Assessment of functional lung impairment in patients with thyroid disorders

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Background and objective Many thyroid diseases can lead to pulmonary problems. Hypothyroidism reduces respiratory drive and can cause obstructive sleep apnea, pleural effusion, skeletal muscle myopathy, and decreased carbon monoxide diffusing capacity, whereas hyperthyroidism increases respiratory drive and can cause dyspnea on exertion. Thus, the aim of this study was to evaluate and compare the frequency of clinical presentations, the extent of lung functional endurance (spirometric and diffusion lung capacity), and arterial blood gases affection between patients with hypothyroidism and hyperthyroidism when compared with normal euthyroid volunteers and find out who could compromise the respiratory system more.

Patients and methods This study included 90 participants (30 patients with hyperthyroidism, 30 patients with hypothyroidism, and the remaining 30 were normal healthy volunteers as control) referred from the Endocrinology and Internal Medicine Departments in Ain Shams University Hospitals and Misr University for Science and Technology according to their serum free thyroid hormone 3, free thyroid hormone 4, and thyroid-stimulating hormone values. Spirometric function tests and diffusing capacity of the lung for carbon monoxide evaluation were performed for all participants.

Results Respiratory symptoms were more frequent in hypothyroid than in hyperthyroid patients, especially cough, sputum production, and chest wheezes. All spirometric functional parameters and respiratory muscle function were decreased (whether or not significant) among patients with hypothyroidism and hyperthyroidism compared with normal euthyroid controls. More statistically significant respiratory functional impairment was noticed among patients with hypothyroidism than among those with hyperthyroidism. Diffusion was more affected in the hypothyroidism group than in the hyperthyroid group, but it was statistically nonsignificant. A statistically significant increase in partial carbon dioxide pressure was observed among patients with hypothyroidism than in patients in hyperthyroidism (However, there was a statistically significant decrease in partial oxygen pressure and pH in patients with hypothyroidism than in those with hyperthyroidism.). Although oxygen saturation was lower in hypothyroidism, it was statistically nonsignificant.

Conclusion Hypothyroidism causes greater respiratory system endurance compared with hyperthyroidism. Early diagnosis and hormonal replacement may be of value.

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Introduction

Many thyroid diseases can lead to pulmonary problems, including hypothyroidism, hyperthyroidism, nodular goiter, and thyroid cancer. Both hypothyroidism and hyperthyroidism cause respiratory muscle weakness and decrease pulmonary function. Hypothyroidism is characterized by hypoventilation, whereas dyspnea and hyperventilation are typical symptoms of hyperth yroidism. Hypothyroidism reduces respiratory drive and can cause obstructive sleep apnea or pleural effusion, whereas hyperthyroidism increases respiratory drive and can cause dyspnea on exertion. Compression of the trachea, which may be positional, can occur with nodular goiters and thyroid cancer, and the latter can metastasize to the lungs. Hypothyroidism is a relatively common problem worldwide, often with insidious onset and is relatively asymptomatic. Some patients with hypothyroidism have alveolar hypoventilation (depressed ventilatory drive) [1]. In the extreme case of myxedema coma, there can be marked hypercapnia. Severe hypothyroidism is associated with marked depression in hypoxic venti latory drive and hypercapnic ventilatory drive, whereas less severe hypothyroidism causes a moderate redu ction in hypoxic ventilatory drive [2]. Skeletal muscle myopathy occurs with hypothyroidism. Respiratory muscle strength is reduced in patients with hypothyroidism and improves with treatment; the reduction is caused by both myopathy and neuropathy [3]. Diffusing capacity of the lung for carbon monoxide (DL_{CO}) may be low and increase during treatment. Nonobese hypothyroid patients have normal lung volumes, whereas obese hypothyroid patients have moderate reductions in vital capacity and lung volume. Lung volumes are usually normal, but studies have shown findings suggestive of restrictive pattern of impairment [4]. This has been attributed to decrease in both expiratory and

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inspiratory muscle strength. Most of the restrictive defects seen among these patients have been thought to be a consequence of obesity and microatelectasis [5]. Hypothyroidism should be considered in patients with respiratory failure who are difficult to wean. Pleural and also pericardial and peritoneal effusions can occur in patients with severe chronic hypothy roidism. The effusions are exudates, indicative of increased capillary permeability. Obstructive sleep apnea is more common among patients with hypoth yroidism [6]. Possible mechanisms for obstructive sleep apnea in patients with hypothyroidism include depressed ventilatory drive and narrowing of the airway due to enlargement of the tongue, pharynx, or larynx due to mucinous edema (myxedema). Mildly elevated thyroid-stimulating hormone (TSH) consistent with subclinical hypothyroidism is common among patients with idiopathic pulmonary hype rtension [7]. Hyperthyroidism is associated with increased ventilatory drive in response to hypoxemia and hypercapnia. The mechanism for increased vent ilatory drive is uncertain, but β-adrenergic blockade reduces it to normal, suggesting that adrenergic stimulation plays a role. With exercise, hyperthyroid patients are more dyspneic compared with controls for the same level of work, but there was no difference in dyspnea for the same level of ventilation. Thus, increased ventilatory drive seems to account for dyspnea on exertion in hyperthyroid patients [8]. Hyperthyroidism is associated with respiratory abnor malities, leading to an increase in respiratory rate, respiratory muscle weakness, and pulmonary hyper tension [9]. The mechanism responsible for reduced pulmonary compliance in patients with hyperth yroidism is not clear, but there are several proposed theories: changes in functional residual capacity, pulmonary congestion and edema, increased intrathoracic blood volume, and changes in the recoil of alveolar septa [10]. Hyperthyroidism can also cause abnormalities in pulmonary function, with reductions in forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) that improves with treatment. The mechanism of pulmonary hypertension in these patients is unclear, but pulmonary pressures drop with institution of medical therapy for hyperth yroidism [11]. Obstructive disease in patients with dysfunctional thyroid diseases may not only be due to the direct effect of hormones on lung function but might also be due to the present cardiac diseases that often accompany thyroid disorders. The aim of this study was to evaluate and compare the frequency of clinical presentations, the extent of lung functional endurance (spirometric and diffusion lung capacity), and arterial blood gases (ABGs) affection between patients with hypothyroidism and hyperthyroidism when compared with normal euthyroid volunteers and find out who could compromise the respiratory system more.

