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PREVALENCE OF LARYNGOPHARYNGEAL REFLUX DISEASE IN PATIENTS DIAGNOSED WITH HYPOTHYROIDISM

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Abstract

Objective. To examine the prevalence of laryngopharyngeal reflux disease (LPRD) in patients with hypothyroidism.

Materials and Methods. A total of 85 patients with hypothyroidism *vs* 31 matched controls were recruited. Demographic data was collected and an RSI questionnaire filled. A score > 10 was considered diagnostic of LPRD. The average score of every question was computed for all patients and compared to the corresponding average score in controls.

Results. Mean age of hypothyroidism patients was 44.92 ± 13.77 years (83% females). One third of subjects were smokers and 10% had allergy. In 78.8% of the cases Hashimoto's disease was the etiological factor and 22.4% patients had history of thyroidectomy. At the time of examination, only 30% had a TSH > 4.2 mU/L. There was a borderline significance where more patients than controls had a RSI > 10 (24.7% patients *vs*. 9.1% controls), but with non-significant difference (p = 0.077). Similarly, closer examination of those with TSH > 4.2mU/L compared to those with controls revealed a higher prevalence in the former group, but statistically non-significant (p = 0.275). A comparison between those with TSH > 4.2 mU/L and cases diagnosed with hypothyroidism and normal TSH revealed no significant difference in the prevalence of LPRD. All laryngopharyngeal questions had a score higher in the hypothyroid group than controls.

Conclusion. LPRD is more prevalent in hypothyroidism patients compared to normal individuals, but with non-statistically significant difference. The prevalence of symptoms should alert physicians to the possibility of LPRD and prompt further diagnostic tests and therapeutic intervention.

Key words: Hypothyroidism, Thyroid disease, LPRD.

INTRODUCTION

Hypothyroidism is a common endocrinological condition worldwide. In the United States and Europe, up to

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2% of adults have overt hypothyroidism, while 4-10% have subclinical hypothyroidism (1-3). In other regions of the world, it was found that 4.8% of adult men and 12.8% of adult women have sublicinal hypothyroidism (4).

It is well known that hypothyroid patients experience a broad range of symptoms as a result of their condition, including fatigue, weakness, weight gain, cold intolerance, and other more specific symptoms such as myalgia and bradycardia. Less well described are the potential laryngologopharyngeal effects of hypothyroidism. At least two studies have suggested that the primary laryngologic complaint in hypothyroid patients is a change in voice quality (5-6). Among hypothyroid patients that present to an ENT clinic, dysphonia may be present in up to 77% (7). Less frequent, but still significant complaints include dry cough (6) and lump sensation (5). These symptoms have been attributed to the laryngeal manifestations of hypothyroidism. The larynx being a hormonal target is affected markedly by the thyroid hormones next to sex hormones.

Myxedematous changes in the laryngeal mucosa and muscles have been coined to explain the phonatory and pharyngeal symptoms in patients with hypothyroidism.

The symptoms of lump sensation, throat clearing, cough and change in voice quality can also be attributed to other etiologies as well, such as laryngopharyngeal reflux disease (LPRD). This later is defined as the backflow of gastric contents into the laryngopharynx (8). Broadly speaking, the condition includes anyone with laryngopharyngeal "episodes," defined according to pharyngeal pH criteria, per Postma *et al*. (2002). This common condition is found in up to 20% of normal controls (9-10) and roughly 50% of patients with a throat-related complaint.

As a confounding entity, LPRD is certainly an important diagnosis to keep in mind when evaluating hypothyroid patients with laryngeal complaints. No studies, to our knowledge, have explored the relation between LPRD and hypothyroidism. The purpose of this study was to examine the prevalence of LPRD in a hypothyroid patient population. The results of our study may lead to more comprehensive management for patients with hypothyroidism. Those suffering from throat or laryngeal complaints, otherwise attributed to their hypothyroidism, may have concomitant LPRD that, when properly addressed, could lead to relief of the troublesome symptoms.

