Acoustic Voice Analysis in Subclinical Hyperthyroidism

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ABSTRACT

Objective: To investigate the effect of subclinical hyperthyroidism on voice quality using acoustic analysis.

Study Design: Cross-sectional comparative study.

Place and Duration of the Study: Department of Endocrinology and Metabolism, Ankara Diskapi Yildirim Beyazit Research and Education Hospital, Ankara, Turkey, from January to June 2020.

Methodology: A total of 115 participants, with 60 patients with subclinical hyperthyroidism and 55 healthy volunteers, were evaluated and compared. Healthy volunteers with similar age and gender distributions were also evaluated and compared. Acoustic variables including average fundamental frequency (F_0), relative average perturbation (RAP), jitter, shimmer, noise-to-harmonic ratio (NHR), and voice turbulence index (VTI) were measured and recorded.

Results: In the patient group, acoustic voice analysis results were obtained for F_0 224.97%, jitter 0.85%, RAP 0.51%, shimmer 3.16%, NHR 0.12 dB, and VTI 0.047, respectively. In the control group, these respective values were 219.60%; 0.74%; 0.46%; 3.11%; 0.12 dB; and 0.045, respectively. There was no statistically significant difference between the groups (p>0.05).

Conclusion: Subclinical hyperthyroidism does not cause a significant change in voice quality.

Key Words: *Acoustic analysis, Subclinical hyperthyroidism, Voice, Frequency*.

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INTRODUCTION

Normal serum free thyroxine (fT4) and triiodothyronine (fT3) in the presence of biochemically subnormal thyroid-stimulating hormone (TSH) levels (<0.5 mU/L) is referred to as subclinical hyperthyroidism. The prevalence of subclinical hyperthyroidism population-wide ranges from 0.7 to 12.4%.[1-5] Although some clinical symptoms such as weight loss, heat intolerance, increased sweating, and palpitations are caused by excessive thyroid hormones, these symptoms and signs are mostly mild and laboratory findings are usually not severe.

Objective acoustic evaluation of pathological sounds has been performed for nearly three decades now.[6]

The computerised multidimensional acoustic voice analysis provides both visual and numerical information. These analytical methods enable a better assessment of both the effects of diseases and treatments such as voice rehabilitation.

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Previous studies reported an impaired voice quality in patients with hypothyroidism.[7-9] Moreover, thyroid hormone replacement therapy in hypothyroid patients has been shown to cause an improvement in voice quality.[10] The data related to the association between hyperthyroidism and voice quality is scarce. Few studies showed impaired voice quality in patients with hyperthyroidism.[11,12] Overt hyperthyroidism is an important cause of sympathetic activation which may lead to impaired voice quality.[13] This study aimed to evaluate the voice quality in patients with subclinical hyperthyroidism by using acoustic analysis.

METHODOLOGY

This cross-sectional study was carried out at Ankara Diskapi Yildirim Beyazit Research and Education Hospital, Ankara, Turkey, between January 1 and June 1 2020. The sample size for the study was determined using the alpha level ($\alpha = 0.05$) of significance, population effect size (ES= 0.5), and power [$(1-\beta) = 0.80$].[14] One hundred and two participants (51 in each group) to be included in the sample. Patients with a diagnosis of subclinical hyperthyroidism who applied to the endocrinology outpatient clinic were evaluated. Healthy participants, who were distributed similarly by gender and age, were also analysed. All participants were over 18 years of age. Subjects with a history of severe voice usage or smoking, who had undergone neck radiotherapy and neck surgery, or those with a large multinodular and goitre plongeant were left out of the research.

Table I: Comparison of clinical and laboratory baseline features.

	Results*		p-value
	Patient	Control	
Men/women, n (%)	18/42 (30/60)	18/37 (32.7/67.3)	0.753
Increased thyroid volume (goiter), n (%)	31 (51.7)	6 (10.9)	<0.001
Age, years	47.5 (34.25-55.75)	43.6 (30.0-52.0)	0.436
TSH, mIU/L	0.28 (0.06-0.26)	2.32 (1.17-3.11)	<0.001
fT4, ng/dl	1.19 (±0.17)	1.05 (±1.18)	0.041
fT3, pmol/L	3.30 (2.95-3.47)	3.03 (2.90-3.10)	0.003
Anti-TPO, IU/L	96.6 (26.0-88.0)	224.7 (10-290)	0.005
TSI, IU/L	6.56 (3.85-10.55)	-	

Abbreviation: TSH; Thyroid-stimulating hormone, TSI; Thyroid-stimulating immunoglobulin, SD; Standard deviation, IQR; Interquartile range.