Patients and methods

Patient selection

This study was conducted between January 2011 and June 2013. All participants in the present study were selected as newly diagnosed patients (had never been treated for thyroid dysfunction state) recruited and referred for treatment of their thyroid hormonal disorder (either hypothyroidism or hyperthyroidism) in the Endocrinology and Internal Medicine Departments in Ain Shams University Hospitals and Misr University for Science and Technology. All included participants were subjected to full clinical examination, and proper occupational, medical, and family history was taken. According to the serum free thyroid hormone 3 (FT3), free thyroid hormone 4 (FT4), and TSH values we included a total of 90 participants. After an overnight fast, serum FT3 and FT4 levels were assessed using the chemiluminescent competitive enzyme immunoassay method with Immulite 2000 (BIODPC; Shengang Shiang. Taichung country, Taiwan ROC). Serum TSH analysis was performed using the enzyme chemiluminescent immunometric assay method with the same analyzer. All participants underwent full medical assessment and laboratory examinations, and none of the participants had a history of smoking, any respiratory illness, or any other systemic diseases affecting the respiratory system (other than thyroid disorders). Following the approval of the local ethics committee, written informed consent was obtained from all of the participants. The study sample was divided into three age-matched groups: the hyperthyroid group, the hypothyroid group, and the euthyroid (control) group; each group consisted of 30 participants. Hyperthyroidism was defined as serum TSH level less than 0.4 mIU/l and increased serum FT4 level (>25 pmol/l). Hypothyroidism was defined as serum TSH level greater than 5 mIU/l and decreased serum FT4 level (<9 pmol/l). Euthyroid was defined as serum FT3, FT4, and TSH levels within the normal reference range (TSH between 0.4 and 4.0 mIU/l, FT4 between 9.0 and 25 pmol/l, and FT3 between 3.5 and 7.8 pmol/l). The exclusion criteria were as follows: presence of clinically evident cardiovascular diseases, renal diseases, pituitary/hypothalamic disorders, diabetes mellitus, and pregnancy. Patients with BMI greater

than 30 kg/m^2, patients with a history of smoking and respiratory illness, and patients on levothyroxine treatment were also excluded from the study.

Pulmonary functional assessment

Spirometry was performed at the beginning of the study for each patient to measure all respiratory parameters, including FVC, FEV1, the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC), forced expiratory flow (FEF) 25–75%, and peak expiratory flow rate (PEFR). Predicted values and the percentage of predicted values were calculated for each participant based on the participant's height, age, and sex and presented as FVC% predicted, FEV1% predicted, FEV1/FVC% predicted, FEF 25–75% predicted, and PEFR% predicted. Maximum inspiratory pressure (PI_{max}) and maximum expiratory pressure (PE_{max}) were measured for respiratory muscle function analysis. Predicted values and the percentage of predicted values were calculated for each participant based on the participant's height, age, and sex. Single-breath DL_{CO} was measured using a rapid carbon monoxide and methane analyzer, which was calibrated before each measurement. Values for DL_{CO} were obtained and were reported as percent predicted values. All instrum entation met American Thoracic Society standards, and tests were performed following them. Lung volumes were obtained and were reported as percent predicted values. Spirometric analysis was performed with Jaeger Master Scobe (Erich Jaeger GmbH & Co. KG, Wrtzburg, Germany)) (version 4.5). Spirometric volumes were expressed as ml, and DL_{CO} values were expressed as ml/mmHg/min. The assessment of predictive values for DL_{CO} and other spirometric parameters was predicated on the guidelines of American Thoracic Society (1995) [12].

Arterial blood gases

ABGs were obtained for the determination of partial oxygen pressure (PO_2), partial carbon dioxide pressure (PCO_2), oxygen saturation (SaO_2), pH, and bicarbonate levels.

Statistical analyses

For normally distributed variables, values were expressed as mean and SD of parametric data and were assessed using Student's *t*-test. The analysis of variance and χ^2-tests were used when assessing the percentages of the groups, and Pearson's correlation was used to compare the groups. A *P*-value less than 0.05 was considered as significant. Differences in mean between groups were tested using a *t*-test. Correlation between continuous variables was tested with Spearman's rank correlation analysis. Statistical analysis was performed using SPSS statistical software system (version 16.0; SPSS Inc., Chicago, Illinois, USA).