PATIENTS AND METHODS

Participants were recruited from a private endocrinology clinic at the American University of Beirut Medical Center. Any patient with a diagnosis of hypothyroidism between the ages of 18-65, was informed of a study taking place at the "Hamdan Voice Unit" examining the association between hypothyroidism and laryngopharyngeal reflux disease**.** The study was approved by the Institution review Board before initiation. A total of 85 patients diagnosed with hpothyroidism who were on treatment were enrolled in this

study. Thirty percent of these had a TSH level above 4.2 micro-unit/mL, and most of the remaining subjects were euthyroid. During the same period, thirty one subjects matched according to allergy and smoking status-matched controls were also recruited. Exclusion criteria included any history of laryngeal manipulation or any current symptoms of upper respiratory tract infection.

All participants have read and signed the informed consent approved by the Institutional Review Board at the American University of Beirut. Demographic data included: age, gender, smoking status, allergy using a validated questionnaire (11,12), etiology, history of thyroi-dectomy and their last TSH. A range between 0.27 and 4.20 mU/L was considered as normal.

All participants were asked the 9 questions on the Reflux Symptom Index (RSI) (13), and their responses were recorded by one of two research assistants following an assigned protocol for using the validated scale. Any RSI score above 10 was considered diagnostic of LPRD. The prevalence of LPRD in patients diagnosed with hypothyroidism was compared to controls. In addition to the recording of the total score of RSI in all subjects and the frequency of scores above 10 indicative of LPRD, the average score of every question was computed for all patients with hypothyroidism and compared to the corresponding average score of controls. A $p < 0.05$ was considered as statistically significant.

The authors have also examined the prevalence of LPRD in patients diagnosed with hypothyroidism with TSH >4.2 micro-unit/ml, in patients with normal TSH level and in controls. A comparison was made and a $p < 0.05$ was considered as statistically significant.

Frequencies and means (± standard deviation) were used to describe categorical and continuous variables, respectively. At the bivariate level, normal distribution was not assumed for the total reflux symptoms in Table 3 and *Wilcoxon-Mann and Whitney Rank Sum Test* was used to determine any significant differences in means of each continuous variable when compared between patients and controls. In Table 4, the *independent t-test* was used for age. *Pearson chi square test* was applied for categorical variables in Tables 2 and 4 to assess existence of any correlation. When expected count cells were less than 5, Fisher's exact test was applied instead of Pearson's chi square. All analyses were conducted using the Statistical Package for the Social Sciences version 17 software package. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Demographic Data

Prevalence of laryngopharyngeal reflux disease in patients and controls

The mean age of patients with hypothyroidism was 44.92±13.77 years, with 83% being females. Almost one third of the subjects were smokers and close to 10% had allergy. In 78.8% of the cases Hashimoto's disease was the etiological factor and in 22.4% patients

Table 1. Descriptive data of patients and controls

	Patient (n=85)	Control (n=31)
Age (mean ± SD)	44.92 ± 13.77	39.29 ± 13.32
Gender		
Males	14 (16.5%)	17 (54.8%)
Females	71 (83.5%)	14 (45.2%)
Smoking		
No	55 (64.7%)	20 (64.5%)
Yes	30 (35.3%)	11 (35.5%)
Allergy		
Absent	77 (90.6%)	28 (90.3%)
Present	8 (9.4%)	3 (9.7%)
Etiology		N/A
Hashimotos/Idiopathic	67 (78.8%)	
Subacute	18 (21.2%)	
Thyroidectomy		N/A
No	66 (77.6%)	
Yes	19 (22.4%)	
*TSH		N/A
Hyper-thyroid	8 (9.4%)	
Eu-thyroid	46 (54.1%)	
Hypo-thyroid	26 (30.6%)	
Missing	5 (5.9%)	

*TSH: Hyper-thyroid (<0.27); Eu-thyroid (0.27 - 4.20); Hypo-thyroid (>4.20).

had history of thyroidectomy. At the time of examination, only 30% had a TSH above 4.2 mU/L. See Table 1.

