Thyroid Function in Patients with Cystic Fibrosis: No Longer a Concern?

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Background: Development of goiter and hypothyroidism has been reported in patients with cystic fibrosis (CF) since the 1970s, especially when treated with iodine-based expectorants. With iodine-containing expectorants no longer in routine use, the prevalence of thyroid dysfunction in CF patients is unknown. This cross-sectional study assessed thyroid function status in a large cohort of CF patients.

Methods: Sera from ambulatory subjects were obtained from an Institutional Review Board (IRB)-approved biorepository of patients seen at the Emory CF Center between January 1, 2011, and December 31, 2014. Sera from hospitalized subjects were obtained from banked specimens from an IRB-approved inpatient clinical trial. Demographics, forced expiratory volume in one second (FEV1), and medication use were assessed from medical records. Thyroid function tests were measured from the stored sera. Multivariate regression models assessed associations between covariates and thyrotropin (TSH), free thyroxine (fT4), and thyroid dysfunction risk.

Results: A total of 89 subjects (54% male, 91% white, $M_{\text{age}} = 24.4$ years, median FEV1 63%) were included in the analyses. One subject was on thyroid hormone replacement, 93% were on pancreatic enzyme replacement, and 68% received antibiotics within six months. None had computed tomography scans with intravenous contrast within six months. One patient had positive thyroid peroxidase (TPO) antibodies. Of the 87 subjects with measured TSH values, seven (8%) had abnormal levels (range 0.2–7.6 $\mu\text{IU/mL}$; one overt, four subclinical hypothyroidism, and two subclinical hyperthyroidism). Of the 56 subjects with measured fT4 values, 19 (34%) had slightly low levels (range 0.49–0.79 ng/dL; 17 isolated mild hypothyroxinemia). A positive correlation between age and body mass index (BMI; $p < 0.001$) and a negative correlation between age and FEV1 ($p = 0.041$) were seen. Age, sex, race/ethnicity, BMI, FEV1, hospitalization status, use of pancreatic enzyme or thyroid hormone replacement, recent antibiotic use, and TPO antibody positivity were not predictive of TSH, fT4, or thyroid dysfunction risk. Stratified analyses by hospitalization did not predict TSH or fT4.

Conclusions: Although 24 (27%) of the patients had abnormal serum thyroid function tests, overt thyroid dysfunction was rare in this cohort of 89 patients with CF. The degree of hypothyroxinemia was marginal, likely due to non-thyroidal illness. There were no significant predictors of thyroid dysfunction.

Introduction

CYSTIC FIBROSIS TRANSMEMBRANE conductance regulator (CFTR), a protein defective in cystic fibrosis (CF), has been found in human thyroid epithelium (1). Development of goiter and hypothyroidism has been reported in CF patients since the 1970s, especially when patients with CF were treated with iodine-based expectorant (2). The findings by Dolan *et al.* (2) have been replicated by Azizi *et al.* (3), and showed that 44% of CF patients given high-dose iodine developed goiter, and 83% of those developed hypothyroidism. This development of iodine-related goiter or hypothyroidism

may be due to failure to escape from the acute Wolff-Chaikoff effect (4), and was hypothesized to be related to potential underlying abnormalities in the thyroid gland. However, the mechanism for the development of hypothyroidism in these patients with CF has not been clear. Segall-Blank *et al.* showed intact intrathyroidal organification and normal serum thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) (5), while a study by De Luca *et al.* showed exaggerated TSH responses to TRH in CF patients (6). The lower total triiodothyronine (T3) levels seen in CF patients in the studies by Azizi *et al.* and Segall-Blank *et al.* were thought to be likely related to nonthyroidal illness with

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impaired thyroxine (T4) to T3 conversion, as CF patients frequently had height and weight below normal and suffered from intermittent illnesses (3,5).