Table II: Comparison of acoustic voice analysis of patients with subclinical thyrotoxicosis and control patients.

	Results*		p-value
	Patient	Control	
F0 (Hz)	224.97 (158.41-245.40)	219.60 (168.20-237.70)	0.662
Jitt (%)	0.85 (0.53-1.43)	0.74 (0.45-1.21)	0.243
RAP (%)	0.51 (0.32-0.86)	0.46 (0.27-0.72)	0.191
Shim (%)	3.16 (2.39-4.72)	3.11 (2.29-3.76)	0.229
NHR (dB)	0.12 (0.11-0.14)	0.12 (0.11-0.13)	0.345
VTI	0.047 (0.038-0.061)	0.045 (0.035-0.055)	0.187

*Jitt; jitter, RAP; relative average perturbation, Shim; shimmer, NHR; noise-to-harmonic ratio, VTI; voice turbulence index. *Continuous variables were expressed as medians (interquartile ranges). Mann-Whitney U-test was used to compare the variables.*

Blood samples were obtained from the patients and the control group early in the morning after an eight-hour fast. TSH, free T3 (FT3), and free T4 (FT4) parameters were studied using an Abbott Architect I 2000 SR®. TSI (thyroid-stimulating immunoglobulin) and anti-TPO (anti-thyroid peroxidase TPOAb were also used for the differential diagnosis. Normal reference ranges of hormone test results were accepted as 0.45-4.95 mIU/L for TSH; 0.79-17.90 ng/dl for fT4; 2.63-5.70 pmol/L for fT3; and <5.61 IU/mL for anti-TPO. TSI analysis was carried out in another health centre, since it was not available in the hospital for just a few patients who have indications. The reference ranges indicated by the centre performing the test were used. An ultrasonographic scan was performed with Logiq E9 (6–15 MHz linear probe; GE Medical Systems, Milwaukee, WI, USA®). The volume of each lobe was calculated using the ellipsoid model formula (length × thickness × width × 0.52).[15] The same formula was used to assess thyroid volume (TV) was used to calculate nodule size. No Goiter was defined as a total TV of >18 mL in men and >13 mL in women.[16]

A Kay/Pentax Video stroboscope was used for the visualisation of the larynx, and a Computerized Speech Lab Model (CSL) 4500® was used for acoustic analysis of vocal quality. Visualisation was approached using video-laryringostroboscopy (VLS), in which a 70-degree rigid endoscope to the Karl Storz Laryngostrobe model 8020 (Karl Storz Endoscopy Ltd, Slough, UK®) and a 30-mm single-chip color Storz endoscopic telecam (Dx pal 202320®) was passed through the oral cavity and into the posterior oropharynx, so that the laryngeal cavity could be visualised. The subject was then asked to vocalise /i/ as in “meet” while using their normal pitch and loudness. These stroboscopic images were used to determine true vocal fold edema, erythema, closure, mucus, and vocal fold edges. It was noted if vocal fold masses or lesions were present or not.

The voice samples were recorded in a soundproofed space at volume levels that the individuals found tolerable. Each participant had their voice assessed using the Kay Pentax CSL (computer speech laboratory) Model 4500®. The CSL, a computer-interfaced system, contains both hardware and software designed to analyse components of the speech signal. The patient's verbal signal was recorded by the device MDVP (Multi-Dimensional Voice Program) while the subject was sat in a quiet office. The following acoustic variables were measured: average fundamental frequency (F_0); relative average perturbation (RAP); jitter; shimmer; noise-to-harmonic ratio (NHR); and voice turbulence index (VTI). The voice quality evaluation module analysis system was used to measure the other factors by having the participant maintain the vowel "a" for 4 seconds.

The analysis was conducted using SPSS version 22, and explanations of the variables' modes of expression were provided beneath the tables. Numbers and percentages were used to represent categorical variables. The Kolmogorov-Smirnov test was used to determine if the data had a normal distribution. While the appropriate chi-square test was preferred in non-numerical proportional comparisons, the Mann-Whitney U or t-test was used according to the normality distribution in the comparison of numerical variables. The acceptable threshold for statistical significance was $p<0.05$.

RESULTS

The fiber video-laryngoscopic imaging showed that the vocal fold mucosa movement, morphology, and closure were

normal in all patients. Although there were no difference in the groups' distributions of age and gender, there were notable variations in the levels of TSH, FT4, and FT3, respectively. The proportion of subjects with normal thyroid volume was 48.3% in the patient group and 89.1% in the control group (p<0.001), while the frequency of goiter was 51.7% and 10.9%, respectively (p<0.001, Table I).

