REVIEW

Voice changes in reproductive disorders, thyroid disorders and diabetes: a review

Ewa Stogowska[1], **Karol Adam Kamiński**[2], **Bartosz Ziółko**[3] and **Irina Kowalska**[1]

[1]Department of Internal Medicine and Metabolic Diseases, Medical University of Bialystok, Bialystok, Poland
[2]Department of Population Medicine and Civilization Diseases Prevention, Medical University of Bialystok, Bialystok, Poland
[3]Techmo, Kraków, Poland

Correspondence should be addressed to I Kowalska: irina.kowalska@umb.edu.pl

Abstract

The subject of vocal changes accompanying pathological conditions, although still not well explored, seems to be promising. The discovery of laryngeal receptors for sex hormones and thyroid hormones can strongly support the hypothesis of changes in voice due to various endocrinopathies. On the other hand, the impairment of the proper function of the vocal apparatus can also be caused in the process of the microvasculature complications of diabetes mellitus. This review was a comprehensive summary of the accessible literature concerning the influence of selected endocrinopathies on subjective and objective voice parameters. We analysed a total number of 16 English-language research papers from the PubMed database, released between 2008 and 2021, describing vocal changes in reproductive disorders such as polycystic ovary syndrome and congenital adrenal hyperplasia, thyroid disorders in shape of hypo- or hyperthyroidism and type 2 diabetes mellitus. The vast majority of the analysed articles proved some changes in voice in all mentioned conditions, although the detailed affected vocal parameters frequently differed between research. We assume that the main cause of the observed conflicting results might stem from non-homogeneous methodology designs of the analysed studies.

Key Words

- voice
- polycystic ovary syndrome
- congenital adrenal hyperplasia
- thyroid
- diabetes

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Introduction

Physiology of speech

Speech, as the fundamental medium of human thoughts expression, distinguishes mankind from all other species. The word formation begins in the brain cortex and is followed by the activation of the phonatory apparatus, in which the basal part is constituted by the vocal folds. Their oscillation during the air expiration is the first physical step of sound production. Vocal folds are made up of the striated muscles allowing their proper movement, the squamous mucosal epithelium affording their humidification and the elastic collagen fibres. The opening and closure of the space between the vocal cords, that is rima glottidis, are enabled by the vagus nerve, which branches provide sensory and motor larynx innervation. The next and final part of the vocal apparatus, where the definitive voice formation takes place, is a vocal tract, consisting of, sequentially, the pharynx, the soft palate, the nasal cavity and the lips (1, 2). The anomalies of any of mentioned structures can lead to less or more expressed voice changes, which can be measured in various manners.

Assessment of vocal function

The subjective assessment of vocal function, i.e. perceptual evaluation, consists of the auditory impression of the patient's voice by the professional evaluator. The voice might be perceptually assessed using various evaluating techniques, for example, GRBAS scale, based on the voice analysis in terms of the overall grading of the voice (G), roughness (R), breathiness (B), asthenia (A) and strain (S) (3).

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The objective voice assessment contains the evaluation of multiple acoustic parameters like, for instance, fundamental frequency (F0), jitter, shimmer, harmonic-to-noise ratio (HNR) or maximum phonation time (MPT). The fundamental frequency (F0), given in Hz, is a count of a vocal fold vibration in a time unit, posing an acoustic reflection for perceptually assessed pitch. Jitter, measured in %, describes the cycle to cycle frequency variation, while shimmer, also given in %, is defined as the acoustic wave amplitude variation. HNR, assessed in dB, gives information about the ratio between periodic and non-periodic speech integrants (4).

The patient's perception of changes in their daily functioning connected with vocal dysfunction can be quantified by the use of some measures like, for example, Voice Handicap Index (VHI). This measure, proposed in 1997 by Jacobson *et al.* (5), focuses on the impact of vocal changes on three various dimensions – functional, emotional and physical, assessing 'the impact of a person's voice disorders on his or her daily activities', 'affective responses to a voice disorder' and 'self-perceptions of laryngeal discomfort and the voice output characteristics', respectively. The scale consists totally of 30 questions, 10 for each domain. Another similar grading system, compiled by Rosen *et al.* (6), is an abbreviated version of VHI, named VHI-10, using 10 questions concerning the patients' self-assessment of their quality of life connected with voice changes.