In the CF patients with evidence of undernutrition, selenium deficiency may also have played a role in the decreased total T3 levels, as inefficient thyroid hormone synthesis and metabolism in relation to inadequate hepatic deiodinase activity have been suggested in selenium deficiency (7). On the other hand, Deluca *et al.* and Sack *et al.* found no significant difference in serum T3 levels between CF patients and age- and sex-matched controls (6,8). Sack *et al.* found an isolated increase in reverse T3 (rT3) in CF patients compared to controls, which was hypothesized to be related to acute hypoxia, as they found no correlation to total T3 levels, weight percentile, or severity of the disease (8).

One of the proposed mechanisms for the development of hypothyroidism in CF patients is altered ion transport in thyroid epithelium, as seen in CFTR-deficient pigs. In this knockout animal model, there were no changes in thyroid histology, growth pattern, or sodium-iodide symporter expression, but there was diminished cAMP-activated chloride secretion, an ion that may act as a counter-ion for iodine accumulation, leading to disruption of iodine accumulation in the thyroid (9). A more recent study by Naehrlich *et al.* found a high prevalence (83.7%) of iodine deficiency in patients with CF in northern Germany, which may be a contributing factor for hypothyroidism in CF (10).

With iodine-containing expectorant no longer in routine use, the prevalence of thyroid dysfunction in CF patients is now unknown (11). A recent small study by Volta *et al.* showed that there was no significant thyroid dysfunction observed in 17 CF patients compared to controls, and concluded that this may be related to improved nutritional status and lack of iodine-containing medication use (12). The present study aimed to assess thyroid function status in both ambulatory and hospitalized CF patients in a larger cohort.

Methods

A cross-sectional study was conducted to assess serum thyroid function in 89 patients with CF seen at the Emory CF Center between January 1, 2011, and December 31, 2014. Institutional Review Board (IRB) approval for the study was obtained from Emory University School of Medicine where patient information and serum samples were collected.

Study subjects and measures

Serum samples from 54 stable outpatient subjects with CF were obtained from an IRB-approved biorepository of patients seen at the Emory CF Center. Serum samples from 35 hospitalized subjects were obtained from banked specimens from an IRB-approved inpatient clinical trial involving patients with CF. TSH, free thyroxine (fT4), and thyroid peroxidase (TPO) antibody titers were measured from the stored sera. Information including age, sex, race/ethnicity, height, weight, forced expiratory volume in one second (FEV1) within six months, use of thyroid hormone or pancreatic enzyme replacement therapy, antibiotic use within six months, and computed tomography (CT) scans within six months were collected from medical records. Body mass index (BMI) was calculated using the following equation: body weight in kilograms/height in meters². FEV1 and use of pancreatic

enzyme supplements were used as surrogate markers of severity of disease.

Laboratory methods

Laboratory measurements of serum thyroid function were performed at the Boston University Iodine, Perchlorate, and Thyroid Function Test Research Laboratory. Sera were stored at -80°C until measurements were taken. Serum TSH, fT4, and TPO antibody levels were measured by enzyme-linked immunosorbent assay (ELISA; Calbiotech, Spring Valley, CA). The inter assay coefficient of variation (CV) for these measurements are <5%. The reference ranges for the assays are: TSH 0.4–4.2 mIU/L and fT4 0.8–2.0 ng/dL. The TPO antibody limit of detection was 5 IU/mL, and levels >75 IU/mL were considered positive.

Statistical analyses

Descriptive statistics are reported as mean ± standard deviation (SD) or median (range). Demographics are reported in frequency. To compare the differences between hospitalized and ambulatory patients, a two-sample *t*-test was used for continuous variables and a chi-square test was used for categorical variables. Spearman correlation was used to assess univariate correlations between continuous covariates, including age, BMI, FEV1, TSH, and fT4.

