

The increased risk of globus pharyngeus in patients with chronic thyroiditis: a case control study

S. KARAHATAY¹, A. AYAN², U. AYDIN¹, S. INCE², O. EMER², E. ALAGOZ²

¹Department of Otolaryngology, Head and Neck Surgery, Gulhane Military Medical School, Ankara, Turkey

²Department of Nuclear Medicine, Gulhane Military Medical School, Ankara, Turkey

Abstract. – OBJECTIVE: A correlation between globus pharyngeus and thyroid gland inflammation has been mentioned in previous studies. However, the potential risk of globus pharyngeus in chronic thyroiditis patients has not been shown so far. The aim of this study is to investigate a possible association between chronic thyroiditis and globus pharyngeus.

PATIENTS AND METHODS: The study was performed in an ultrasound (US) center of a tertiary health care institution. Ninety-two patients who were under examination for suspected thyroid pathologies or undergoing follow-up for a previously diagnosed thyroid disease were enrolled in the study. The patients were divided into two groups according to the existence of globus symptoms. Subsequently, all patients underwent high-resolution thyroid ultrasounds. The patients whose ultrasound findings were suggestive of chronic thyroiditis constituted the second subgroup. The demographic data of the patients and other ultrasound findings including the volume of the thyroid glands and nodules, if any, were noted as well.

RESULTS: Sixty-seven female (73%) and 25 male (27%) patients were enrolled in the study. Thirty-two (35%) of the 92 patients constituted the globus pharyngeus group according to their responses to the questionnaire and the US findings were concordant with chronic thyroiditis in 36 (39%) patients. The correlation between chronic thyroiditis and globus sensation was significant ($p = 0.004$), and the odds ratio was calculated as 3.7 (95% CI = 1.5-9.11). Other parameters including age, sex, thyroid volume and nodule status were not significantly related to globus pharyngeus in this particular patient series.

CONCLUSIONS: In the presented study, the risk of globus pharyngeus occurrence was calculated as 3.7-fold higher in patients with chronic thyroiditis. Being a preliminary report, it is necessary to confirm this finding and understand the pathophysiological mechanism via further investigations with a larger patient series.

Key Words:

Globus pharyngeus, Chronic thyroiditis, Ultrasound.

Introduction

Globus pharyngeus is a common condition in otolaryngology practice that constitutes approximately 4% of all new patient referrals¹. Although patients may express discomfort through various complaints, the term globus is usually defined as a “sensation of a lump in the throat” and “a feeling of something stuck in the throat”. The historical nomenclature of “globus hystericus” has been abandoned, as many organic conditions were proven to result in this sensation², including gastro-esophageal reflux, abnormal upper esophageal sphincter function, esophageal dysmotility, cervical heterotopic gastric mucosa, tongue base hypertrophy, epiglottic lesions, thyroid diseases, and cervical osteophytes, as well as psychological factors³. Aside from the benign diseases listed above, globus pharyngeus may also be related to malignancies. For example, 3% of hypopharyngeal cancer patients may present with globus sensation as the first and only symptom of the disease⁴. This large spectrum of etiologic conditions necessitates an extensive workup. As the etiologic conditions have yet not been clearly elucidated, unfortunately, no consensus on diagnostic tools has been established thus far³. Moreover, despite all the efforts of diagnosis and treatment, 40% of patients may still be symptomatic after approximately an eight-year period².

The possible links between the thyroid gland and globus pharyngeus have been a source of investigation. The high prevalence of globus in

women, the persistent nature of complaints, and the anatomical proximity of the gland to the localization of the discomfort are considered clues to the association. Moreover, the resemblance between the well-known compression symptoms of large goiters and globus sensation encouraged researchers to perform a series of studies. However, almost all articles able to be reached have mainly investigated the relationship between globus sense and thyroid nodules or enlarged goiters, but chronic thyroiditis, the other common thyroid disease, has been overlooked. Only in a few studies have findings indicating a relationship between inflammation in the thyroid gland and globus pharyngeus been mentioned in addition to other findings of these studies^{5,6}. However, no articles focusing primarily on the potential risk of globus pharyngeus in chronic thyroiditis patients were found by reviewing the literature.