There was a borderline significance where more patients diagnosed with hypothyroidism than controls had a RSI above 10 (24.7% among patients compared to controls 9.1% had LPRD). See Table 2. **S**imilarly closer examination of the prevalence of LPRD in those with TSH >4.2 mU/L and controls revealed a higher prevalence in the former group (23.1% *vs.* 9.7%) with no significant difference (p value 0.275). A comparison between those with hypothyroidism but normal TSH level at the time of investigation and those with TSH> 4.2 mU/L, revealed no significant difference (0.632 respectively). See Tables 2a and 2b**.**

Average Scores of laryngopharyngeal reflux symptoms in patients and controls

Looking at the average score which reflects the severity or degree (0-5) of the symptoms in the RSI in both groups, hypothyroid and controls, all nine laryngopharyngeal questions in the questionnaire had a score higher in the hypothyroid group compared to controls. The symptoms with the highest grades were clearing of throat (1.15±1.35), sensation of something tickling in the throat (1.01 ± 1.26) and heartburn, chest

Table 2. Reflux among patients and controls

*Reflux	Patient	Control	p-value
No	64 (75.3%)	28 (90.3%)	0.077[o]
Yes	21 (24.7%)	3 (9.7%)	

* RSI: No ≤10; Yes > 10
[o]Borderline significance

Table 2a. Reflux among patients with hypothyroidism (TSH>4.2) and controls

*Reflux	Patients (n=26)	Control (n=31)	p-value
No	20 (76.9%)	28 (90.3%)	0.275
Yes	6 (23.1%)	3 (9.7%)	

* RSI: No ≤ 10; Yes > 10

Table 2b. Reflux among patients with TSH >4.2 (hypothyroidism) in comparison to those with normal TSH range 0.27 - 4.20 (Euthyroidism)

*Reflux	Hypothyroidism	Eu-thyroidism	p-value
No	20 (76.9%)	33 (71.7%)	0.632
Yes	6 (23.1%)	13 (28.3%)	

* RSI: No ≤ 10; Yes > 10

Table3: Reflux Symptom Index among patients and controls

	Patients mean ± SD	Controls mean ± SD	p-value
Hoarseness or a problem voice	0.82 ± 1.26	0.55 ± 0.85	0.459
Clearing of throat	1.15 ± 1.35	0.77 ± 0.99	0.219
Excess throat mucus or postnasal drip	0.76 ± 1.25	0.42 ± 0.85	0.292
Difficulty swallowing food, liquids or pills	0.73 ± 1.17	0.26 ± 0.73	0.013*
Coughing after you ate or lie down	0.52 ± 0.85	0.35 ± 0.66	0.541
Breathing difficulties or choking episodes	0.48 ± 0.96	0.13 ± 0.43	0.063?
Troublesome or annoying cough	0.39 ± 0.80	0.16 ± 0.45	0.214
Sensations of something sticking throat or a lump in throat	1.01 ± 1.26	0.52 ±0.93	0.040*
Heartburn, chest pain, indigestion, or stomach acid coming up	1.12 ± 1.33	1.06 ± 1.37	0.830

* Significant results (p<0.05)
? Borderline significance

pain, or indigestion (1.12±1.33) with a significant difference in prevalence in sensation of lump in throat and difficulty in swallowing (p=0.04 and 0.013, respectively).