Multivariate linear regression models were used to predict TSH and fT4. The potential predictors assessed included age, sex, race/ethnicity, BMI, FEV1, hospitalization status, use of thyroid hormone replacement, use of pancreatic enzyme replacement therapy, recent antibiotic use, TPO antibody positivity, and fT4 for prediction of TSH and TSH for prediction of fT4. Stratified analyses by hospitalization for prediction of TSH or fT4 were also performed. A multivariate logistic regression model was used to predict the presence of thyroid dysfunction. The potential predictors assessed included age, sex, race/ethnicity, BMI, FEV1, hospitalization status, use of thyroid hormone replacement, use of pancreatic enzyme replacement, recent antibiotic use, and TPO antibody positivity. CT scans within six months of serum collection were not used as a potential predictor in the analyses, as no subjects received intravenous iodine-based radiographic contrast with CT scans.

Statistical analyses were performed using SAS v9.3 (SAS Institute, Cary, NC), and results were considered statistically significant if the two-tailed *p*-value was <0.05.

Results

Demographic characteristics of the 89 study subjects and comparison between hospitalized and ambulatory subjects are presented in Table 1. The median FEV1 was lower in hospitalized subjects compared with ambulatory subjects, suggestive of increased severity of disease in hospitalized subjects. All hospitalized subjects had antibiotic use within six months of serum sample collection, while 47.2% of ambulatory subjects had recent antibiotic use. None of the subjects who received antibiotics received doxycycline, a tetracycline antibiotic known to cause black deposition in the thyroid gland (13). Other demographic characteristics were similar between the two groups.

The available serum thyroid function and TPO antibody status, as well as frequency of abnormal serum TSH or fT4

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND COMPARISON OF HOSPITALIZED VERSUS AMBULATORY SUBJECTS

	All (n = 89)	Hospitalized (n = 35; 39.3%)	Ambulatory (n = 54; 60.7%)	p-Value (hospitalized vs. ambulatory)
Age, years	24.4 ± 11.2	26.7 ± 6.6	22.9 ± 13.2	0.16
BMI, kg/m ² (n = 88)	20.3 ± 3.8	19.8 ± 3.2	20.5 ± 4.2	0.51
FEV1, % (n = 79)	63 (6–134)	45 (14–114)	71 (6–134)	<0.001*
Sex				
Male	48 (53.9%)	18 (51.4%)	30 (55.6%)	0.70
Female	41 (46.1%)	17 (48.6%)	24 (44.4%)	
Race/ethnicity				
White	81 (91%)	32 (91.4%)	49 (90.7%)	1.00
African American	8 (9%)	3 (8.6%)	5 (9.3%)	
Thyroid hormone replacement				
No	88 (98.9%)	35 (100%)	53 (98.1%)	1.00
Yes	1 (1.1%)	0 (0%)	1 (1.9%)	
Pancreatic enzyme replacement (n = 88)				
No	6 (6.8%)	0 (0%)	6 (11.1%)	0.08
Yes	82 (93.2%)	34 (100%)	48 (88.9%)	
Recent antibiotic use (n = 88)				
No	28 (31.8%)	0 (0%)	28 (52.8%)	<0.001*
Yes	60 (68.2%)	35 (100%)	25 (47.2%)	

Data are shown as $M \pm SD$, median (range), or frequency (%).

* $p < 0.05$.

BMI, body mass index; FEV1, forced expiratory volume in one second.

values, are presented in Table 2. Comparison of the hospitalized and ambulatory subjects show no statistically significant differences in median TSH and fT4, and the frequency of abnormal TSH, fT4, and positive TPO antibodies between the two groups. Of the 24 subjects who had abnormal serum thyroid function tests, 17 had slightly low fT4 levels with normal TSH levels (fT4 range 0.66–0.79 ng/dL), two slightly elevated TSH with normal fT4 levels (TSH 4.4 mIU/L with fT4 0.81 ng/dL, and TSH 5.3 mIU/L with fT4 0.96 ng/dL), one slightly elevated TSH with low fT4 levels (TSH 6.8 mIU/L, fT4 0.49 ng/dL), and two isolated mildly elevated TSH (TSH 4.7 and 7.6 mIU/L; no fT4 levels available). One subject had a mildly suppressed TSH and normal fT4 levels (TSH 0.3 mIU/L, fT4 1.75 ng/dL), and one had a lower serum TSH with slightly low fT4 levels (TSH 0.2 mIU/L,

fT4 0.77 ng/dL). The full details of serum thyroid function measurements are presented in Appendix 1.