Continuous variables were expressed as means ± standard deviation, or medians (interquartile ranges), depending on the normality of their distribution and categorical variables as numbers with percentages for the description of baseline characteristics. While the t-test was used for fT4 comparison, the Mann Whitney U-test was preferred for other continuous variables and Chi-square test was used for categorical variables.

Acoustic voice median values were obtained for F0 (%) 224.97; Jitt (%) 0.85; RAP (%) 0.51; Shim (%) 3.16; NHR (dB) 0.12; and VTI 0.047 in the patients with subclinical hyperthyroidism. In the control group, these values were determined to be F0 (%) 219.60; Jitt (%) 0.74; RAP (%) 0.46; Shim (%) 3.11; NHR (dB), 0.12; and VTI, 0.045, respectively. There were no statistically significant differences between the two groups, despite the fact that all of the results were typically higher in the patient group (p-values=0.662 [F0], 0.243 [Jitt], 0.191 [RAP], 0.229 [Shim], 0.345 [NHR], and 0.187 [VTI], respectively). All these results and comparative analyses are summarised in Table II and Figure 1.

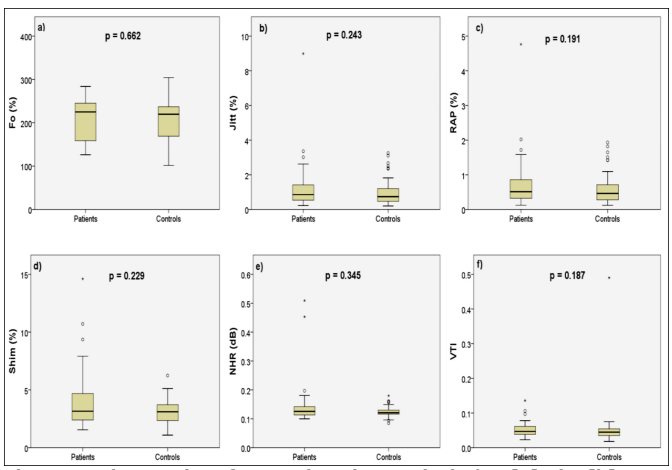

Figure 1: The results of acoustic voice analysis (Fo [a], Jitt [b], RAP [c], Shim [d], NHR [e] and VTI [f]) were shown schematically. The first figure on the charts refers to patients and the second figure refers to the control group.

DISCUSSION

Thyroid hormone receptors on the vocal cords may influence the characteristics of the voice. It may be difficult to interpret that whether the effect of thyroid hormones on voice is a direct receptor-mediated effect or not. For this reason, patients with prominent clinical findings, such as overt hyperthyroidism, which may cause secondary effects on voice through sympathetic hyperreactivity, were excluded. The direct effects of thyroid hormones on voice quality were investigated. It was demonstrated that subclinical hyperthyroidism does not affect acoustic variables.

Diseases and diagnostic-management procedures such as laryngeal intubation, vocal cord-related surgeries, cord polyps, and related issues can lead to the deterioration of voice quality by direct mechanical effect due to their proximity to the vocal cords.[17,18] In rare conditions, non-close diseases and procedures can impair voice quality, such as large plongeant multinodular goiter and thyroid and parathyroid operations.[19,20] This study was designed to select patients without these local effects. Patients with a history of neck surgery or radiotherapy were also excluded. All patients' laryngeal examinations were normal. Although some of the patients had goiter, none of them was large enough to pressure the surrounding tissue. Therefore, the results can be interpreted as free from mechanical influences.

Many hormones are known to affect voice quality, regardless of the direct mechanical effect. The relationship between some hormones, such as growth hormones, sex steroids, and voice quality has been shown in many studies.[21] Sex steroid hormone receptors have been found in all layers of the membranous vocal fold, not withstanding the contradicting findings.[22] The presence of thyroid hormone receptors on the laryngeal tissue has also been demonstrated.[23] Due to the presence of these receptors, thyroid hormones are believed to have direct effects on laryngeal tissue and vocal cords. Therefore, the authors think that even in cases of mild thyroid disease, voice quality changes may occur.

Many studies have shown that speech and voice quality is impaired in hypothyroidism.[14,24] This rate varies between 9-81%, depending on the severity of hypothyroidism.[24,25] Clinically, symptoms are often loss of vocal range, reduced voice frequency, vocal fatigue, hoarseness, low voice, and decreased voice intensity. Polysaccharide and fluid accumulation in the lamina propria of the vocal fold, nervus vagus edema, and myxedema in the cricothyroid muscle are potential mechanisms in etiopathogenesis.[14,23] These histopathologic findings are similar to the changes made by androgens on vocal folds in women.