Results

In the present study, the average age of the hypothyroid patients (25 female and five male), hyperthyroid patients (23 female and seven male), and healthy euthyroid individuals (18 female and 12 male) were 44.35±12.25, 45.49±13.23, and 43.26±10.18 years, respectively (*P*=0.534) which was statistically nonsignificant. The number of female participants was significantly higher than the number of male participants in both the hypothyroid and hyperthyroid groups than in the euthyroid control group (*P*<0.001). There were statistically nonsignificant values among the three studied groups as regards weight and height (*P*=0.443 and 0.654, respectively) (Table 1).

Table 1 Demographic parameters and thyroid function values of the participants

Variables	Hypothyroidism group (*n*=30) (mean±SD)	Hyperthyroidism group (*n*=30) (mean±SD)	Euthyroidism group (*n*=30) (mean±SD)	*P*-value
Sex				
Male	5	7	12	<0.001
Female	25	23	18	
Age (years)	44.35±12.25	45.49±13.23	43.26±10.18	0.534
Weight (kg)	65±23.34	63±20.12	64±33.09	0.443
Height	162±18.77	161±11.32	165±13.21	0.654

Table 2 Thyroid function test values of the studied groups

Variables	Hypothyroidism group (*n*=30) (mean±SD)	Hyperthyroidism group (*n*=30) (mean±SD)	Euthyroidism group (*n*=30) (mean±SD)	*P*-value
TSH	24.81±20.01	0.13±18.54	3.5±23.6	0.001
FT3	1.12±19.43	21.45±11.34	6.3±19.84	0.001
FT4	4.33±18.65	37.34±12.78	11.97±18.55	0.001

FT, free thyroid hormone; TSH, thyroid-stimulating hormone.

There was a statistically significant difference among the studied groups as regards TSH, FT3, and FT4; *P*-value was 0.001 for each (Table 2).

There was a statistically significantly higher frequency of the respiratory symptoms among hypothyroid and hyperthyroid patients than among euthyroid volunteers. There was a significantly greater incidence of cough, sputum, chest wheezes, and chest pain among hypothyroid than among hyperthyroid patients, which occurred in 21/30 (70%) versus 3/30 (0.1%), in 17/30 (56.7%) versus 5/30 (16.7%), 15/30 (50%) versus 2/30 (0.07%), and in 3/30 (0.1%) versus 0/30 (0%), respectively. However, there was a nonsignificant difference as regards dyspnea that was found in 25/30 (83.3%) and 28/30 (93.3%) hypothyroid and hyperthyroid patients, respectively (Table 3).

In the present study, there was a statistically significant decrease in pulmonary functional parameters as regards FEV1%, FVC%, FEF 25–75%, and maximum mid-expiratory flow/peak expiratory flow (MMEF/PEF%) among patients with hypothyroidism compared with normal euthyroid controls (*P*=0.001 for FEV1, <0.0001 for each FVC% and FEF 25–75%, and 0.01 for MMEF/PEF%). However, there was a statistically nonsignificant decrease found in FEV1/FVC% in the hypothyroid group compared with the control group (*P*=0.543). As regards DL_{CO}%, it showed a significant decrease in the hypothyroidism group compared with the euthyroidism group (*P*=0.01). As regards respiratory muscle function assessed with Pi_{max}% and Pe_{max}%, a statistically significant decrease was found in both Pi_{max}% and Pe_{max}% in the hypothyroid group compared with the

Table 3 Frequency of common respiratory symptoms among the studied groups

Variables	Dyspnea [*N* (%)]	Cough [*N* (%)]	Sputum [*N* (%)]	Wheezes [*N* (%)]	Chest pain [*N* (%)]	Hemoptysis [*N* (%)]	*P*-value
Hypothyroidism (*n*=30)	25/30 (83.3)	21/30 (70)	17/30 (56.7)	15/30 (50)	3/30 (0.1)	0/30 (0)	<0.001
Hyperthyroidism (*n*=30)	28/30 (93.3)	3/30 (0.1)	5/30 (16.7)	2/30 (0.07)	0/30 (0)	0/30 (0)	<0.001
Euthyroidism (*n*=30)	0/30 (0)	0/30 (0)	0/30 (0)	0/30 (0)	0/30 (0)	0/30 (0)	–

Table 4 Comparison of spirometric function parameters between hypothyroid and euthyroid groups

Variables (spirometric function parameters)	Hypothyroidism group (*n*=30) (mean±SD)	Euthyroidism group (*n*=30) (mean±SD)	*P*-value
FEV1%	85.96±4.51	94.96±3.16	0.001
FVC%	77.58±5.32	99.89±3.44	<0.0001
FEV1/FVC%	93.01±13.72	95.58±2.95	0.543
FEF 25–75%	72.12±33.12	98.96±23.66	<0.0001
MMEF/PEF%	82±17.45	97.98±11.33	0.01
DL_{CO}%	85.69±8.78	98.89±9.11	0.01
Pi_{max}%	79.35±25.42	98.52±4.33	<0.0001
Pe_{max}%	81.44±23.18	99.16±9.25	0.001

%, percent of the predicted value in relation to the expected value; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEF 25–75%, forced expiratory flow 25–75%; FEV1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF/PEF%, maximum mid-expiratory flow/peak expiratory flow; Pe_{max}%, maximum expiratory pressure; Pi_{max}%, maximum inspiratory pressure.

