

## Main Article

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# Presbylarynx: is diabetes mellitus a risk factor for vocal atrophy? A prospective case-control study

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## Abstract

**Objective.** To evaluate the prevalence of diabetes mellitus type 2 in subjects with presbylarynx.

**Method.** A case-control, prospective study was carried out on consecutive subjects who presented to the otorhinolaryngology department.

**Results.** The study comprised 174 subjects (60 males and 114 females) with a mean age of 73.99 years (65–95 years). Presbylarynx was identified in 71 patients (41 per cent). Among patients with diabetes mellitus type 2, 20 patients (77 per cent) exhibited endoscopic signs of presbylarynx. A statistically significant difference was found between presbylarynx versus no presbylarynx concerning diabetes mellitus type 2 ( $p < 0.001$ ). Subjects with diabetes mellitus type 2 were approximately eight times more likely to have presbylarynx compared to subjects without diabetes mellitus type 2.

**Conclusion.** In this study, 77 per cent of patients with diabetes mellitus type 2 had endoscopic signs of presbylarynx. A multivariable analysis, which took into account co-morbidities of the elderly, identified diabetes mellitus type 2 as a possible risk factor for presbylarynx. Many physiopathological mechanisms might explain this result, as diabetes mellitus type 2 is known to affect muscular, neurological and vascular systems.

## Introduction

Population ageing is one of the challenges that worldwide healthcare systems face in the twenty-first century, and dysphonia is one of the common but undertreated health problems of the elderly.<sup>1,2</sup> The incidence of voice disorders in the geriatric population is estimated to range from 12 per cent to 35 per cent.<sup>3–8</sup> Among the various causes of geriatric dysphonia, presbylarynx is attracting considerable attention.<sup>3–7,9</sup>

Presbylarynx can be defined as age-related morphological changes in the larynx. It includes structural and functional changes such as vocal fold bowing attributed to connective tissue loss and muscle atrophy, which produces a vocal fold approximation deficit.<sup>10</sup> The changes in vocal characteristics associated with the ageing process are called presbyphonia, and include auditory-perceptual changes such as hoarseness, breathiness, pitch changes, instability and vocal fatigue.<sup>10–16</sup>

Given that the larynx is primarily a musculoskeletal organ, age-related degeneration that affects the human body will also affect the larynx.<sup>11</sup> Santos *et al.* described an association between functional impairment and the presence of presbylarynx. In that study, the mean value of muscle mass in the presbylarynx and non-presbylarynx groups was statistically different, with a lower mean for subjects with presbylarynx.<sup>17</sup> This suggests that diseases which may influence the muscular system may play a role in the age-related changes of the larynx, and diabetes mellitus is an example of those diseases.

Despite the consensus that diabetes mellitus affects the muscular, neurological and vascular systems, all of which are essential components of the phonatory apparatus, no prior study has examined the endoscopic findings associated with the ageing process of the larynx in elderly subjects with diabetes mellitus.<sup>18</sup>

It remains unclear as to how diabetes mellitus may influence the presence or severity of presbylarynx. The present case-control study examined the laryngeal findings of elderly patients with diabetes mellitus in order to contribute to our knowledge regarding the ageing process of the larynx, and to identify possible risk factors for noticeable presbylarynx.

## Materials and methods

This study was carried out in accordance with the guidelines of the Declaration of Helsinki on human studies.

This case-control, prospective, observational, cross-sectional study included a total of 194 consecutive subjects who presented to the otorhinolaryngology department, within a tertiary centre, from January to September 2020. All patients were evaluated by the same otorhinolaryngologist, and a comprehensive medical history was obtained from each subject. All of the patients underwent a complete otorhinolaryngological examination. The most frequent complaints that had motivated referral to the otorhinolaryngology department were hypoacusis, dizziness and dysphonia.

The inclusion criteria were: the ability to provide an accurate medical history, and age of 65 years or older (retirement age).

The exclusion criteria were: neurological diagnoses, such as Parkinson's disease, dementia or essential tremor; autoimmune diseases; and a history of thoracic or head and neck surgery, cancer, radiotherapy, thyroid pathology, vocal fold mass lesions, acute laryngitis or vocal fold paralysis.

Data regarding gender and age were collected.

### Diagnosis of presbylarynx

Each subject underwent fibre-optic videolaryngoscopy with stroboscopy (EndoStrobe, type CD11F/R; Xion, Berlin, Germany). Video recordings were obtained with a charge-couple device camera, and the videolaryngoscopic images were evaluated independently by two experienced otorhinolaryngologists.

No information regarding the demographics or clinical complaints was provided to the evaluators. Presbylarynx was considered when both observers identified two or more of the following endoscopic findings: vocal fold bowing, prominence of the vocal processes in abduction and a spindle-shaped glottal gap.<sup>5,13</sup>

### Diabetes mellitus and other chronic medical illnesses

Clinical charts were reviewed and all chronic medical illnesses were registered (based on the International Classification of Diseases, ninth revision). The integrated healthcare informatics system enabled the assessment of diagnoses made by the primary care family physician or by a medical specialist in the tertiary centre.

