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Abstract

Objectives: Hypothyroidism adversely affects pulmonary function, which may improve by thyroxine therapy. Limited studies about the effect of hypothyroidism on spirometric parameters in adult patients were conducted in Basra, south of Iraq. Moreover, the effect of thyroxine therapy on spirometric parameters was not covered by these studies. In this study, pulmonary function in adult's hypothyroid patients was evaluated by spirometry to detect any impairment, type of impairment, and to evaluate the effect of thyroxine therapy.

Methods: A comparative study was conducted in Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) in Al-Faiha teaching hospital, Basrah, Iraq. Subjects are divided into four groups: uncontrolled hypothyroid group (n=72), controlled hypothyroid group (n=60), newly diagnosed hypothyroid group (n=52), and control group (n=110). Spirometry was done to all subjects in sitting position, it's repeated at least three times and the best result was recorded.

Results: A significantly ($p<0.05$) less spirometric parameters and more abnormal pulmonary function test (PFT) were noticed in hypothyroid groups, the reduction were more pronounced in the uncontrolled hypothyroid group. The abnormality in PFT was mostly of restrictive type. A significantly ($p<0.05$) negative correlation has been found between thyroid-stimulating hormone (TSH) and spirometric parameters, while the correlation of fT4 is significantly ($p<0.05$) positive with FVC% and FEV%.

Conclusion: In hypothyroidism, high TSH and low fT4 are recognized causes of a reduction in spirometric parameters. Therefore, spirometry can be used to detect pulmonary function changes in hypothyroidism.

Keywords: adult hypothyroidism; Basrah; spirometry.

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Introduction

Hypothyroidism is a common endocrine disorder resulting from a deficiency of thyroid hormone secretion. It's mostly caused by autoimmunity or dietary iodine deficiency [1, 2]. The prevalence of hypothyroidism is affected by many factors such as age, gender, and geographical area of the population [3]. The clinical manifestations of hypothyroidism include dry skin, cold intolerance, increased body weight, constipation, hair loss, dyspnea, hoarseness of voice, coarse puffy appearance, fatigue, bradycardia, diastolic hypertension, goiter, hypothermia, and menstrual disturbance in female [4–6]. The respiratory system is commonly affected by disorders of thyroid gland function [7], the respiratory problems in hypothyroidism range from mild dyspnea to life-threatening complications such as a respiratory system failure. Dyspnea resulted from hypoventilation, decreased respiratory muscle strength, and glucosamine deposition in the lung [8, 9]. Respiratory failure occurs in severe hypothyroidism when alveolar ventilation and gas exchange across the respiratory membrane are greatly reduced [10]. Although the lung volumes and pulmonary function test (PFT) may be normal in the early stage of hypothyroidism, they may progress to a restrictive pattern [11]. Reduction in spirometric parameters in hypothyroidism [12–15] may be improved by thyroxine therapy [15, 16]. Limited studies were conducted in Basra, south of Iraq, to demonstrate the effect of hypothyroidism on spirometric parameters in adult patients. Moreover, the effect of thyroxine therapy on spirometric parameters was not covered by these studies. Hypothyroidism adversely affects pulmonary function, which may improve by thyroxine therapy. Therefore, in this study pulmonary function in adult hypothyroid patients was evaluated by spirometry to detect any impairment, type of impairment, and to evaluate the effect of thyroxine therapy.

Subjects and methods

The study was conducted in Al-Faiha Specialized Diabetes, Endocrine, and Metabolism Center (FDEMC) during the period from November 2017 to July 2018 in FDEMC. The study was approved by the college council and ethical committee in the College of Medicine, Basra University. The aim of the study was explained to all participants and a written agreement was taken from them, subjects are divided into four groups:

(1) **Uncontrolled hypothyroid group:** consists of 72 hypothyroid patients on thyroxine replacement therapy, their serum total thyroid-stimulating hormone (TSH) level is >5 mIU/L [5, 6]. Although patients in this group are metabolically similar to those in the newly diagnosed hypothyroid group, the severity of changes in pulmonary function may be related to the duration of hypothyroidism.
(2) **Controlled hypothyroid group:** consists of 60 hypothyroid patients on thyroxin replacement therapy, their serum total TSH is within the normal reference range (0.4–4.0 mIU/L) [5, 17]. Although patients in this group are metabolically similar to those in the control (euthyroid) group, the improvement of changes in pulmonary function is time-dependent.
(3) **Newly diagnosed hypothyroid group**: consists of 52 newly diagnosed hypothyroid patients, their serum total TSH >5.5 mIU/L and fT4 <0.89 ng/dL [4, 18].
(4) **Control (euthyroid) group:** consists of 110 apparently healthy persons, their serum total TSH and fT4 are within the normal reference values (0.4–4 mIU/L and 0.9–1.7 ng/dL, respectively).

