current smoker, n (%)	3.8	3.7	3.9	.13

SHPT, secondary hyperparathyroidism; BMI, body mass index; ESRD, end-stage renal disease.

Statistical analysis

A *P*-value <.05 was considered statistically significant. All analyses were performed using Stata 16.0/MP for Linux (College Station, TX, USA). Missing data were handled using the missing-indicator method.

RESULTS

Study population

Of 189 433 older (age ≥66 years) ESRD adults, the majority of patients were 70–79 years of age, of White race, unemployed and had diabetes as the primary cause of ESRD (Table 1). Approximately half were females. The most common co-morbidities were hypertension followed by diabetes mellitus. The majority of patients lived in the Southern and Mid-Western regions of the USA. Of this entire cohort, 123 388 (65%) were treated for SHPT. Of this cohort, 93.5% were on hemodialysis and 92% had a claims diagnosis code of SHPT. Among SHPT treated patients, 25.4% were aged ≥80

years whereas among SHPT untreated patients, 35.2% were aged ≥80 years. Of the treated group, 16.2% had functional impairment whereas 25.8% of the untreated group had functional impairment. Otherwise, the treated and untreated groups were similar (Table 1).

Risk of dementia by SHPT treatment

The incident rate of dementia was 6 cases per 100 person-years among SHPT treated patients compared with 11 cases per 100 person-years in untreated patients (Table 2). The median time to dementia diagnosis was 8.6 years [95% confidence interval (CI): 8.5–8.9 years]. Over the study period, 16.5% (n = 136 858) of untreated SHPT patients were diagnosed with dementia, compared with 17.4% (n = 52 575) among those with treated SHPT. Compared with untreated SHPT patients, the risk of dementia was 42% lower [adjusted hazard ratio (aHR) = 0.58, 95% CI: 0.56–0.59] in SHPT treated patients after adjusting for age, sex, race/ethnicity, employment status, geographic region, BMI, dialysis modality

Table 2. Risk of incident dementia in older ESRD patients with secondary hyperparathyroidism (SHPT) comparing those who received treatment during dialysis in our study cohort (A) or only in patients with a diagnosis code of SHPT (B) with those who did not receive treatment, and also comparing treatment by parathyroidectomy compared with cinacalcet (C). Adjusted hazard ratio (aHR) and 95% confidence interval (CI) is reported

SHPT treatment	Incident rate (cases/100 person-years)	Risk of incident dementia [aHR (95% CI)][a]
A. Entire cohort		
No	11	Reference
Yes	6	0.58 (0.56–0.59)
B. Restricted only to patients with claims diagnosis of SHPT		
No	10	Reference
Yes	6	0.63 (0.62–0.65)
C. Restricted only to patients receiving either treatment		
Cinacalcet	7.3	Reference
Parathyroidectomy	6.2	0.91 (0.66–1.26)

[a]Adjusted for age at diagnosis sex, race/ethnicity, employment, geographic region, body mass index, dialysis modality type, primary cause of end-stage renal disease, comorbidities (hypertension, diabetes mellitus, cerebrovascular disease, atherosclerotic heart disease, heart failure, peripheral vascular disease, cancer, functional impairment, alcohol dependence and smoking) and days of previous medication prescription.

Table 3. The impact of secondary hyperparathyroidism treatment on incident dementia stratified by age, sex, race and diabetes status compared with no treatment. Hazard ratios were adjusted for age at diagnosis, sex, race/ethnicity, employment, geographic region, body mass index, dialysis modality type, primary cause of end-stage renal disease, comorbidities (hypertension, diabetes mellitus, cerebrovascular disease, atherosclerotic heart disease, heart failure, peripheral vascular disease, cancer, functional impairment, alcohol dependence and smoking) and days of previous medication prescriptions

Effect modifier	Incident dementia [aHR (95% CI)]			
Age	66–69	70–79	≥80	
No treatment	Ref	Ref	Ref	
Treatment	0.58 (0.54–0.61)	0.58 (0.56–0.60)	0.60 (0.57–0.62)	
$P_{interaction}$		.93	.45	
Sex	Male	Female		
No treatment	Ref			
Treatment	0.60 (0.57–0.62)	0.56 (0.54–0.58)		
$P_{interaction}$		.01		
Race	White	Black	Asian	Other
No treatment	Ref	Ref	Ref	Ref
Treatment	0.61 (0.59–0.62)	0.50 (0.48–0.53)	0.51 (0.46–0.57)	0.62 (0.50–0.75)
$P_{interaction}$		<.001	.01	.86
Diabetes	No	Yes		
No treatment	Ref	Ref		
Treatment	0.59 (0.56–0.61)	0.57 (0.55–0.59)		
$P_{interaction}$		.34		

type, the primary cause of ESRD, days of previous medication prescription and comorbidities (hypertension, diabetes mellitus, cerebrovascular disease, atherosclerotic heart disease, heart failure, peripheral vascular disease, cancer, functional impairment, alcohol dependence and smoking) (Table 2A).