A common symptom of hyperthyroidism is a deeper voice.[11] Unfortunately, there is not much research examining the connection between voice quality and hyperthyroidism. A recent study published an assessment of acoustic and perceptual voice in hyperthyroid patients.[14] In this study, 27 hyperthyroid patients were compared in terms of their acoustic and perceptual voice assessment results before and

after hyperthyroidism treatment. While there were no changes in acoustic sound analysis results except MPT, all perceptual analysis results showed improvement with treatment.[14] In a second recently published study, (Fo), jitter, HNR, and Maximum Phonation Time data were evaluated in 18 female hyperthyroid patients. All variables showed impairments due to hyperthyroidism, but the most affected was Fo.[12] These two studies were conducted with a very low number of patients, and no information was given on whether hyperthyroidism is overt or subclinical. Since the clinical occurrence of overt hyperthyroidism is related to secondary effects such as increased sympathetic activation, it is difficult to distinguish whether the resulting changes in voice quality are due to secondary causes or the direct effects of the thyroid hormone itself. Because this study consisted of patients with subclinical hyperthyroidism, those who were generally not symptomatic, and those with sympathetic hyperreactivity findings are absent. For this reason, the current study can be regarded as the first study in the literature that shows the direct effect of subclinical hyperthyroidism on voice in its most simple form.

This study does have certain limitations. First, the research has a small patient population and was conducted in a single centre. Second, it lacked a control group of individuals with overt hyperthyroidism and elevated sympathetic nervous system sensitivity. Lastly, subjective voice assessment with perceptual voice analysis was not performed on these patients, and video-laryngoscopic examination did not perform in the control group. Despite these limitations, this study is important, as it demonstrates the lean effect of thyroid hormone excess only in patients with subclinical hyperthyroidism. Larger randomised controlled trials are needed to clarify this potential effect.

CONCLUSION

The results of almost all acoustic voice analysis parameters, including the number of sound waves, frequency, amplitude, and speech efficiency produced by the vocal cords in patients with subclinical hypothyroidism, were similar to the control group, showing non-significant effect of the disease on voice.

ETHICAL APPROVAL:
Ethics committee approval was obtained from Sakarya University Faculty of Medicine. (Number. 16214662/050.01.04/882, date: 20.01.2020).

PATIENTS' CONSENT:
Informed consent was obtained from all the participants in this study.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
TD: Data gathering, idea owner of this study.
MK: Study design.
HC: Statistical analysis.
MA: Owner of this study.
EC: English translation.
CV: Writing, the manuscript.
MC: Preparing tables and references.
All the authors have approved the final version of the manuscript to be published.

REFERENCES

1. Fade JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf)* 1991; **34(1)**:77-84. doi: 10.1111/j.1365-2265.1991.tb01739.x.
2. Sawin CT, Geller A, Wolf PA, Belangar JA, Baker E, Bacharach P, *et al*. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 1994; **331(19)**:1249-52. doi: 10.1056/NEJM199411103311901.
3. Sundbeck G, Jagenburg R, Johansson PM, Eden S, Lindstent G. Clinical significance of low serum thyrotropin concentration by chemiluminometric assay in 85-year-old women and men. *Arch Intern Med* 1991; **151(3)**:549-56.
4. Franklyn JA, Black EG, Betteridge J, Sheppard MC. Comparison of second and third generation methods for measurement of serum thyrotropin in patients with overt hyperthyroidism, patients receiving thyroxine therapy, and those with nonthyroidal illness. *J Clin Endocrinol Metab* 1994; **78(6)**:1368-71. doi: 10.1210/jcem.78.6.8200938.
5. Eggertsen R, Petersen K, Lundberg PA, Nyström E, Lindstent G. Screening for thyroid disease in a primary care unit with a thyroid stimulating hormone assay with a low detection limit. *BMJ* 1988; **297(6663)**:1586-92. doi: 10.1136/bmj.297.6663.1586.
6. Uloza V, Saferis V, Uloziene I. Perceptual and acoustic assessment of voice pathology and the efficacy of endolaryngeal phonomicrosurgery. *J Voice* 2005; **19(1)**:138-45. doi: 10.1016/j.jvoice.2004.01.009.
7. Gupta OP, Bhatia PL, Agarwal MK, Mehrotra ML, Mishr SK. Nasal, pharyngeal, and laryngeal manifestations of hypothyroidism. *Ear Nose Throat J* 1977; **56(9)**:349-56.
8. Aronson AE. Professional Voice: The Science and Art of Clinical Care. *Mayo Clin Proc* 1991; **66(12)**:1292-93.
9. Ritter FN. The effects of hypothyroidism upon the ear, nose and throat: A clinical and experimental study. *Laryngoscope* 1967; **77(8)**:1427-79. doi: 10.1288/00005537-196708000-00016.
10. Birkent H, Karacalioglu O, Merati AL, Akcam T. Gerek M. Prospective study of the impact of thyroid hormone replacement on objective voice parameters, *Ann Otol Rhinol Laryngol* 2008; **117(7)**:523-27. doi: 10.1177/000348940811700710.
11. Canaris GJ, Steiner JF, Ridgway EC. Do traditional symptoms of hypothyroidism correlate with biochemical disease? *J Gen*