Patients were collected from FDEMC, control subjects are either relative of hypothyroid patients or staff of Basrah College of Pharmacy. Total serum TSH and free T4 (fT4) were measured by electrochemiuminescence immunoassay (Roche's Cobas e411 analyzer. Hitachi high-Technologist Cooperation, Japan) and pulmonary function by spirometer (spirolab III MIR. Medical International Research, Italy). Patients with respiratory diseases, chronic systemic diseases, and drug history (e.g., amiodarone) affecting the results of PFT and smoking history are excluded from the study. Spirometry was done in sitting position, it's repeated at least three times and the best result was recorded.

Statistical analysis

Computerized SPSS version 20 program is used for the analysis of the results of the study. Quantitative data are tabulated as mean ± SD; post hoc one-way analysis of variance (ANOVA) with Bonferroni correction was used to test the differences among means of the groups. Qualitative data are tabulated as numbers (%) and tested with the Pearson Chi-square test. $p<0.05$ was considered statistically significant.

Results

Tables 1 and 2 show no significant difference in age, gender, and BMI among control and hypothyroid groups. A significantly higher TSH level is observed in uncontrolled and newly diagnosed hypothyroid groups compared with control and controlled hypothyroid groups, while fT4 is significantly more in a controlled hypothyroid group compared with other groups. The results in Table 3 show that the FVC, FVC%, FEV1, and FEV1% are significantly less in uncontrolled hypothyroid group compared with the control group. Moreover, FVC and FEV1 are significantly less in controlled hypothyroid group compared with the control group. No significant difference exists among the four groups about FEV1/FVC, PEF, PEF%, FEF 25–75%, and $FEF\%_{(25-75\%)}$.

Table 4 demonstrates that the pattern of spirometric results was normal in 33.3, 53.3, and 44.2% of uncontrolled, controlled, and newly diagnosed hypothyroid groups, respectively. These are statistically different ($p<0.001$) from that in the control group (98.2%). Moreover, the pattern of spirometric results is significantly different ($p=0.028$) in the controlled hypothyroid group when compared with the uncontrolled hypothyroid group. While no significant difference exists between newly diagnosed and uncontrolled hypothyroid group ($p=0.55$) and between newly diagnosed and controlled hypothyroid group ($p=0.54$). Table 5 shows a significant negative correlation of TSH with FVC% ($p<0.001$), FEV1% ($p<0.001$), FEV1/FVC% ($p<0.001$), PEF% ($p=0.020$), and FEF% (25–75%) ($p=0.015$). Moreover, a significant positive correlation of fT4 with FVC% ($p=0.004$) and FEV1% ($p=0.004$) was found.

Discussion

Pulmonary function impairment in hypothyroidism is caused by central and peripheral reasons. Centrally, low thyroid hormones lead to suppression of hypoxic and hypercapnic ventilatory drives. Peripherally, low thyroid hormone causes peripheral myopathy with reduced strength of respiratory muscle due to changes in type 1 muscle fiber, decreased utilization of fatty acid, increased glycogen

Table 1: General characteristics of subjects. Data tabulated as mean ± SD, post hoc ANOVA test with Bonferroni correction was used to test the differences between the individual groups.

Parameter	Control group (1) n=110	Uncontrolled hypothyroid group (2) n=72	Controlled hypothyroid group (3) n=60	Newly diagnosed hypothyroid group (4) n=52	p-Value
Age (year)	42.5 ± 9.2	41.4 ± 11.8	44.12 ± 12.8	41.17 ± 12.4	[a]p=1.00 [b]p=1.00 [c]p=1.00 [d]p=1.00 [e]p=1.00 [f]p=1.00
BMI (kg/m^2)	30.9 ± 8.2	32.85 ± 7.4	32.34 ± 6.8	32.18 ± 6.8	[a]p=0.55 [b]p=1.00 [c]p=1.00 [d]p=1.00 [e]p=1.00 [f]p=1.00
Serum TSH (mU/L)	2.40 ± 2.9	14.28 ± 17.7	1.68 ± 0.97	15.06 ± 24.7	[a]p<0.001* [b]p=1.00 [c]p<0.001* [d]p<0.001* [e]p=1.00 [f]p<0.001*
Serum fT4 (5 µg/dL)	1.08 ± 0.17	0.90 ± 0.44	1.65 ± 1.16	1.05 ± 0.76	[a]p=0.49 [b]p<0.001* [c]p=1.00 [d]p<0.001* [e]p=1.00 [f]p<0.001*