The aim of this study is to investigate a possible association between chronic thyroiditis and globus pharyngeus.

Patients and Methods

This study was performed in an ultrasound (US) center of a tertiary health care institution and the design of the study was approved by the institutional Review Board. This center is only interested in patients under examination for suspected thyroid pathologies or undergoing follow-up for a previously diagnosed thyroid disease. The study was conducted with patients who were

referred to this center between January 2015 and August 2015. Exclusion criterion were previous upper aerodigestive tract cancers, including thyroid cancers, previous surgery involving the head and neck region that might alter swallowing function, previous external beam radiation or radioiodine ablation therapy, acute upper airway infections, acute or sub-acute thyroiditis, or having thyroid nodules greater than 3 cm. The eligible patients were asked whether they had ever experienced a feeling of “a lump in their throats” or “something stuck in their throats” for more than three months. According to their responses, the patients were divided into two groups. Then, the patients underwent thyroid US examinations. The US examinations were performed by thyroid radiologists who were unaware of the patients’ study groups, and they used a high-resolution US system equipped with 14-MHz linear probe (GE Logiq 9, Milwaukee, WI, USA). The US findings encompassing the thyroid gland volumes, the nodule status, and the sizes of the nodules, if any, were noted. During the examinations, special attention was paid to evaluating chronic thyroiditis-related grayscale US features. These features were enlarged, hypoechoic, heterogeneous glands with lobulated contours, hypoechoic areas separated by echogenic fibrous septa, or a small gland with a heterogeneous echo pattern (Figure 1). Finally, the patients were again subdivided into two groups according to their US-based chronic thyroiditis diagnoses. No further blood tests for chronic thyroiditis diagnosis were performed to comply with the Ethical Committee-

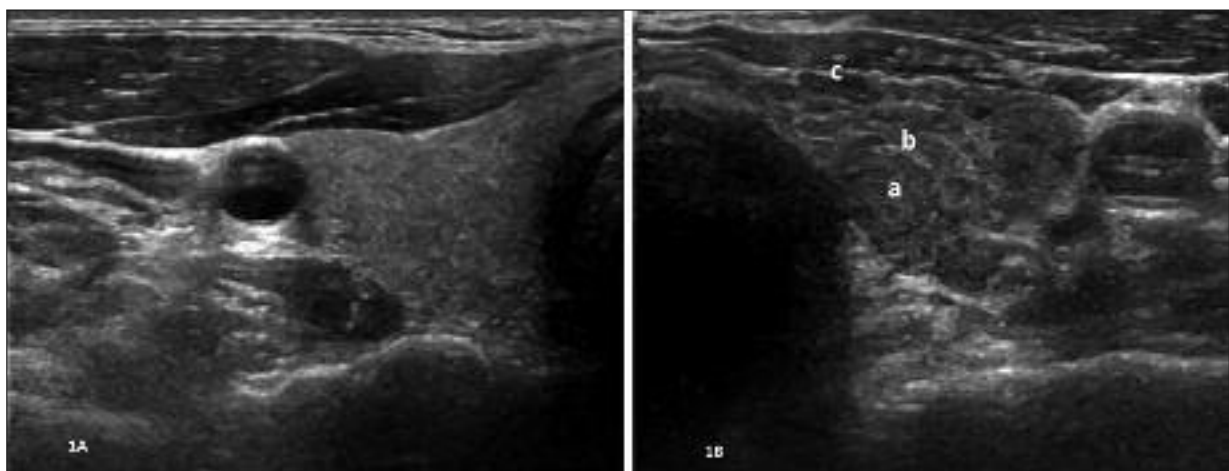


Figure 1. High-resolution thyroid ultrasound images. **A**, Normal ultrasound findings. Note the homogeneous echotexture. **B**, Ultrasound findings of a 32 year old woman with chronic thyroiditis **a**, heterogeneous echotexture **b**, hypoechoic micronodules (1-6 mm) with surrounding echogenic septations **c**, contour irregularity.

approved study design. However, the patients' medical records were reviewed and the thyroid autoantibody levels were noted when found, as well as the thyroid scan results.