Risk of dementia by treatment in subgroups

The magnitude of the beneficial effect of SHPT treatment differed by sex ($P_{interaction}$ = .01) and race ($P_{interaction}$ ≤.01), but not by age or diabetic status (Table 3). Among female patients, SHPT treatment was associated with a 44% reduction in incident dementia risk (aHR = 0.56, 95% CI: 0.54–0.58) compared with a 40% (aHR = 0.60, 95% CI: 0.57–0.62) reduction in males. Among patients of Asian race, SHPT treatment was associated with a 49% reduction (aHR = 0.51, 95% CI: 0.46–0.57) and among those of Black race treatment was associated with a 50% reduction (aHR = 0.50, 95% CI: 0.48–0.53) in dementia risk. Among patients of White race, SHPT treatment was associated with a 39% reduction in dementia risk (aHR = 0.61, 95% CI: 0.59–0.62).

Risk of dementia by type of treatment

The incident rate of dementia was 6 cases per 100 person-years in medically treated patients and 5 cases per 100 person-years in surgically treated patients who underwent parathyroidectomy. When comparing parathyroidectomy with medical treatment, there was no difference in the risk of dementia (aHR = 1.12, 95% CI: 0.75–1.67).

Risk of Alzheimer's disease by treatment

The incident rate of Alzheimer's disease was 1 case per 100 person-years in SHPT treated patients compared with 2 cases per 100 person-years in SHPT untreated patients. After adjusting for confounders, the risk of Alzheimer's disease was 33% lower (aHR = 0.67, 95% CI: 0.64–0.71) in SHPT treated patients compared with SHPT untreated patients (Table 4).

Sensitivity analysis

The risk of incident dementia in treated patients was 0.58 (95% CI: 0.56–0.59) times lower than in untreated

Table 4. Risk of Alzheimer's disease in older end-stage renal patients with secondary hyperparathyroidism (SHPT) comparing those who received treatment during dialysis with those who did not receive treatment. Adjusted hazard ratio (aHR) and 95% confidence interval (CI) is reported

SHPT treatment	Incident rate (cases/100 person-year)	Risk of Alzheimer's disease [aHR (95% CI)]
No	2	Reference
Yes	1	0.67 (0.63–0.70)

[a]Adjusted for age at diagnosis sex, race/ethnicity, employment, geographic region, body mass index, dialysis modality type, primary cause of end-stage renal disease, comorbidities (hypertension, diabetes mellitus, cerebrovascular disease, atherosclerotic heart disease, heart failure, peripheral vascular disease, cancer, functional impairment, alcohol dependence and smoking) and days of previous medication prescription.

patients and E-value was 2.84 for the estimate and 2.78 for the CI, which seems moderately robust. To explain away the observed association, a risk ratio of 2.84 between an unmeasured confounder and each of SHPT treatment and dementia conditional on the measured covariates is needed. An association between an unmeasured confounder and each of SHPT treatment and dementia would require a risk ratio of 2.78 each to make the CI cross 1. We performed two additional sensitivity analyses. If we limited our study population to those with a diagnosis code of secondary hyperparathyroidism only (n = 162 861), the incident rate of dementia was 10 cases per 100 person-years in untreated SHPT patients and 6 cases per 100 person-years in treated patients (Table 2B). Compared with untreated SHPT patients, the risk of dementia was 36% lower (aHR = 0.63, 95% CI: 0.62–0.65) in treated patients. If we restricted the study population to patients who received cinacalcet or parathyroidectomy after dialysis initiation (n = 25 018), there was no difference in risk of incident dementia between the two treatments (Table 2C).

DISCUSSION

In this national study of 189 433 dementia-free Medicare beneficiaries on dialysis for at least 1 year, patients who were treated for SHPT had a 42% lower risk of incident dementia and a 37% lower risk of Alzheimer's disease compared with those who were not treated. Among SHPT treated patients, females, patients of Black or Asian race, had the lowest risk of dementia with treatment. There was no difference in dementia risk in patients who were treated medically compared with surgically.

Prior studies have demonstrated that in the general adult population, the prevalence of dementia is ~5%, primarily occurring in older adults [36]. In contrast, in patients with ESRD, 10% of younger patients develop dementia and up to 16% of older patients develop dementia [2, 5]. A total of 12 modifiable risk factors have been identified, accounting for 40% of all dementias [37]. However, in older patients, with ESRD, a state of end-organ damage, majority of these either cannot be modified or even if addressed, will not impact dementia risk. For example, medications to control blood pressure do not mitigate vascular dementia among

ESRD patients [38]. However, high PTH which occurs in SHPT affects nearly all ESRD patients, has been associated with cognitive impairment, is treatable, and may represent a modifiable risk factor for incident dementia.