BMI, body mass index; TSH, thyroid-stimulating hormone; fT4, free thyroxine. [a]p, [b]p, [c]p, [d]p, [e]p, and [f]p indicate the difference between group (1 and 2), (1 and 3), (1 and 4), (2 and 3), (2 and 4), (3 and 4) respectively. p <0.05 is considered statistically significant.

Table 2: Gender distribution of subjects. Chi-square test was used to test the differences between the individual groups. Results presented as numbers (percentages).

Gender	Control group (1) n=110	Uncontrolled hypothyroid group (2) n=72	Controlled hypothyroid group (3) n=60	Newly diagnosed hypothyroid group (4) n=52	p-Value (X^2 value)
Male	18 (16.4%)	14 (19.4%)	8 (13.3%)	6 (11.5%)	[a]p=0.691 (0.285)
Female	92 (83.6%)	58 (80.6%)	52 (86.7%)	46 (88.5%)	[b]p=0.662 (0.275) [c]p=0.485 (0.651)

[a]p, [b]p, and [c]p indicate the difference between group (1 and 2), (1 and 3), (1 and 4), respectively. p <0.05 is considered statistically significant.

consumption, and reduced muscle endurance [19, 20]. Also, pulmonary fibrosis due to deposition of mucopolysaccharides in the lungs [11, 21], pleural effusion [14], and reduced secretion of surfactant by alveoli [22, 23] have been reported in hypothyroidism. Moreover, deficiency of thyroid hormone increases bronchial hyperactivity due to reduced expression of β2 adrenoceptors in bronchi [24].

The results in Table 2 of this study show that hypothyroidism affects females more than males, this agrees with other researchers [25, 26]. Autoimmunity is the most common cause of hypothyroidism in developed countries; autoimmune diseases are associated with the female gender [27]. Age, gender, and BMI were not significantly differenced among four studied groups (Table 1); this indicates that the hypothyroid groups are well-matched with the control group. No significant effect of hypothyroidism on BMI was reported by Roel et al. [13] and Sadek et al. [28]. While Abdulhussein et al. [12], Iyer et al. [25], and Maiti et al. [8]

Table 3: Results of spirometric parameters in an adult hypothyroid patient. Data tabulated as mean ± SD, post hoc ANOVA test with Bonferroni correction was used to test the differences between the individual groups.

Parameter	Control group (1) n=110	Uncontrolled hypothyroid group (2) n=72	Controlled hypothyroid group (3) n=60	Newly diagnosed hypothyroid group (4) n=52	p-Value
FVC (L)	2.88 ± 0.6	2.51 ± 0.6	2.53 ± 0.6	2.64 ± 0.7	[a]p<0.001* [b]p 0.003* [c]p 0.135 [d]p1.00 [e]p 1.00 [f]p 1.00
FVC%	86.89 ± 11.4	76.63 ± 13	84.28 ± 14.5	82.38 ± 14.9	[a]p<0.001* [b]p 1.00 [c]p 0.251 [d]p 0.006* [e]p 0.047 [f]p 1.00
FEV1(L)	2.45 ± 0.05	2.10 ± 0.6	2.07 ± 0.5	2.25 ± 0.6	[a]p<0.001* [b]p <0.001* [c]p 0.188 [d]p 1.00 [e]p 0.79 [f]p 0.51
FEV1%	87.03 ± 12.5	75.58 ± 17.3	81.73 ± 16.6	81.90 ± 15.7	[a]p<0.001* [b]p 0.158 [c]p 0.277 [d]p 0.128 [e]p 0.139 [f]p 1.00
FEV1/FVC%	85.66 ± 8.3	83.95 ± 11.8	82.28 ± 10.7	84.66 ± 10.3	[a]p 1.00 [b]p 0.23 [c]p 1.00 [d]p 1.00 [e]p 1.00 [f]p 1.00
PEF (L/s)	5.55 ± 1.2	5.30 ± 1.3	5.20 ± 1.2	5.17 ± 0.9	[a]p 1.00 [b]p 0.41 [c]p 0.38 [d]p 1.00 [e]p 1.00 [f]p 1.00
PEF%	82.31 ± 14.1	78.96 ± 18.5	81.20 ± 20.6	80.80 ± 15.4	[a]p 1.00 [b]p 1.00 [c]p 1.00 [d]p 1.00 [e]p 1.00 [f]p 1.00
FEF(25–75%) (L/s)	3.28 ± 0.6	3.32 ± 0.5	3.27 ± 0.5	3.30 ± 0.8	[a]p 1.00 [b]p 1.00 [c]p 1.00 [d]p 1.00 [e]p 1.00 [f]p 1.00
$FEF\%_{(25-75\%)}$	90.29 ± 12.9	92.60 ± 14.4	93.91 ± 18	91.15 ± 16.2	[a]p 1.00 [b]p 0.08 [c]p 1.00 [d]p 1.00 [e]p 1.00 [f]p 1.00