Statistical Analysis

Statistical analyses were performed to reveal the thyroid gland-dependent risk factors, especially chronic thyroiditis, in globus sensation occurrence using the chi-square test, odds ratio (OR), Student's *t*-test, and Wilcoxon-Mann-Whitney test, and a *p* value of less than 0.05 was considered statistically significant.

Results

In total, 92 patients were eligible for the study: 67 females (73%) and 25 males (27%). The mean ages and standard deviations of the female patients and male patients were 50.1 ± 15.8 years and 54 ± 16.8 years, respectively. Thirty-two (35%) of the 92 patients constituted the globus pharyngeus group according to their responses to the questionnaire. The US findings were concordant with chronic thyroiditis in 36 (39%) patients, and these patients were sub-grouped as the chronic thyroiditis group. By reviewing the medical records, the autoantibody levels of 20 of the 32 patients in the chronic thyroiditis group were higher than the reference levels, and two additional patients had thyroid scans revealing chronic thyroiditis. Finally, 22 of the 36 patients in the chronic thyroiditis group also had laboratory findings suggestive of a US-based chronic thyroiditis diagnosis. The mean calculated thyroid volume was 12.5 ± 8.37 ml for the whole study group. The existence of at least one nodule in one thyroid lobe was accepted as having a nodule-positive status. Thirty-two of the 98 patients had unilateral and 35 patients had bilateral thyroid nodules. Eventually, 67 (73%) patients in total were noted as nodule-positive.

The mean age and standard deviations of the patients with and without globus pharyngeus were 47.9 ± 13.3 years and 52.9 ± 17.3 years, respectively, and the difference was insignificant ($p = 0.158$). The number of the female patients (22 of the 67) with globus sensation was higher than that of the male patients with globus sensation (10 of the 25). However, sex was not significantly related to globus pharyngeus occurrence in the presented study ($p = 0.521$). The median total thyroid volumes between the first and third quartile limitations of the patients with and without globus pharyngeus sensation were 10.81 (7.1-16.2) ml and 9.45 (6.93-13.81) ml, and the difference was insignificant ($p = 0.519$).

Regardless of the sizes of the thyroid nodules, 24 of the 67 nodule-positive patients were suffering from globus pharyngeus. On the other hand, 43 of the 60 patients without globus pharyngeus were harboring at least one nodule in one thyroid lobe. Keeping in the mind that nodules greater than 3 cm had been excluded from the study, no correlation was found between thyroid nodules and globus pharyngeus in this series of patients ($p = 0.732$). The results are summarized in Table I.

In the presented study, 19 of the 36 patients who were diagnosed with chronic thyroiditis were suffering from globus sensation, and 43 of the 56 patients who were without a chronic thyroiditis diagnosis were without globus sensation, as well. The correlation between chronic thyroiditis and globus sensation was significant ($p = 0.004$), and the OR was calculated as 3.7 (95% CI = 1.5-9.11) (Table II).

Discussion

Globus pharyngeus sensation is a common complaint reported by up to 46% of apparently healthy individuals at some time in their lives⁷, and it constitutes approximately 4% of new referrals to otolaryngology clinics¹. Several organ-

Table I. Demographics and US findings of patients with and without globus pharyngeus.