DISCUSSION

Laryngopharyngeal reflux disease (LPRD) is among the most common diagnoses made by laryngologists and has been reported to affect roughly 50%

Table 4: Possible correlations with the total reflux index (RSI)

	Total Reflux (RSI)		p-value
	Absent (≤10)	Present (>10)	
Age (mean± SD)	42.97 ± 13.37	51.05 ± 13.51	0.026*
Gender			0.172
Male	13 (92.9%)	1 (7.1%)	
Female	51 (71.8%)	20 (28.2%)	
TSH			0.888
Hyper-thyroid	6 (75.0%)	2 (25.0%)	
Eu-thyroid	33 (71.7%)	13 (28.3%)	
Hypo-thyroid	20 (76.9%)	6 (23.1%)	

* Significant results ($p<0.05$)

of patients with throat or vocal complaints (8). It is a term that has been described by Koufman to coin the laryngeal manifestations of gastroesophageal reflux, which include among others dysphonia, throat clearing, cough, globus pharyngeus, and dysphagia (8,14). The backflow of the refluxate material into the esophagus is known to result in an array of mucosal changes that range from reflux esophagitis to Barret's esophageus and esophageal adenocarcinoma. The degree and extent of injury is related not only to the duration of exposure of the mucosa to the refluxate material but also to the nature of the refluxate and the proximal extent of exposure (15,16). When the refluxate material reaches the larynx, a different clinical presentation arises and is referred to as LPRD. The lack of protective mechanisms such as peristalsis and bicaorbonate, makes the laryngopharyngeal mucosa more vulnerable and fragile. It has been reported that as few as three reflux episodes per week and a pH up to 5.0 can damage the laryngeal mucosa (17). The most common laryngeal findings include mucosal edema, diffuse or localized erythema, various muscle tension patterns, and thick mucus. Rarer but more serious manifestations or complications associated with LPRD include laryngospasm and laryngeal cancer (14, 18).

Several tests have been used to diagnose LPRD and these include: Reflux Symptom Index (RSI), Reflux Finding Score (RFS), Double probe pH monitoring, Pepsin (sputum) as a marker of LPR, Sensory testing; Laryngopharyngeal sensory descrimination testing (FEESST), Esophagoscopy, Barium esophagography and Bernstein acid perfusion (19-23). The reflux symptoms Index was described by Belfaski as a compilation of nine reflux related laryngeopharyngeal symptoms. The severity of the symptoms has been graded from 0 to 5 with a total score of above 10 being indicative of the presence of LPRD. In a study conducted on 25 subjects documented to have LPRD by pH metry, the validity and reliability of the RSI has been reported (24). In our investigation the RSI was used as a diagnostic for LPRD in patients with hypothyroidism.

The literature indicates that laryngopharyngeal symptoms are more

often than not ignored in hypothyroidism in view of the more significant systemic manifestations of this disease in relation to the cardiovascular, neuromuscular and ocular systems (25). The results of our study indicate higher prevalence of LPRD in patients with hypothyroidism compared to controls, even though the difference was not statistically significant. This was evident in both the overall group of patients with hypothyroidism vs. controls (24.7% *vs.* 9.7%) and in those with TSH> 4.2 *vs.* controls (23.1% *vs.* 9.7%). Comparison between all three groups, those with TSH>4.2 mU/L, those diagnosed with hypothyroidism and normal TSH at the time of investigation of this study and controls revealed no significant difference as all p values were less than 0.05.

The lack of significant difference in the prevalence of LPRD in the overall group diagnosed with hypothyroidism and controls might be attributed to the fact that all patients were already on treatment and only 30% were practically hypothyroid at the time of diagnosis, even though all 52 patients enrolled in the study were diagnosed as being hypothyroid. The lack of significant difference in the prevalence of LPRD in patients with TSH>4.2 mU/L and those with normal TSH can be accounted for by the possible slow and progressive myxedematous tissue changes that can occur once patients develop hypothyroidism and that might or might not revert to normal after the initiation of therapy and normalization of the TSH level. Of course this remains a hypothesis because of the lack of laryngeal examination to document myxedematous changes in the vocal folds and the absence of studies in the literature examining the effect of thyroidal hormonal therapy on the laryngeal tissues in patients diagnosed with hypothyroidism.