There was a significant moderate positive correlation between age and BMI, suggesting an increase in BMI with increasing age ($r = 0.406$; $p < 0.001$). There was also a significant weak negative correlation between age and FEV1, suggesting decrease in FEV1 with increasing age ($r = -0.231$; $p = 0.041$). There were no significant correlations between age, BMI, FEV1, and TSH or fT4, or between BMI and FEV1.

There were no significant predictors of TSH ($p = 0.63$), fT4 ($p = 0.095$), or development of thyroid dysfunction ($p = 0.39$). When multivariate analyses were repeated separately for hospitalized and ambulatory patients, there were no significant predictors of TSH or fT4 (data not shown).

TABLE 2. SERUM THYROID FUNCTION AND FREQUENCY OF THYROID DYSFUNCTION WITH COMPARISON OF HOSPITALIZED VERSUS AMBULATORY SUBJECTS

	All	Hospitalized	Ambulatory	p-Value (hospitalized vs. ambulatory)
TSH, μ IU/mL (n = 87)	1.5 (0.2–7.6)	1.3 (0.2–6.8)	1.6 (0.5–7.6)	0.12
fT4, ng/dL (n = 56)	0.84 (0.49–1.97)	0.84 (0.49–1.97)	0.83 (0.69–1.88)	0.71
Positive TPO antibody (n = 56)				
Negative	55 (98.2%)	35 (100%)	20 (95.2%)	0.38
Positive	1 (1.8%)	0 (0%)	1 (4.8%)	
Abnormal TSH (n = 87)				
No	80 (92%)	30 (88.2%)	50 (94.3%)	0.42
Yes	7 (8%)	4 (11.8%)	3 (5.7%)	
Abnormal fT4 (n = 56)				
No	37 (66.1%)	22 (62.9%)	15 (71.4%)	0.52
Yes	19 (33.9%)	13 (37.1%)	6 (28.6%)	

Data are shown as median (range) or frequency (%).

TSH, thyrotropin; fT4, free thyroxine; TPO, thyroid peroxidase.

Discussion

Although development of goiter and hypothyroidism in patients with CF has been described since the 1970s, especially in the setting of excess iodine exposure (2,3), a recent study of 17 patients reported no significant thyroid dysfunction in patients with CF (12). Studies to determine the potential mechanism of thyroid dysfunction in patients with CF have reported conflicting results. As iodine-containing expectorants are no longer in routine use, it was hypothesized that goiter and hypothyroidism previously described in patients with CF were due to excess iodine exposure and subsequent failure to escape from the Wolff–Chaikoff effect, rather than intrinsic dysfunction of the thyroid directly caused by CF. In this study of CF patients with varying disease severity as assessed by FEV1, no subjects had recent excess iodine exposure, and significant overt thyroid dysfunction was not observed. Only one patient had mildly positive TPO antibodies, suggesting a low prevalence of concurrent autoimmune thyroid disease in this patient population. Although 27% of subjects developed abnormal serum thyroid function tests, the degree of abnormality was marginal. The mild abnormal thyroid function tests are likely from nonthyroidal illness, given the chronic disease state of these patients, although FEV1 did not predict development of thyroid dysfunction in the multivariate analysis. With improvement of nutritional status in patients with CF in recent years, as evidenced by normal mean BMI in the cohort, nutritional deficiencies such as selenium or iodine deficiency leading to hypothyroidism is likely less prevalent compared with in the past.

This study is the largest study assessing thyroid function in patients with CF. Serum thyroid function and thyroid antibody status were measured for concurrent autoimmune thyroid disease assessment. Several measures of disease severity were also obtained, such as FEV1, BMI, pancreatic enzyme replacement, or recent antibiotic use. One limitation of the study is that it was not possible to assess iodine status in the patients. A high prevalence of iodine deficiency has been reported in CF patients in Germany (10). Although the median urinary iodine levels in the U.S. population are adequate (14), the iodine status of the CF patients in this population is not known. If iodine deficiency is more prevalent in these patients, it may be one of the factors leading to mild thyroid dysfunction.