	Patients with globus	Patients w/o globus	<i>p</i> -value	Test
Age (mean $\pm$ SD) years	47.9 ± 13.3	52.9 ± 17.3	0.158	Student's <i>t</i> -test
Gender (male/female)	10/22	15/45	0.521	Chi-square test
Total thyroid volume [(median (25%-75%)] ml	10.81 (7.1-16.2)	9.45 (6.93-13.81)	0.519	Wilcoxon-Mann-Whitney test
Thyroid nodule status (with/without)	24/8	43/17	0.732	Chi-square test

Table II. Chronic thyroiditis frequency among patients with and without globus pharyngeus.

	Patients w/o globus	Patients with globus	Total
Patients w/o thyroiditis	43 (47%)	13 (14%)	56 (61%)
Patients with thyroiditis	17 (19%)	19 (20%)	36 (39%)
Total	60 (65%)	32 (35%)	92 (100%)

Chi-square test $p = 0.004$ and OR: 3.7 (95% CI = 1.5-9.11).

ic pathologies and psychological conditions have been reported in the etiology of this unique entity³. The wide variety of the etiological spectrum warrants a time- and effort-consuming diagnostic workup, and a multidisciplinary collaboration is often mandatory. In most cases, reaching the exact diagnosis is achieved through the elimination of other possible etiologic conditions. However, some patients complaining of globus pharyngeus may remain with unknown etiology despite all the efforts². On the other hand, no consensus has been established yet in the algorithm of the diagnostic procedures.

The relationship between thyroid pathologies and globus pharyngeus sensation has always been a source of interest. Consorti et al⁸ compared the frequency and severity of the globus pharyngeus symptoms of patients before and shortly after the thyroidectomy surgeries. After classifying the patients regarding of their complaint levels with a modified symptom scale, they reported that approximately 58% of the patients with thyroid disease were in the moderate or severe symptom group, and only 20% of the patients were completely asymptomatic. Three months after the surgeries, an improvement in the conditions of the patients in the moderate or severe symptom group was reported. However, the authors also stated that new symptoms had emerged after the surgeries in the asymptomatic group. The authors attributed this unexpected finding to a repetitive strain injury of the paralaryngeal muscles. In their remarkable study, Nam et al⁹ aimed to identify the characteristics of thyroid nodules that can cause globus symptoms. After excluding patients with other possible causes of globus pharyngeus, the authors obtained the symptom scores of patients having only one thyroid nodule, and they compared demographic, ultrasonographic, and pathologic data between the groups. In conclusion, they stated that whether solid or cystic, nodules larger than 3 cm or located on and anterior to the trachea could cause globus symptoms. Marshall et al¹⁰

conducted a work to investigate a possible association between thyroid nodules and globus pharyngeus. They stated that impalpable, US-detectable thyroid nodules were significantly more common in patients with globus pharyngeus than in controls. The study was conducted between 1993 and 1995, and a 7.5-MHz probe was used, which was accepted as a high-resolution US during these time spans. Burns and Timon⁵ published a two-year prospective study with the longest follow-up period compared to other articles. Fifty-eight of the 200 patients were found to have symptoms of globus pharyngeus before the surgeries, and 80% of these patients' symptoms were resolved post-operatively, indicating the relationship between globus pharyngeus and thyroid pathologies.

All the studies summarized above were mainly focused on the association between nodule status, including size and location, and globus pharyngeus. In only two articles, chronic inflammation of the thyroid gland was literally mentioned. In their study, Burns and Timon⁵ concluded that patients with histological features of inflammation showed the greatest symptom improvements two years after the surgery. Being inspired by the latter study, Banks et al⁶ investigated an association between compressive symptoms and thyroid inflammation. As a conclusion, the authors stated that in addition to size of the gland, there were other factors in the development of compressive symptoms, and inflammation of the gland might be one of those factors. No articles able to be reached directly focused on the risk of thyroiditis in globus pharyngeus occurrence; hence, we conducted this study.