### Statistical analysis

All statistical analyses were performed using SPSS software version 24 (IBM, Armonk, New York, USA); *p*-values below 0.05 were considered statistically significant.

A descriptive analysis of patient characteristics was performed using frequencies (for categorical variables), or mean and standard deviation (SD) values (for continuous variables). Normal distribution was established using the Shapiro-Wilk test, with thorough analysis of skewness and kurtosis. Differences among paired groups were evaluated using the chi-square test (for categorical variables), or independent sample *t*-test or Mann-Whitney U test (for continuous variables).

A multivariable logistic regression was performed to identify the chronic medical illnesses predictive of presbylarynx.

## Results

### Study population

The study population included a total of 174 caucasian subjects (60 males and 114 females) with a mean age of 73.99 years (SD = 6.37; range, 65–95 years).

**Table 1.** Most frequent chronic medical illnesses of study population

Chronic disease	Presbylarynx?		<i>p</i> -value*
	Yes	No	
Cardiovascular	52 (73.2)	65 (63.1)	0.217
DM type 2	20 (28.2)	6 (5.8)	<0.001
Dyslipidaemia	34 (47.9)	58 (56.3)	0.347
Osteoarticular	37 (52.1)	42 (40.8)	0.186
High BMI	30 (42.3)	48 (46.6)	0.681
Gastrointestinal disorder	21 (29.6)	19 (18.4)	0.126
Renal disorder	9 (12.7)	5 (4.9)	0.114
Psychiatric disorder	30 (42.3)	13 (12.6)	<0.001
Ophthalmological disorders	18 (25.4)	26 (25.2)	1.000
Hypoacusis	23 (32.4)	31 (30.1)	0.877
Tinnitus	6 (8.5)	10 (9.7)	0.988
Dizziness	7 (9.9)	10 (9.7)	1.000
Sleep disorder	6 (8.5)	8 (7.8)	1.000
Respiratory disorder	34 (47.9)	22 (21.3)	<0.001

Data represent numbers (and percentages) of cases, unless indicated otherwise. \*Chi-square test. DM = diabetes mellitus; BMI = body mass index

The most frequent chronic medical illnesses were: cardiovascular diseases, diabetes mellitus type 2, dyslipidaemia, osteoarticular diseases, obesity or being overweight, gastrointestinal disorders, renal disorders, psychiatric disorders, ophthalmological disorders, otoneurological disorders, sleep disorders, and respiratory disorders (Table 1).

### Presbylarynx

Presbylarynx was identified in 71 patients (41 per cent), with no statistically significant predilection associated with gender ( $p = 0.254$ ). The mean age of the patients with presbylarynx was statistically higher (76.29 years; SD = 6.28) ( $p < 0.001$ ).

Among patients with presbylarynx, a glottal gap was identified in 22 patients (31 per cent), with no statistically significant predilection associated with gender ( $p = 0.222$ ). The mean age of the patients with presbylarynx and glottal gap was slightly higher (78.14 years; SD = 6.17), but the difference between the groups was not statistically significant ( $p = 0.099$ ).

### Diabetes mellitus type 2

Diabetes mellitus type 2 was identified in 26 patients (15 per cent), with no statistically significant predilection associated with gender ( $p = 0.007$ ) or age ( $p = 0.844$ ).

Among patients with diabetes mellitus type 2, 20 patients (77 per cent) exhibited endoscopic signs of presbylarynx. A statistically significant difference was found between presbylarynx versus non-presbylarynx groups concerning diabetes mellitus type 2 ( $p < 0.001$ ).

On the multivariable logistic regression model, subjects with diabetes mellitus type 2 were approximately eight times more likely to have presbylarynx compared to subjects without diabetes mellitus type 2 (Table 2).

## Discussion

The normal ageing process affects human function broadly and profoundly, including voice.<sup>2</sup> Thus, studies of voice

**Table 2.** Results of univariate and multivariate logistic regression model of diabetes mellitus and presbylarynx

Variable	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Diabetes, yes (reference: no)	6.340	2.340–16.78	<0.001	7.972	2.259–28.13	0.001

OR = odds ratio; CI = confidence interval

changes in the elderly are extremely relevant, because of the expansion of the ageing population, and the impact of dysphonia on the emotional and social function of older adults.<sup>19</sup>

Given that the larynx is primarily a musculoskeletal organ, research on systemic diseases with potential effects on the musculoskeletal system is of paramount interest, to improve knowledge regarding vocal changes in the elderly.

Generally, the elderly have multiple medical problems, and no single medical issue can be evaluated and treated in isolation.<sup>20</sup> Among the many systemic diseases that influence the voice, diabetes mellitus is attracting considerable attention. Thus, this study primarily aimed to evaluate the prevalence of diabetes mellitus in subjects with presbylarynx.