In conclusion, overt thyroid dysfunction was rare in this cohort of 89 patients with CF. Although 24 (27%) of patients had abnormal serum thyroid function tests with 19 (34%) of the measured serum fT4 levels being abnormal, the vast majority of those abnormal tests were mild. With iodine-containing expectorant no longer in routine use, mild thyroid dysfunction seen in this cohort is likely related to nonthyroidal illness, rather than intrinsic thyroid dysfunction.

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Author Disclosure Statement

The authors report no conflict of interest.

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(Appendix follows →)

APPENDIX TABLE 1. SERUM THYROID FUNCTION MEASUREMENTS OF ALL SUBJECTS

<i>TSH (mIU/L)</i>	<i>fT4 (ng/dL)</i>	<i>TPO antibody</i>
0.2	0.77	Negative
0.3	1.75	Negative
0.4	0.83	Negative
0.5	0.99	Negative
0.5	0.77	Negative
0.5	N/A	N/A
0.6	0.83	Negative
0.6	0.97	Negative
0.6	0.87	Negative
0.6	0.76	Negative
0.6	0.97	Negative
0.7	1.6	Negative
0.7	0.81	Negative
0.7	N/A	N/A
0.7	N/A	N/A
0.7	N/A	N/A
0.8	0.8	Negative
0.9	0.79	Negative
1.0	N/A	N/A
1.0	0.89	Negative
1.0	0.84	Negative
1.0	1.31	Negative
1.0	0.83	Negative
1.0	0.74	Negative
1.0	N/A	N/A
1.1	0.76	Negative
1.1	1.33	Negative
1.1	0.73	Negative
1.1	0.91	Negative
1.1	N/A	N/A
1.2	1.34	Negative
1.2	0.85	Negative
1.2	N/A	N/A
1.2	N/A	N/A
1.2	N/A	N/A
1.2	N/A	N/A
1.3	N/A	N/A
1.3	N/A	N/A
1.3	N/A	N/A
1.4	0.84	Negative
1.4	0.85	Negative
1.4	N/A	N/A
1.4	N/A	N/A
1.4	N/A	N/A
1.5	N/A	N/A
1.5	N/A	N/A
1.6	0.71	Negative
1.6	0.86	Negative
1.6	N/A	N/A
1.7	N/A	N/A
1.7	N/A	N/A
1.8	0.65	Negative
1.8	1.05	Negative
1.9	N/A	N/A
2.0	0.87	Negative
2.0	0.73	Negative
2.0	0.7	Negative
2.0	0.69	Negative
2.1	0.66	Negative
2.1	0.99	Negative
2.1	1.02	Negative
2.2	0.76	Negative

(continued)

APPENDIX TABLE 1. (CONTINUED)

<i>TSH (mIU/L)</i>	<i>fT4 (ng/dL)</i>	<i>TPO antibody</i>
2.2	1.88	Negative
2.2	N/A	N/A
2.3	N/A	N/A
2.3	N/A	N/A
2.4	0.78	Negative
2.5	0.66	Negative
2.5	0.81	Negative
2.6	0.83	Negative
2.6	1.06	Negative
2.6	N/A	N/A
2.8	0.8	Negative
2.9	0.99	Negative
3.0	0.88	Negative
3.0	0.73	Negative
3.1	0.86	Negative
3.2	N/A	N/A
3.2	N/A	N/A
3.3	0.97	Positive
3.3	N/A	N/A
3.8	0.72	Negative
3.8	N/A	N/A
4.4	0.81	Negative
4.7	N/A	N/A
5.3	0.96	Negative
6.8	0.49	Negative
7.6	N/A	N/A
N/A	1.97	Negative
N/A	N/A	N/A

TSH, thyrotropin; fT4, free thyroxine; TPO, thyroid peroxidase.