The existing literature demonstrates a mixed relationship between SHPT and cognitive impairment. Previous cross-sectional studies in SHPT patients demonstrate impairments inconsistently across various cognitive domains of executive function, memory, attention or global cognitive function [17, 39–43]. Increasing SHPT disease severity, characterized by higher PTH levels, has also been associated with greater gray matter volume on magnetic resonance imaging and worse scores on the Montreal Cognitive Assessment (MoCA), indicative of global cognitive function [8]. Two previous studies noted an association between PTH and Alzheimer's disease using two different definitions of the disease [11, 12]. In contrast, another study did not find an association between PTH and Alzheimer's disease but rather with developing vascular dementia [14]. A study by Chou and colleagues demonstrated improved global cognitive function and dementia rating scores following surgical treatment of SHPT [16]. However, thus far, no study has evaluated whether the risk of incident dementia differs by treated or untreated SHPT. Our study demonstrated a significant reduction in both incident dementia and Alzheimer's disease with SHPT treatment, suggesting a link between high PTH levels and cognitive impairment.

Prior studies have also identified risk factors for incident dementia specifically in ESRD patients including older age at hemodialysis initiation, underweight BMI, patients with diabetes, those with a history of transient ischemic attack or stroke, or those who were institutionalized [5]. Interestingly, we did not find that the benefit of SHPT treatment differed by age or diabetic status.

Our study also found that up to 35% of older ESRD patients with SHPT are not treated. While this may reflect disease severity or temporal shifts in the treatment landscape or practice patterns, it may also reflect a lack of consensus exists regarding optimal SHPT treatment regimens resulting in significant treatment variation. Despite recommended treatment targets by organizations such as the Kidney Disease Outcomes Quality Initiative (KDOQI) and the Kidney Disease: Improving Global Outcomes (KDIGO), studies have demonstrated that PTH levels in the United States are rising [1, 19, 44]. The percentage of dialysis facilities reporting PTH levels <300 pg/mL declined from 82% in 2010 to 22% in 2014, whereas the percentage of dialysis facilities reporting PTH upper target of ≥600 pg/mL increased from 7% in 2010 to 62% in 2014 [44]. Surgical parathyroidectomy is ultimately required in 15% of dialysis patients at 10 years and in 38% at 20 years [45]. In our study, both medical and surgical treatments had a lower risk of incident dementia. Furthermore, we noted that the risk of incident dementia was comparable between medically treated and surgically treated patients. If we restricted our study population to patients who only received cinacalcet or parathyroidectomy after dialysis initiation, there was no significant difference in risk of incident dementia between the two treatments as shown by the hazard ratio crossing the reference line.

Our study has several limitations including those associated with large retrospective databases such as missing values, coding errors, confounding by indication and selection bias. The retrospective design of the study is a major limitation. Additionally, Medicare is not necessarily the primary payor for all older patients on hemodialysis in the USA, and therefore our results may not be entirely generalizable to all older dialysis patients. However, Medicare is the single largest insurer for older ESRD patients, and therefore this inclusion criterion is frequently used to study this population of patients [46]. Another potential limitation is that some patients may have received over-the-counter medications or medications that were bundled with a dialysis payment that were not captured. A major limitation of our study is the lack of PTH levels, serum calcium, phosphate and alkaline phosphatase, which were not available due to limitations of the datasets and could render uncertainty about the diagnosis. However, because PTH levels begin to rise in stage 3 CKD, nearly all dialysis patients have elevated PTH levels [24–26]. In our study population, 92% had a diagnosis code for SHPT. It was also difficult to measure and factor into the analyses SHPT disease severity, appropriateness of no treatment, adherence to medications or determining if surgical parathyroidectomy was performed appropriately (addressing all four parathyroid glands). It was also difficult to determine who would be overtreated for SHPT and have low PTH levels, a risk factor for ABD. Although we wanted to focus our study on patients with elevated PTH which is typical of SHPT, we did examine risk factors for ABD including dialysis modality, drug-induced osteoporosis and those that were prescribed bisphosphonates. Of the study population, 3.2% had at least one inpatient or outpatient claim of drug-induced osteoporosis within 1 year since ESRD diagnosis and 2.0% were ever prescribed bisphosphonates during the study follow-up (1.3% within 1 year since ESRD diagnosis). Based on this, the minority of our study population may have had ABD, but without a histopathologic diagnosis, we are unable to know the exact number. However, our findings have built upon existing literature and demonstrate an association between SHPT and incident dementia, identify subgroups who have the greatest beneficial effects of treatment, and emphasize the need for SHPT treatment in older patients with ESRD.

As the prevalence of older patients on dialysis grows and the risk of incident dementia rises, it is critical to understand potentially modifiable risk factors. Our work demonstrates that patients who are treated for SHPT have a significantly lower risk of developing dementia. These findings should be incorporated into shared treatment decision-making and encourage treatment for SHPT to reduce the risk of incident dementia.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

CONFLICT OF INTEREST STATEMENT

No authors report a conflict of interest relevant to this research. D.L.S. reports personal fees from Sanofi-Aventis and Novartis outside the submitted work. The results presented in this article have not been published previously in whole or part, except in abstract format. No authors have any disclosures or conflicts to report.

(See related article by Magagnoli, Galassi and Cozzolino. Beyond vessels and bones: can CKD-MBD treatment improve uraemic subjects' minds? *Nephrol Dial Transplant* 2022; 37: 2039–2041)

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