Table 5 Comparison of spirometric function parameters between hyperthyroid and euthyroid groups

Variables (spirometric function parameters)	Hyperthyroidism group (*n*=30) (mean±SD)	Euthyroidism group (*n*=30) (mean±SD)	*P*-value
FEV1%	90.43±22.34	94.96±3.16	0.523
FVC%	86.34±21.11	99.89±3.44	0.01
FEV1/FVC%	94.01±23.71	95.58±2.95	0.534
FEF 25–75%	95.88±21.54	98.96±23.66	0.354
MMEF/PEF%	92.45±17.33	97.98±11.33	0.335
DL_{CO}%	94.37±7.34	98.89±9.11	0.542
Pi_{max}%	93.41±12.33	98.52±4.33	0.341
Pe_{max}%	90.54±18.32	99.16±9.25	0.521

%, percent of the predicted value in relation to the expected value; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEF 25–75%, forced expiratory flow 25–75%; FEV1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF/PEF%, maximum mid-expiratory flow/peak expiratory flow; Pe_{max}%, maximum expiratory pressure; Pi_{max}%, maximum inspiratory pressure.

euthyroid group ($P<0.0001$ and $P=0.001$, respectively) (Table 4).

In the present study, there was a decrease in pulmonary functional parameters with regard to FEV1%, FVC%, FEV1/FVC%, FEF 25–75%, and MMEF/PEF% among patients with hyperthyroidism compared with the normal euthyroid controls but it was nonsignificant except for FVC% ($P=0.01$; significant) ($P=0.523$ for FEV1, 0.534 for FEV1/FVC%, 0.354 for FEF 25–75%, and 0.335 for MMEF/PEF%). As regards DL_{CO}%, it showed a nonsignificant decrease in the group with hyperthyroidism than those with euthyroidism ($P=0.542$). As regards respiratory muscle function assessed with Pi_{max}% and Pe_{max}%, a statistically nonsignificant decrease was found in both Pi_{max}% and Pe_{max}% among those with hyperthyroidism than in those with euthyroidism ($P=0.341$and 0.521, respectively) (Table 5).

All pulmonary functional parameters as regards FEV1%, FVC%, FEV1/FVC%, FEF 25–75% and MMEF/PEF%, DL_{CO}%, and respiratory muscle function assessed by means of Pi_{max}% and Pe_{max}% were decreased (whether or not significant) among patients with hypothyroidism and hyperthyroidism compared with the normal euthyroid control volunteers (Tables 4 and 5). More respiratory functional impairment was noticed among patients with hypothyroidism than those with hyperthyroid state. A greater statistically significant decrease in FVC%, FEF 25–75%, and MMEF/PEF% ($P=0.0001$, <0.0001, and 0.01, respectively) was found in the hypothyroid group, but the decreased FEV1% and FEV1/FVC% among hypothyroid patients was statistically nonsignificant when compared with hyperthyroid patients ($P=0.325$ and 0.554, respectively). Diffusion was more affected in the hypothyroid group than in the hyperthyroid group, but it was statistically nonsignificant as well ($P=0.052$). There was a significantly greater decrease in respiratory muscle function (Pi_{max}% and Pe_{max}%) in the hypothyroid group compared with the hyperthyroid one ($P=0.001$ and 0.01, respectively) (Table 6).

Although within normal reference ranges, the present study showed a statistically significant decrease in pH and PO_2 ($P=0.001$and <0.001, respectively) among hypothyroid patients compared with euthyroid normal volunteers, but decreased SaO_2% in hypothyroidism was statistically nonsignificant ($P=0.435$). However, there was a statistically significant increase in PCO_2 in patients with hypothyroidism when compared with euthyroid control ($P=0.001$) (Table 7).

Although within normal reference ranges, the present study showed a statistically nonsignificant increase in pH and PO_2 and SaO_2% ($P=0.453$, 0.332, and 0.653, respectively) among hyperthyroid patients compared with euthyroid normal volunteers. However, there was a statistically significant decrease in PCO_2 in patients with hyperthyroidism when compared with euthyroid controls ($P=0.04$) (Table 8).

When the hypothyroidism and hyperthyroidism groups were compared with each other in the present study, a statistically significant increase in PCO_2 was observed

Table 6 Comparison of spirometric function parameters between hypothyroid and hyperthyroid groups

Variables (spirometric function parameters)	Hypothyroidism group ($n=30$) (mean±SD)	Hyperthyroidism group ($n=30$) (mean±SD)	*P*-value
FEV1%	85.96±4.51	90.43±22.34	0.325
FVC%	77.58±5.32	86.34±21.11	0.0001
FEV1/FVC%	93.01±13.72	94.01±23.71	0.554
FEF 25–75%	72.12±33.12	95.88±21.54	<0.0001
MMEF/PEF%	82±17.45	92.45±17.33	0.01
DL_{CO}%	85.69±8.78	94.37±7.34	0.052
Pi_{max}%	79.35±25.42	93.41±12.33	0.001
Pe_{max}%	81.44±23.18	90.54±18.32	0.01

%, percent of the predicted value in relation to the expected value; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEF 25–75%, forced expiratory flow 25–75%; FEV1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF/PEF%, maximum mid-expiratory flow/peak expiratory flow; Pe_{max}%, maximum expiratory pressure; Pi_{max}%, maximum inspiratory pressure.