What is more important is the higher average score of all laryngopharyngeal symptoms in patients with hypothyroidism compared to controls. The higher severity of all 9 laryngopharyngeal symptoms in our patient group can be explained on several basis: One is the known motility and transport functions disorders in patients with hypothyroidism. Several studies have confirmed a reduction in the motor activity of the stomach, intestine and colon (26,27). Changes in the motor activity of the digestive system may result in distention of the stomach and change in bowel habits. A recent esophageal scintigraphic study by Yaylali *et al.* on thirty females subjects with hypothyroidism, revealed a marked increase in the mean esophageal transit time and gastric emptying (28). However, there is no correlation between abnormalities in gastrointestinal system kinetics and level of hypothyroidism (26). The possible mechanism for these findings is the accumulation of mucinous material (mucopolysaccharides) in the gastrointestinal system mucosa, leading to dysmotility (29, 30). In LPRD, the basic pathophysiology involves dysfunction of the upper esophageal sphincter (UES). While UES tone has not specifically been studied in hypothyroid patients, it is known that hypothyroidism does negatively affect

esophageal motility, leading to delayed motor activity and increased emptying time (28-31). This delayed peristalsis may be a set up for the refluxate material to reach the larynx and manifest as atypical symptoms of LPRD. Of course this remains a hypothesis in the absence of esophageal endoscopy and manometric studies.

A second possible mechanism is the myxedematous changes that can affect not only the vocal folds, but also the laryngeal mucosa and muscles. Animal studies conducted by Ritter *et al.* on laryngeal connective tissue staining strongly confirmed the presence of hyaluronic acid-containing mucoprotein (32). Likewise human studies have demonstrated the presence of acid mucopolysaccharides in the vocal folds (33). Edema of the intrinsic laryngeal muscles may also hypothetically contribute to the foreign body sensation and difficulty in swallowing (34, 35). Swelling or increase in laryngeal muscle mass my hider or limit the cephalo-caudal movement of the laryngeal framework during swallowing. Of course this remains a hypothesis that needs further investigation. What is evident in the literature, on the other hand, is the correlation between laryngeal edema and the presence of atypical symptoms in patients with LPRD (36).

A third but less likely mechanism is vocal fold paralysis due to hyperplasia of the gland or even edema of the nucleus ambiguous of the vagus nerve as reported by many (32-35, 37,38). The paralysis or impaired mobility can be attributed to stretching of the recurrent laryngeal nerve, compression, perineural fibrosis and/or inflammation. Patients with glottic insufficiency may complain of throat clearing, aspiration and difficulty in swallowing in addition to their phonatory symptoms such as vocal fatigue, hoarseness and loss of power (39). The lack of laryngeal examination does not allow to either refute or confirm the above two hypotheses, namely the presence of myxedematous mucosal changes and impaired vocal fold mobility.

Our study carries two limitations: One is the lack of laryngeal imaging such as endoscopy to assess the presence or absence of myxedematous changes or vocal fold mobility, and second is the lack of any manometric study to examine esophageal motility or dysfunction. Nevertheless, this is the first study to explore the prevalence of LPRD in patients diagnosed with hypothyroidism. The results of this study shed more light on the gastrointestinal dysfunction and related laryngeal effect.

In conclusion, it is crucial to recognize LPRD especially in patients whose symptoms may be attributed to a concomitant condition, such as hypothyroidism. Hypothyroidism is a condition whose normal laryngeal manifestations may mask an underlying LPR. Thus, it is important to understand the nature of LPRD in these patients and provide more comprehensive management for neck symptoms in patients with hypothyroidism. Based on the results of our study, LPRD is more prevalent in patients with hypothyroidism compared to normal individuals with no statistically significant difference. The prevalence of these symptoms should alert the treating physician to the possibility of LPRD and

prompt further diagnostic tests and therapeutic intervention.

Conflict of interest

The authors declare that there is no conflict of interest.

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