Pathophysiology of possible voice changes in hormonal disorders

While the dependence of a proper phonatory apparatus function on an interplay between neuromuscular and respiratory systems seems obvious, the impact of the endocrine system on voice formation still remains highly debated in the literature. The theory of vocal changes due to hormonal influence may be supported by the detection of receptors for androgens, estrogens and progesterone (7, 8), as well as thyroid hormones (9) in the human vocal fold. Furthermore, a few research papers hypothesize the voice changes in diabetes mellitus (DM) due to its microvascular complications.

The multifaceted mechanism of possible voice changes can vary between individual endocrinopathies.

Reproductive disorders

The impact of the sex hormones on voice parameters seems to be undeniable even for non-professionalists, taking into consideration if only easily audible voice changes during adolescence, when the hormonal alternations in both genders cause lowering the male voice by even one octave and the female voice by one-third (1). Although numerous studies indicate the possible influence of the sex hormones fluctuations on vocal parameters over the menstrual cycle, during hormonal replacement therapy or in postmenopausal women (1, 10, 11, 12, 13), there is a limited number of analysis concerning voice changes in reproductive disorders such as polycystic ovary syndrome (PCOS) or congenital adrenal hyperplasia (CAH).

PCOS is the most common endocrinopathy among women of reproductive age, with a prevalence of 4– 12% (14) and, according to Rotterdam criteria, can be diagnosed after fulfilling two out of three following signs or symptoms: (a) oligo- or anovulation, (b) clinical or biochemical hyperandrogenism and (c) polycystic ovarian morphology on ultrasonography, with the concurrent exclusion of other possible causes of presented abnormalities (15).

CAH is an autosomal recessive inherited endocrinopathy characterized by the deficiency of the enzymes controlling cortisol biosynthesis. The most common form of this condition, occurring in 95% of cases, is a 21-hydroxylase deficiency, leading to the insufficient production of cortisol and often aldosterone, together with the simultaneous androgens overproduction. CAH due to 21-hydroxylase deficiency can be divided into classic and non-classic forms. Classic phenotype, as a severe form of CAH, causes early symptoms occurring in childhood. This type of CAH can be subdivided into salt-losing and non-salt-losing types, depending on the aldosterone production. Non-classic CAH is a mild form of this endocrinopathy, being diagnosed more often in early adulthood. A common denominator of all three CAH phenotypes is excessive androgens concentrations.

The symptoms related to the increased testosterone level vary broadly from hirsutism, acne or androgenic alopecia in both PCOS and non-classical CAH to symptoms of virilization in the classic CAH phenotype (16). The possible influence of PCOS- or CAH-related hyperandrogenism on the vocal changes remains unclear. In their research, Nygren *et al.* (17) propounded the theory that excessive levels of androgens in women affected by CAH can lead to thyroarytenoid muscle hypertrophy, which correlates with lowered fundamental frequency and deepening the patients' voice. This hypothesis can also possibly explain the voice changes due to PCOS-related hyperandrogenism. However, no detailed research devoted to the influence of PCOS on vocal folds has been performed so far.

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Thyroid disorders

The hormonal changes associated with the thyroid gland disorders might appear in a shape of an insufficient or excessive thyroid hormones secretion, named, respectively, hypothyroidism or hyperthyroidism.

The primary hypothyroidism is a result of thyroid hormone deficiency with the simultaneous correct hypothalamus–pituitary axis function and its prevalence is calculated as around 3–5% in the European society (18). While the most common cause of primary hypothyroidism in well-developed countries with no iodine deficiency is chronic autoimmune thyroiditis also known as Hashimoto's disease, other less-frequent causes include iodine deficiency, iodine or lithium-containing drugs administration, surgical thyroidectomy or radioiodine treatment. The clinical symptoms of hypothyroidism can manifest not only as weight gain, chronic fatigue, cold intolerance, dry skin, hair loss, myxedema or menstrual cycle abnormalities but also as voice changes, for instance, hoarseness (19). The possible mechanism of observed vocal symptoms might stem from vocal fold oedema due to the accumulation of mucopolysaccharides in lamina propria, cricothyroid muscle oedema and weakness, vocal cord constriction by the enlarged thyroid gland, as well as vagus nerve oedema (9).