Table 7 Comparison of arterial blood gases parameters between hypothyroid and euthyroid groups

Variables (arterial blood gases parameters)	Hypothyroidism group ($n=30$) (mean±SD)	Euthyroidism group ($n=30$) (mean±SD)	*P*-value
pH	7.35±19.13	7.40±15.27	0.001
PCO_2 (mmHg)	40.81±1.21	35.11±8.19	0.001
PO_2 (mmHg)	87.23±19.23	97.58±21.21	<0.001
SaO_2%	96.78±13.23	98.95±11.44	0.435

PCO_2, partial carbon dioxide pressure; PO_2, partial oxygen pressure; SaO_2, oxygen saturation.

Table 8 Comparison of arterial blood gases parameters between hyperthyroid and euthyroid groups

Variables (arterial blood gases parameters)	Hyperthyroidism group ($n=30$) (mean±SD)	Euthyroidism group ($n=30$) (mean±SD)	*P*-value
pH	7.42±19.12	7.40±15.27	0.453
PCO_2 (mmHg)	32.45±3.16	35.11±8.19	0.04
PO_2 (mmHg)	98.87±29.18	97.58±21.21	0.332
SaO_2%	99.25±14.32	98.95±11.44	0.653

PCO_2, partial carbon dioxide pressure; PO_2, partial oxygen pressure; SaO_2, oxygen saturation.

among patients with hypothyroidism compared with those with hyperthyroidism (P=0.001). However, there was a statistically significant decrease in PO_2 and pH in patients with hypothyroidism compared with hyperthyroid state (P=0.001 for each). Although SaO_2 was lower in hypothyroidism, it was statistically nonsignificant (P=0.346). Regardless of whether the increase or decrease in values were significant, all were within the within normal reference ranges, as shown in Table 9.

Discussion

There is so much speculation about ventilation parameters and thyroid diseases. Thyroid gland by its anatomical location and its action can alter the airflow dynamics and cellular metabolism at the macrolevel and the microlevel in the disease condition [13]. Respiratory system components (respiratory center, upper airway, and lower respiratory system) can be affected by deficiencies in body hormones as well as excess hormonal secretion [14]. Thyroid hormone is one of the major body hormones. Its deficiency has been associated with multiple cardiovascular complications, respiratory failure, and coma [15]. Hypothyroidism is associated with diminished ventilatory drive for both hypoxia and hypercapnia. It is well known that alveolar ventilation is increased in hyperthyroidism [16]. Because the ventilatory responses to both hypercapnia and hypoxia are increased in hyperthyroidism, it has generally been considered that thyroid hormones could increase the sensitivity of the central and peripheral chemoreceptors [17]. Thus, this study aimed to evaluate and compare the frequency of clinical presentations, the extent of lung functional endurance (spirometric and diffusion lung capacity), and ABGs affection between patients with hypothyroidism and hyperthyroidism when compared with normal euthyroid volunteers, as well as between hypothyroid or hyperthyroid states, and find out who could compromise the respiratory system more. In the present study, the number of female participants was significantly higher than the number of male participants in both the hypothyroid and hyperthyroid groups than in euthyroid control volunteers (P<0.001), but there were statistically nonsignificant values among the three studied groups as regards age, weight, and height. This is in accordance with the findings of Kek *et al.* [18], who found that the prevalence in women was 6–8 and 3% in men. Cakmak *et al.* [19] also showed a similar finding in their study as 116 (126) female patients had subclinical hypothyroidism. In the present study, there was a statistically significantly higher frequency of the respiratory symptoms among hypothyroid and hyperthyroid patients compared with control euthyroid volunteers. There was a significantly greater incidence of cough, sputum, chest wheezes, and chest pain among hypothyroid than among hyperthyroid patients, which occurred in 21/30 (70%) versus 3/30 (0.1%), in 17/30 (56.7%) versus 5/30 (16.7%), and in 3/30 (0.1%) compared with 0/30 (0%), respectively. However, there was a nonsignificant difference as regards dyspnea that was found in 25/30 (83.3%) versus 28/30 (93.3%) of hypothyroid and hyperthyroid patients, respectively. These results are in accordance with those of Birring *et al.* [20], who concluded that patients with hypothyroidism had a significantly higher prevalence (2–3-fold increase) of respiratory symptoms compared with controls [cough (P=0.01), breathlessness (P=0.01), sputum (P=0.004), and wheeze (P=0.04)]. They found an evidence of airway inflammation as reflected by an increased inflammatory cell count, absolute neutrophil count, absolute lymphocyte count, and sputum IL-8 concentration. Similar abnormalities have been observed in a diverse range of conditions, including chronic obstructive pulmonary disease, cryptogenic fibrosing alveolitis, and nonasthmatic chronic cough. This suggests that these findings should be regarded as a nonspecific indication of airway inflammation rather than indicative of a specific disease process, thus supporting the hypothesis that there is airway dysfunction and inflammation in patients with hypothyroidism that may explain the more frequent respiratory symptoms among this group of patients linking hypothyroidism to idiopathic chronic cough and chronic obstructive pulmonary disease with chronic sputum production and chest wheezes as well in nonsmokers. The airways and the thyroid have common embryological origins, and it is plausible that the associated lung inflammation and dysfunction is due to the spread of the chronic inflammatory process from the thyroid to the lungs [21]. In addition, decreased levels of thyroid hormones lead to decreased expression of β-adrenergic receptors, which often causes bronchial tree hyperreactivity. Birring *et al.* [22] noted that in patients with low levels of thyroid hormone there is an