Besides the well-known diagnostic role of US in nodular thyroid disease, high-resolution US is also proven an effective tool in the management of chronic thyroiditis, especially in Hashimoto thyroiditis. The main histopathologic indications of chronic thyroiditis are the diffuse infiltration of the thyroid parenchyma with lymphocytes and fibrosis. This disruption of the normal thyroid

tissue structure results in a special sonographic appearance. Findings in grayscale US include an enlarged, hypoechoic, heterogeneous gland with lobulated contours, hypoechoic areas separated by echogenic fibrous septa or a small gland with a heterogeneous echo pattern are considered consistent with the diagnosis of chronic thyroiditis¹¹⁻¹³. These characteristic sonographic appearances have a 95% predictive value especially for micronodular Hashimoto thyroiditis¹³. Moreover, normal thyroid US findings were proven to be correlated with normal function tests and normal thyroid antibodies¹⁴. Thus, in this study, the thyroid US findings were used in diagnosing patients with chronic thyroiditis. According to our ethically approved study design, no extra thyroid tests were performed, including thyroid-stimulating hormone (TSH) and thyroid antibodies, which are also effective in the diagnosis and follow-up of the disease. However, by reviewing the medical reports of the patients, 20 of the 36 patients in the chronic thyroiditis group presented antibody levels over the reference value, and additional patients' thyroid scan findings were suggestive of chronic thyroiditis. Eventually, in 22 of the 36 patients with chronic thyroiditis, the US findings based diagnoses were also strengthened by the previously performed laboratory tests.

The association of the thyroid nodules with globus pharyngeus is well known. Therefore, patients having thyroid nodules greater than 3 cm were excluded from the presented study to minimize their additional effect on globus sensation⁹. Presumably, due to these patient selection criteria, thyroid nodules were not found to be significantly related to globus pharyngeus in the presented study. In addition, the mean total thyroid volume was not significantly different between patient groups with or without globus pharyngeus. On the other hand, thyroiditis was found to be a risk factor for globus pharyngeus in the presented series of patients. While the relation between these two entities has been mentioned previously, to best of the authors' knowledge, this is the first report that reveals the increased risk of globus pharyngeus in chronic thyroiditis patients. Future studies are needed to elucidate the pathophysiology of the globus pharyngeus occurrence in chronic thyroiditis patients. However, despite the lack of proven evidence, one can speculate that chronic and mild inflammation in the thyroid gland may give rise to the persistent globus "sense" instead of a manifested "pain", which is a well-known symptom of acute or sub-acute

thyroiditis. In other words, globus sensation may be considered a vague symptom of painful chronic thyroiditis, an entity that has been reported in a very few number of patients^{15,16}. It is also conceivable that underlying mechanisms which may trigger the autoimmune responses in chronic thyroiditis may also be an etiological cause for the globus sensation¹⁷.

Regarding gender, female patients constituted the majority of the whole study group (73%), the patient group with globus pharyngeus (69%), and the group with chronic thyroiditis (78%). This finding is concordant with the female dominant nature of thyroid diseases. Hypothetically, the previously reported high prevalence of globus pharyngeus in women^{1,2,5,6,17} may be related to the high prevalence of chronic thyroiditis in women, as well. However, in the presented study, sex was not found to be significantly related to the risk of globus pharyngeus occurrence. This finding may also be indicative of the greater impact of chronic thyroiditis rather than the gender's impact on the occurrence of globus sensation.

Conclusions

Thyroid nodules have been reported as one of the causes of the globus pharyngeus previously. However, no articles directly focusing on the potential risk of chronic thyroiditis in relation to the occurrence of globus pharyngeus have yet been published to best of the authors' knowledge. In the presented investigation, the risk of globus pharyngeus occurrence was calculated as 3.7-fold higher in patients with chronic thyroiditis. Being a preliminary report, it is necessary to confirm this finding and understand the pathophysiological mechanism via further investigations with a larger patient series.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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