Intern Med 1997; **12(9)**:544-50. doi: 10.1046/j.1525-1497.1997.07109.x.

12. Kovacic G. Voice and hyperthyroidism: Subjective voice complaints and alterations of the acoustic parameters of the voice. *Res Rev Insights* 2018; **2(1)**:1-4.
13. Chen JL, Chiu HW, Tseng YJ, Chu WC. Hyperthyroidism is characterised by both increased sympathetic and decreased vagal modulation of heart rate: Evidence from spectral analysis of heart rate variability. *Clin Endocrinol (Oxf)* 2006; **64(6)**:611-16. doi: 10.1111/j.1365-2265.2006.02514.x.
14. Junuzović-Žunić L, Ibrahimagić A, Altumbabić S. Voice characteristics in patients with thyroid disorders. *Eurasian J Med* 2019; **51(2)**:101-105. doi: 10.5152/eurasianjmed.2018.18331.
15. Vitti P, Rago T, Mazzeo S, Brogioni S, Lampis M, Liperi A, *et al*. Thyroid blood flow evaluation by color-flow Doppler sonography distinguishes Graves' disease from Hashimoto's thyroiditis. *J Endocrinol Invest* 1995; **18(11)**: 857-61. doi: 10.1007/BF03349833.
16. Kan S, Kizilgul M, Celik B, Beysel S, Caliskan M, Apaydin M, *et al*. The effect of disease activity on thyroid nodules in patients with acromegaly. *Endocr J* 2019; **66(4)**: 301-07. doi: 10.1507/endocrj.EJ18-0502.
17. Lazić MP, Babac S, Vuković M, Kosanovic R, Ivankovic Z. Acoustic voice analysis of patients with vocal fold polyp. *J Voice* 2011; **25(1)**:94-97. doi: 10.1016/j.jvoice.2009.04.002.
18. Ahmed M, Aurangzeb Abbas S, Boota M, Ashfaq M, Rashid AZ, Qureshi MA, *et al*. Should we routinely expose recurrent laryngeal nerve(s) during thyroid surgery? *J Coll Physicians Surg Pak* 2013; **23(3)**:186-9.
19. Xia F, Zhou T, Tao Z, Xia F. A voice acoustic analysis of thyroid adenoma patients after a unilateral thyroid lobectomy. *J Voice* 2012; **26(1)**:23-6. doi: 10.1016/j.jvoice.2010.10.013.
20. Davis J, Harries M. Voice change following thyroid and parathyroid surgery. *Tips Tricks Endocr Surg* 2014; **22(6)**: 199-203.
21. Moore C, Shalet S, Manickam K, Willard T, Maheshwari H, Baumann G. Voice abnormality in adults with congenital and adult-acquired growth hormone deficiency. *J Clin Endocrinol Metab* 2005; **90(7)**: 4128-32. doi: 10.1210/jc.2004-2558.
22. Kirgezen T, Sunter AV, Yigit O, Erdem G. Sex Hormone receptor expression in the human vocal fold subunits. *J Voice* 2017; **31(4)**:476-82. doi: 10.1016/j.jvoice.2016.11.005.
23. Altman KW, Haines GK, Vakkalanka SK, Sanjay P, Keni BS, Peter A, *et al*. Identification of thyroid hormone receptors in the human larynx. *Laryngoscope* 2003; **113(11)**:1931-34. doi: 10.1097/00005537-200311000-00014.
24. Mohammadzadeh A, Heydari E, Azizi F. Speech impairment in primary hypothyroidism. *J Endocrinol Invest* 2011; **34(6)**:431-33. doi: 10.1007/BF03346708.
25. Costa EBM, Pernambuco LA. Vocal self-assessment and auditory-perceptual assessment of voice in women with thyroid disease. *Rev CEFAC* 2014; **16(3)**: 967-72.