Table 9 Comparison of arterial blood gases parameters between hypothyroid and hypothyroid groups

Variables (arterial blood gases parameters)	Hypothyroidism group (n=30) (mean±SD)	Hyperthyroidism group (n=30) (mean±SD)	P-value
pH	7.35±19.13	7.42±19.12	0.001
PCO_2 (mmHg)	40.81±1.21	32.45±3.16	0.001
PO_2 (mmHg)	87.23±19.23	98.87±29.18	0.001
SaO_2%	96.78±13.23	99.25±14.32	0.346

PCO_2, partial carbon dioxide pressure; PO_2, partial oxygen pressure; SaO_2, oxygen saturation.

increased sensitivity of the cough reflex, increased airway hyper-responsiveness, and an increased number of inflammatory cells in sputum. Patients with hyperthyroidism had no increase in the airway resistance to a level considered sufficient to cause dyspnea of airway obstruction, and the increment of minute ventilation during exercise was consistently greater than that of oxygen consumption. Therefore, the dyspnea of hyperthyroidism appears to be related to other factors such as decreased compliance, decreased respiratory muscular strength [23], increased dead space ventilation, and perhaps an abnormal stimulus to respiration. Increased heat (due to increased basal metabolic rate among hyperthyroid patients) may have been a stimulus to the respiratory center. An increase in rate of respiration and ventilation usually accompanies an increase in body temperature. The respiratory center may be stimulated directly by thyroid hormone or its metabolites. Analysis of changes in pulmonary function is complicated by increased frequency of overweight or obesity in hypothyroid patients. Abnormalities attributed in the literature to hypothyroidism actually may have been due to obesity, but, in our study, the average BMI among the studied groups was matched and was within the recommended range for their age and sex. There was no significant difference among them. Hence, the additive effects of obesity on spirometric parameters was ruled out. In the present study, there was a statistically significant decrease in pulmonary functional parameters as regards FEV1%, FVC%, FEF 25–75%, and MMEF/PEF% among patients with hypothyroidism compared with the euthyroid group (P=0.001 for FEV1, <0.0001 for each FVC% and FEF 25–75%, and 0.01 for MMEF/PEF%), whereas nonsignificant decrease was found in FEV1/FVC% in the hypothyroid group compared with the control group (P=0.543). These findings denoted a restrictive lung pattern in hypothyroid patients. This is in accordance with the study conducted by Valjevac and Hadzovic-Dzuvo [24], who demonstrated decreased FVC and FEV1 among the hypothyroid patients and suggested that the degree and the duration of thyroid disorders lead to reduced ventilator lung function in patients with thyroid dysfunction. Cakmak *et al.* [25] and Siafakas *et al.* [26] observed a significant reduction in FVC, FEV1, FEV1%, FEF 25–75, and FEF 25–75%. Sharifi and Amari [27] reported that about 87% of restrictive abnormality ranged from mild to moderate grade among the hypothyroid patients, which improved significantly on treatment. They attributed such decrease in FEV1 and FVC to alveolar hypoventilation and inspiratory muscle power weakness. Sharon *et al.* [28] and Swagata *et al.* [29] also supported the results of the present study as they found that FEV1/FVC values were significantly increased among the hypothyroid patients as compared with controls. This together with the decrease in FVC suggests that there is a mild restrictive pattern among the hypothyroid patients even though the changes in these specific spirometric parameters are not that extreme so as to suggest a diagnosis of restrictive lung disease as per the American Thoracic Society [30] guidelines. They found that 47% of the hypothyroid patients were normal, whereas the rest had some restrictive defects ranging from mild to severe lung impairment. FEF 25–75% is an average FEF rate over the middle 50% of the FVC and it is said to be more sensitive compared with FEV1 for detecting early airway obstruction. The findings of Cakmak *et al.* [25] are in agreement with present study results; they reported a significant decrease in FEF 25–75%. However, Sharon *et al.* [28] observed no significant decrease in FEF 25–75%. PEFR is highly dependent on patient effort as the patient must initially exhale as hard as possible to obtain reproducible data, and it may not be the most suitable variable to detect the early deterioration of the ventilatory functions. These results are not in agreement with those of Swagata *et al.* [29], who did not find any difference in PEFR between cases and controls. Sharon *et al.* [27] also did not find any significant change in PEFR in hypothyroid cases. This may be attributed to the fact that the controls were not taken from individuals residing in the same locality as the patients, and hence the environmental conditions affecting lung functions in controls were not the same as those of cases. However, in accordance with our findings, Koral *et al.* [31], Cakmak *et al.* [25], and Basi *et al.* [32] found a significant decrease in PEFR. The decrease in all values for spirometric parameters in hypothyroid patients may be attributed to low serum T4, which may cause inspiratory muscle power weakness and hypoventilation. As regards DL_{CO}%, in the present study, there was a significant decrease in the group with hypothyroidism than in the euthyroidism group (P=0.01). Cakmak *et al.* [25] observed a significant reduction in DL_{CO} in patients with subclinical hypothyroidism as compared with controls. The findings of Cakmak *et al.* [19] are in agreement with this study results and suggest that DL_{CO} values were lower than that in control group, but not significant. This may be explained by selecting subclinical groups of hypothyroid patients and so DL_{CO} defect may still not overt. As regards respiratory muscle function assessed with Pi_{max}% and Pe_{max}%, a statistically significant decrease was found in both Pi_{max}% and Pe_{max}% among those with hypothyroid state compared with euthyroid volunteers (P<0.0001 and 0.001, respectively). Cakmak *et al.* [19] confirmed the present study results and suggested that muscle strength