Hyperthyroidism, with a prevalence of about 1.2%, is a condition of thyroid hormones overproduction. Its most prevalent causes include autoimmune Graves' disease, toxic multinodular goitre, toxic adenoma or painless thyroiditis. The clinical manifestation of hyperthyroidism comprises tachycardia, increased sweating, heating intolerance, nervousness or weight loss (20). Another often observed symptom is muscle weakness, which possibly can impair the function of laryngeal muscles, affecting the voice parameters.

Type 2 diabetes mellitus

DM, as a state of chronic hyperglycaemia, appears as a consequence of insulin resistance of target tissues and/or an inadequate insulin secretion of pancreatic β-cells. The most prevalent diabetes form is type 2 DM, which affects nearly 90% of the diabetic population. Chronically increased glucose levels can lead to a broad spectrum of micro- and macrovascular complications such as cardiovascular disease, stroke, nephropathy or retinopathy which make diabetes a relevant cause of death and disability worldwide (21). The abnormalities of microvasculature can also lead to diabetes-related neuropathy, myopathy or changes in a connective tissue (22), which possibly affect the function of the vocal apparatus. Voice disorders are reported in 12.5% of diabetic patients, which is over twice more in comparison to healthy individuals (23). In the research conducted by Hamdan *et al.* (24), the authors demonstrated an increased prevalence of laryngeal sensory neuropathy in diabetic patients in comparison to healthy individuals. As a possible consequence of this state, the authors indicate the occurrence of symptoms like spasm, cough or pharyngeal discomfort. What is more, diabetes-related neuropathy can at times affect the cranial nerves, including the vagus nerve, which, sometimes with the accompaniment of diabetic myopathy, can have a strong impact on the alteration of laryngeal function.

The aim of this review is an attempt to summarize the current knowledge concerning subjective and objective voice changes in reproductive disorders, thyroid disorders in shape of hypothyroidism or hyperthyroidism and type 2 DM.

Methods

In this review, we performed a summary of the accessible literature concerning voice changes in reproductive disorders, thyroid disorders and type 2 DM, retrieving the English-language articles from the PubMed database, published between 2008 and 2021 (the last search took place on 10 January 2021). Only studies analysing the acoustic parameters, perceptual evaluation of the voice or the patient's self-assessment of vocal symptoms were included. The terms used in the search comprised 'voice' or 'vocal' and one of the following: 'polycystic ovary syndrome', 'congenital adrenal hyperplasia', 'hypothyroidism', 'hyperthyroidism' or 'type 2 diabetes'. We also checked the references of chosen studies and included the additional eligible articles. Out of 671 initially identified research papers, a total number of 16 studies were finally included in the review. We rejected the research concerning voice changes in children and pregnant women, as well as those using hormonal contraceptives or hormonal replacement therapy and in the patients after radioiodine therapy or with vocal changes connected with complications after thyroid surgery (Fig. 1).

Results

Reproductive disorders

The first attempt to assess the voice changes associated with PCOS was made by Hannoun *et al.* (25). In this