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow; $FEF_{(25-75\%)}$, forced expiratory flow in mid expiration. [a]p, [b]p, [c]p, [d]p, [e]p, and [f]p indicate the difference between group (1 and 2), (1 and 3), (1 and 4), (2 and 3), (2 and 4), (3 and 4) respectively. p<0.05 is considered statistically significant.

Table 4: Pattern of spirometric results in adult hypothyroid patients. Data tabulated as No. (%), Chi-square test was used to test the differences between the individual groups.

Diagnosis		Control group (1) n=110	Uncontrolled hypothyroid group (2) n=72	Controlled hypothyroid group (3) n=60	Newly diagnosed hypothyroid group (4) n=52	Df	p-Value (X^2 value)
Normal spirometry		**108(98.2%)**	**24(33.3%)**	**32(53.3%)**	**23(44.2%)**	**1**	[a]p<0.001* (91.918)
Abnormal spirometry	**T**	**2 (1.8%)**	**48 (66.7%)**	**28(46.7%)**	**29 (45.8%)**		[b]p<0.001* (53.983)
	R	2 (1.8%)	39 (54.2%)	19 (31.7%)	22(42.3%)		[c]p<0.001* (66.589)
	O	0 (0%)	4 (5.6%)	7 (11.7%)	4(7.7%)		[d]p 0.028* (9.128)
	C	0 (0%)	5 (6.9%)	2(3.3%)	3(5.8%)		[e]p 0.55 (2.087)
Df		1	1	1	1		[f]p 0.54 (2.150)

T, total; R, restrictive; O, obstructive; C, combined. [a]p, [b]p, [c]p, [d]p, [e]p, and [f]p indicate the difference between group (1 and 2), (1 and 3), (1 and 4), (2 and 3), (2 and 4), (3 and 4) respectively. p<0.05 is considered statistically significant.

reported significantly increased BMR in hypothyroid patients. High TSH in uncontrolled and recently diagnosed hypothyroid patients resulted from low thyroid hormone levels in those patients [29], while high fT4 in controlled hypothyroid patients is probably explained by exogenous thyroxine therapy, and this is in agreement with Jonklaas et al. [17].

Table 5: Correlation of TSH and fT4 with spirometric parameters in control and hypothyroid subjects. Bivariate correlation test.

		FVC%	FEV1%	FEV1/FVC%	PEF%	FEF% (25–75%)
TSH	r	−0.233	−0.343	−0.247	−0.136	−0.141
	p	<0.001	<0.001	<0.001	0.02	0.015
freeT4	r	0.169	0.167	0.028	0.081	0.095
	p	0.004	0.004	0.638	0.166	0.104

TSH, thyroid-stimulating hormone; fT4, free thyroxin; r, correlation coefficient. p<0.05 is considered statistically significant.