was significantly lower compared with the control group. This result was also coexistent in patients without any symptoms and such reduction is caused by both myopathy and neuropathy. Basi *et al.* [32] reported a significant decrease in the lung functions between those not taking any treatment and those on thyroid hormone replacement therapy, and they attributed the cause to be respiratory muscle weakness and decreased contractile strength due to low serum T4. Martinez *et al.* [33] have confirmed that patients with hypothyroidism develop diaphragmatic dysfunction, which can vary from mild forms associated with reduced tolerance to physical effort to very severe forms of diaphragmatic weakness, which might even imitate diaphragmatic paralysis. This can be attributed to low serum FT4 values. Both inspiratory and expiratory respiratory muscles are weakened in hypothyroidism in a direct linear relationship to the thyroid hormone level and it is reversible with thyroxine therapy [34]. Furthermore, thyroid-deficient muscles have impaired free fatty acid utilization, which enhances their glycogen consumption, thereby reducing skeletal muscle endurance. One of the major inspiratory muscles that are involved in hypothyroidism is the diaphragm. Diaphragm weakness can be very severe and associated with hypoventilation [35]. The changes observed in our spirometric findings can be explained on the basis of research studies by some investigators, which suggest that respiratory center depression, interference of neural conduction or neuromuscular transmission to the respiratory muscles, and respiratory muscle diseases in hypothyroidism may cause alveolar hypoventilation, which may affect central ventilatory control and can impair ventilation [36]. In addition, in hypothyroidism, reduced surfactant phospholipid, phosphatidylglycerol, and phosphatidic acid along with increase in surface-active lipids phosphatidylserine and phosphatidylinositol in alveolar epithelium may decrease alveolar septation and reduce lung compliance and surfactant adsorption [37]. Moreover, mucopolysaccharide deposition in the lungs may cause fibrosis and thickening of the alveolar wall with loss of elastic tissue and may increase the work of breathing [38]. All these changes may reduce ventilator lung functions [39]. In the present study, there was a decrease in pulmonary functional parameters as regards FEV1%, FVC%, FEV1/FVC%, FEF 25–75%, and MMEF/PEF% among patients with hyperthyroidism than among normal euthyroid controls, but it was nonsignificant except for FVC% (P=0.01, so the decreased value was significant) (P=0.523 for FEV1, 0.534 for FEV1/FVC%, 0.354 for FEF 25–75%, and 0.335 for MMEF/PEF%). The low vital capacity may be related to the low lung compliance and to the muscular weakness, which has been observed to accompany the hyperthyroid state. An alternative explanation would be that congestion of the lungs with blood is a major factor causing the low vital capacity. At peak levels of flow, the hydrostatic pressure in the capillaries may force fluid into the interstitial spaces from which colloidal osmotic pressure or lymphatic flow cannot remove it rapidly enough to prevent accumulation. Such an increase in interstitial fluid, although this is pure conjecture, might produce a decrease in pulmonary compliance. As airway resistance measurements were normal, it is unlikely that generalized bronchial obstruction played a prominent part in the observed changes in vital capacity. Increased intrathoracic blood volume and alterations in the retractile properties of alveolar septa due to changes in composition of the alveolar mucoid film may play a role as well [40]. Kendrick *et al.* [41] confirmed the present study result as they found a nonsignificant decrease in spirometric function parameter in the hyperthyroid group compared with the euthyroid group and concluded that patients with hyperthyroidism do not generally have increased airway reactivity; in hyperthyroidism, respiratory muscles are weak and improve following treatment. Exercise capacity is impaired in hyperthyroid patients probably because of a combination of an inefficiently rapid and shallow breathing pattern, an increase in anaerobic metabolism and discomfort associated with the act of breathing. Although exercise capacity increases and the sensation of dyspnea may decrease after treatment, the pattern of breathing does not immediately return to normal. Pino-García *et al.* [42] confirmed the present study results (FVC was 3.54±0.24 vs. 3.21±0.76, FEV1 was 3.11±0.29 vs. 2.82±0.58, and FEV1/FVC% was 87 ±5 vs. 88±6 in the euthyroidism group compared with the hyperthyroidism groups). As regards DL_{CO}%, it showed a nonsignificant decrease among the group with hyperthyroidism than those with euthyroidism (P=0.542). This finding is supported by Myron *et al.* [43], who found that, in hyperthyroid patients, the dimensions of the pulmonary capillary bed, as reflected by DL_{CO} were essentially normal at rest even though the resting blood flow was approximately twice to three times normal. Bates has made similar observations in patients with hyperthyroidism during light exercise, showing that DL_{CO} is low with respect to the oxygen consumption [23], and, by inference, even lower with respect to the cardiac output. Ross *et al.* [44] have shown that increases in pulmonary blood flow induced by epinephrine or norepinephrine are not accompanied by changes in diffusing capacity. Turino *et al.* [45] have shown that diversion of the total resting cardiac output through one lung in a man does not increase DL_{CO} in the overperfused lung. Therefore, failure to find increased DL_{CO} during rest in these