Diabetes mellitus type 2 was identified in 15 per cent of our study population, which is in reasonable accordance with previous series reporting a prevalence of 20 per cent in Europe.<sup>21,22</sup> The prevalence of diabetes in elderly people is high in general, possibly due to changes in body composition, mainly a decrease in lean mass and skeletal mineral density opposed to an increase in body fat.<sup>23,24</sup> The reduction of non-fat tissue includes loss of muscle mass, leading to sarcopenia with decreased muscle functions, while the change in total body fat mass is associated with a higher risk of developing diabetes.<sup>25,26</sup>

In this study, among patients with diabetes mellitus type 2, 77 per cent had endoscopic signs of presbylarynx. A multivariable analysis, which took into account co-morbidities of the elderly, identified diabetes mellitus type 2 as a possible risk factor for a higher prevalence of laryngeal signs linked to the ageing process. As far as we know, this is the first study to evaluate the possible association between diabetes mellitus type 2 and presbylarynx. Many physiopathological mechanisms might explain this result, as diabetes mellitus is known to affect muscular, neurological and vascular systems.

Diabetes mellitus type 2 causes muscle atrophy because of an imbalance in contractile protein synthesis and degradation.<sup>27</sup> A possible mechanism is via decreased muscle protein synthesis, and increased ubiquitin-proteasome, lysosomal-proteasome and caspase 3 mediated protein degradation.<sup>27</sup> Emerging evidence suggests that the inflammation-sensitive nuclear factor B and signal transducer and activator of transcription 3 (STAT3) pathways may contribute to muscle atrophy in those with diabetes mellitus type 2. Given that the larynx is primarily a musculoskeletal organ, if diabetes mellitus type 2 affects muscle mass, it will also affect the larynx. Thus, as observed in this study, it is expected that elderly subjects with diabetes mellitus type 2 will exhibit a higher prevalence of vocal atrophy than the healthy elderly population.

The vascular and neurological consequences of diabetes mellitus type 2 may also play a role in exacerbating the signs of presbylarynx in the elderly. In addition to gross structural changes in the larynx, age-related changes in the innervation of laryngeal muscles have been noted.<sup>7</sup> These innervation alterations include the loss of myelinated and unmyelinated fibres with age, along with increases in myelin-abnormal and myelin-thinning fibres.<sup>2,9</sup> Thus, diabetic neuropathy may accelerate this process. Peripheral

neuropathy is the most common complication of diabetes, and it involves somatic sensory and motor nerves, as well as autonomic nerves. The characteristic peripheral nervous system findings in diabetic patients include: distal nerve fibre degeneration, axonal loss and endoneurial microangiopathy. Both large and small calibre sizes of nerve fibres are affected. Based on pathophysiological mechanisms, diabetes mellitus type 2 can be considered a risk factor for noticeable signs of presbylarynx, as was indeed observed in this case-control study.

This study has some limitations. First, as in many studies of the elderly, our study population contained more women than men, which reflects the elderly demographic trends in our country. Second, this study focused just on endoscopic findings to categorise groups. Third, the assessment of diabetes mellitus type 2 did not include measures of haemoglobin A1c, fasting blood sugar or disease duration. Nevertheless, this is the first case-control study to determine an association between diabetes mellitus type 2 and presbylarynx.

The material and methods used in this study have several advantages. First, our work eliminated all vocal pathological abnormalities other than what could be attributed to presbylarynx. Second, the diagnosis of diabetes mellitus type 2 was based on information registered by medical doctors, which is probably more reliable than information provided by elderly subjects during the ENT consultation.

- This novel study evaluated the association between diabetes mellitus type 2 and presbylarynx
- Among diabetes patients, 77 per cent had presbylarynx
- Multivariable analysis identified diabetes mellitus type 2 as a possible risk factor for laryngeal signs associated with the ageing process
- Many physiopathological mechanisms might explain this result, as diabetes is known to affect muscular, neurological and vascular systems
- Elderly diabetes mellitus type 2 subjects may have a higher prevalence of vocal atrophy than the healthy elderly, as in this study

We will continue to evaluate the association between diabetes mellitus type 2 and laryngeal endoscopic findings. Future studies should consider diabetes mellitus type 2 as a possible risk factor for vocal atrophy. Comparisons of diabetes mellitus type 2 participants of different ages will contribute to a better understanding of the role of diabetes mellitus type 2 in the ageing process of the larynx.

## Conclusion

In this study, among patients with diabetes mellitus type 2, 77 per cent had endoscopic signs of presbylarynx. In addition, a multivariable analysis, which took into account co-morbidities of the elderly, identified diabetes mellitus type 2 as a possible risk factor for a higher prevalence of laryngeal signs associated with the ageing process. As far as we know, this is the first study to evaluate the possible association between diabetes mellitus type 2 and presbylarynx. Many physiopathological mechanisms might explain this result, as diabetes mellitus is known to affect muscular, neurological and vascular systems.

**Competing interests.** None declared

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