Table 3 shows reduced spirometric parameters (FVC, FVC%, FEV1, and FEV%) in hypothyroid groups compared with the control group, the reduction was more pronounced in the uncontrolled hypothyroid group, which could be attributed to the low level of thyroid hormone in this group (Table 1). Low FVC% in the uncontrolled hypothyroid group indicates a restrictive pattern of pulmonary impairment. Although patients in an uncontrolled hypothyroid group are metabolically similar to those in a newly diagnosed hypothyroid group, the value of FVC% is significantly lower in an uncontrolled hypothyroid group. This may be caused by long-standing hypothyroidism, which changes the pulmonary functions and yet not improved by thyroxine replacement therapy probably due to inadequate dose or the need for a longer duration of treatment. Although the patients in control and controlled hypothyroid group are metabolically similar, the values of FVC and FEV1 are significantly lower in the controlled hypothyroid group. Hypothyroidism induced changes in spirometric parameters either irreversible or reversible after a longer duration of treatment. The normal level of TSH and fT4in euthyroid group explains the significantly more values of FVC, FEV1, FVC%, and FEV1% in this group compared with hypothyroid groups. In hypothyroid patients, Cakmak [26] reported reduced FVC, FVC%, and FEV1, Maiti et al. [8] mentioned a significant reduction of FVC, FEV1, and FEV1/FVC, Roel et al. [13] found that both of FVC% and FEV1/FVC were significantly reduced, and Sadek et al. [28] mentioned a reduction in FVC%. Differences in results of previous studies are possibly caused by either environmental factors such as geographical area or nonvironmental factors such as sample size of the study, time of patient's collection, duration of hypothyroid disease, and the presence of comorbidity disease. Maiti et al. [8] and Cakmak [26] have also mentioned low FEV1 in hypothyroid groups. While no significant change in FEV1 of hypothyroid patients was mentioned by Abdulhussein et al. [12], Ramachandran et al. [11], Sadek et al. [28], and Roel et al. [13]. The FEV1 is decreased in obstructive pulmonary diseases. Table 3 demonstrates that PEF and FEF25-75 are not significantly altered in hypothyroid patients. Low FEF25-75 indicates small airway obstruction; hypothyroidism primarily does not cause small airway obstruction. Similarly, Roel et al. [13] did not find a change in FEF 25–75 of hypothyroid patients. While Maiti et al. [8] mentioned that it significantly increased. Whereas Cakmak [26] and Ali [30] mentioned that it's significantly reduced.

The results in Table 4 show a significantly (p<0.001) lower percentage of normal spirometric results in hypothyroid groups (33.3, 53.3, and 44.2%) compared with the control group (98.2%), the most commonly noticed abnormality in the results of spirometry is a restrictive pulmonary defect. A significantly (p=0.028) higher percentage of abnormal spirometry is observed in uncontrolled hypothyroid group (66.7%) compared with a controlled hypothyroid group (46.7%), this may be caused by inappropriate dose or inaccurate use of thyroxine in the uncontrolled hypothyroid group [12, 31]. A significantly (p<0.001) more abnormal spirometry in the controlled hypothyroid group (46.7%) compared with control subjects (1.8%) despite thyroxine treatment may be related to the incomplete improvement of pulmonary function due to severity and duration of hypothyroidism [14, 16]. Improvement of PFT with thyroxine is time-dependent and requires enough duration to be achieved. Restrictive pulmonary disease was reported in 30, 52, and 87% of hypothyroid patients by Abdulhussein et al. [12], Roel et al. [13], and Sharifi and Amari [15], respectively. It seems that pulmonary fibrosis is the cause of the restrictive pattern of PFT in hypothyroid patients [13, 21]. The obstructive pulmonary defect is reported in 15 hypothyroid patients (Table 3). Unrecognized diseases as primary obstructive airway diseases that were not aware by the patients and discovered recently that probably affect or enhance the hypothyroid effect on pulmonary function. Moreover, long-standing duration of hypothyroidism may lead to an obstructive pulmonary defect.

In the present study, a negative correlation of TSH with FVC%, FEV1%, FEV1/FVC%, PEF%, and FEF25–75% and a positive correlation of fT4 with FVC% and FEV1% have been observed (Table 5). Similar results were mentioned by Maiti et al. [8], Abdulhussein et al. [12] found a positive correlation of T4 with FEV1 and FEV1/FVC, Valjevac et al. [11] reported a positive correlation of TSH with FVC, Roel et al. [13] did not find a significant correlation of TSH and fT4 with spirometric parameters. The lower thyroid hormone levels, the higher the TSH level and the more severe hypothyroidism. This causes a more reduction in spirometric parameters.

Conclusion

PFT parameters are significantly reduced in hypothyroid patients compared to euthyroid subjects; the abnormality in PFT, which is mostly of restrictive type. High TSH and

low fT4 are recognized causes of a reduction in the parameters of PFT. Therefore, spirometry can be used to detect pulmonary function changes in hypothyroidism.

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Informed consent: The purpose of the study was clearly defined to all individuals included in this study and signed informed consent was obtained.
Ethical approval: The present study has been done after obtaining informed consent and approved by the College Research Ethics Committee of Medicine, The University of Basrah at its meeting No.1 on November 26, 2017.

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