hyperthyroid patients in response to the increased resting pulmonary blood flow does not necessarily indicate an abnormal response of the vascular bed. It may be that the pulmonary intravascular pressures are not sufficiently increased by the increased blood flow in hyperthyroidism to cause the capillaries to expand. Moreover, in patients with hyperthyroidism, arteriovenous oxygen differences are smaller than normal. Therefore, CO_2 tension in mixed blood may be normal or low, providing no stimulus for capillary bed expansion [46]. As regards respiratory muscle function assessed with Pi_{max}% and Pe_{max}%, a statistically nonsignificant decrease in both Pi_{max}% and Pe_{max}% was found among those with hyperthyroid state than those with euthyroid state (P=0.341and 0.521, respectively). However, these findings are not in agreement with those of Pino-García *et al.* [42], who found a significant decrease in both Pi_{max}% and Pe_{max}% (P<0,05). This may be attributed to a more severe and prolonged disease (confirmed by the higher level of T3 and T4 with more decreased TSH among the studied groups, respectively). However, Mier *et al.* [47], Siafakas *et al.* [48], and McElvaney *et al.* [49] confirmed the present study results. All pulmonary functional parameters with regard to FEV1%, FVC%, FEV1/FVC%, FEF 25–75% and MMEF/PEF%, DL_{CO}%, and respiratory muscle function assessed by Pi_{max}% and Pe_{max}% were decreased (whether or not significant) among patients with hypothyroidism and hyperthyroidism compared with normal euthyroid controls (Tables 4 and 5). More respiratory functional impairment was noticed among patients with hypothyroidism than in those with hyperthyroidism; a statistically significant decrease in FVC%, FEF 25–75%, and MMEF/PEF% (P=0.0001, <0.0001, and 0.01, respectively) was found in the hypothyroid group, but the decreased FEV1% and FEV1/FVC% among hypothyroid patients was statistically nonsignificant when compared with hyperthyroid patients (P=0.325 and 0.554, respectively). Diffusion was more affected in hypothyroid than in the hyperthyroid group, but was statistically nonsignificant as well (P=0.052). A significantly greater decrease in respiratory muscle function (Pi_{max}% and Pe_{max}%) was found in the hypothyroid group than in the hyperthyroid one (P=0.001 and 0.01, respectively). These results were confirmed by Salih *et al.* [50], Goswami *et al.* [51], and Kahaly *et al.* [52], who found more functional impairment among hypothyroid patients than those with hyperthyroid state, but it was statistically nonsignificant. A possible explanation for these results is the fact that the study had included a smaller number of patients with subclinical thyroid diseases among their studies. Martinez *et al.* [33] found that respiratory muscle function was the only significant functional impairment in hypothyroid compared with hyperthyroid patients included in their study, whereas the remaining functional parameters, although lower in hypothyroid, were nonsignificant. In patients with hypothyroidism, the causes for reduced respiratory function are decreased inspiratory muscle strength, hypoventilation, hypercapnia, increased bronchial reactivity, pleural effusion, and protein extravasations into the tissue, which can lead to edema. In patients with hyperthyroidism, possible mechanisms responsible for reduction in respiratory function are increased respiratory rate, respiratory muscle weakness, reduced lung compliance, pulmonary congestion and edema, increased intrathoracic blood volume, and pulmonary hypertension [53]. Although within normal reference ranges, the present study showed a statistically significant decrease in pH and PO_2 (P=0.001and <0.001, respectively) among hypothyroid patients than in euthyroid volunteers, but decreased SaO_2% in hypothyroidism was statistically nonsignificant (P=0.435). However, there was a statistically significant increase in PCO_2 in patients with hypothyroidism when compared with euthyroid controls (P=0.001). This is in agreement with the findings of Surks and Ortiz [54], who found that, although all ABGs results in their patients were within normal range, the SaO_2 parameter and not PaO_2 or $PaCO_2$ was the only one to have changed significantly, using statistical methods. Although within normal reference ranges, the present study showed a statistically nonsignificant increase in pH and PO_2 and SaO_2% (P=0.453, 0.332, and 0.653, respectively) among hyperthyroid patients than in those with euthyroid normal volunteers. However, there was a statistically significant decrease in PCO_2 in patients with hyperthyroidism when compared with euthyroid controls (P=0.04). Engel and Ritchie [55], Zwillich and Weil [56], and Stockley and Bishop [57] confirmed these results and suggested a direct action of the thyroid hormone in the respiratory centers, most likely secondary to increased adrenergic stimulation, and reported increased hypercapnic and hypoxic ventilator responses in hyperthyroid patients, and this increased ventilatory response to CO_2 and hypoxia decreased when thyroid function was normalized. When hypothyroidism and hyperthyroidism groups were compared with each other in the present study, a statistically significant increase in PCO_2 was observed among patients with hypothyroidism than in those with hyperthyroidism (P=0.001). There was a statistically significant decrease in PO_2 and pH in patients with hypothyroidism compared with hyperthyroid state (P=0.001 for each). Although SaO_2 was lower in

hypothyroidism, it was statistically nonsignificant (P=0.346). Regardless of whether the increased or decreased values were significant, all were within the within normal reference ranges.

Conclusion

Our study showed that a thyroid disorder causing hyperthyroidism and hypothyroidism could cause disorders of respiratory function and ventilation. Hypothyroidism causes more respiratory system endurance than hyperthyroidism. Early detection and diagnosis and hormonal replacement may be of value as most of these impairments are reversible with adequate treatment.

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Conflicts of interest

There are no conflicts of interest.

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