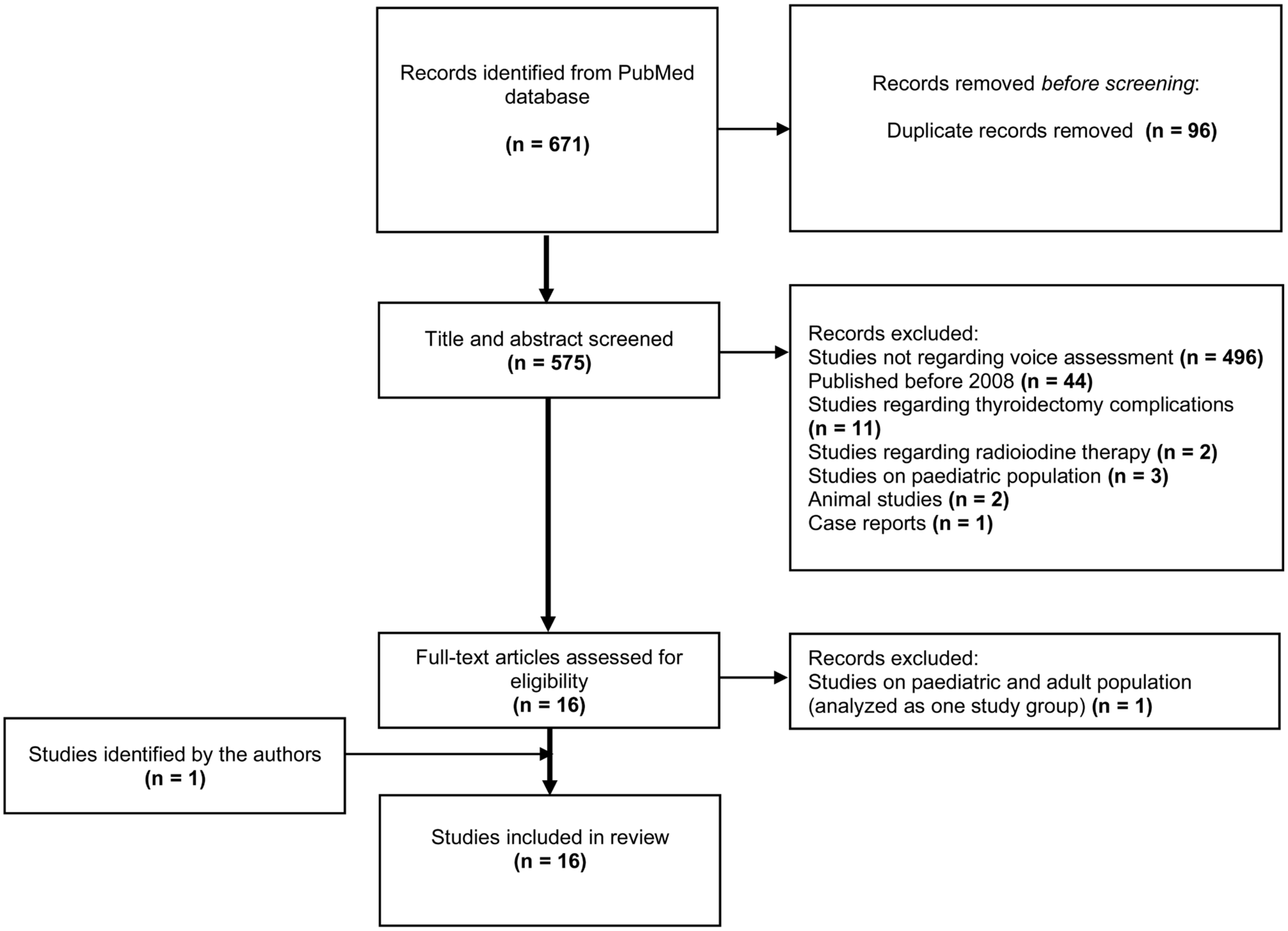

Figure 1
A flowchart of the literature search process.

research, the women affected by PCOS and their healthy counterparts were compared in terms of vocal symptoms, as well as the acoustic and laryngeal abnormalities. Concerning subjective complaints, a statistically significant difference among the two compared groups was noticed in the prevalence of throat clearing, lump in the throat, deepening of voice and difficulties being heard. Among assessed acoustic variables, the significant differences between the PCOS group and healthy subjects were found only in increased relative average perturbation (RAP) and decreased MPT in a study group.

In 2013, Gugatschka *et al.* (26) compared the acoustic parameters, as well as the patients' subjective impression concerning vocal symptoms between the women diagnosed with PCOS and a healthy control group. The results revealed no significant difference in neither subjective nor objective vocal features comparing both analysed groups.

In another study, Aydin *et al.* (27) examined vocal characteristics in women with PCOS and compared them to healthy matched individuals. The authors assessed the patient's voice complaints using various scales, including VHI-10, as well as the acoustic parameters. Furthermore, the women were examined by the laryngologist in the aspect of supraglottic hyperfunction, glottal closure configuration, the regularity of vocal fold edge, the vocal fold amplitude and mucosal wave. The study showed a significantly more frequent occurrence of vocal tract pathologies in a group of PCOS patients, including supraglottic hyperfunction, interpreted by the authors as abnormal muscle tension pattern, incomplete glottal closure configuration and impaired vocal fold vibration. Despite the discovered laryngeal abnormalities, the analysis did show no significant differences in both vocal complaints and acoustic measurements between the patients and the healthy group (Table 1).

One of the first studies concerning detailed vocal characteristics in women affected by CAH due to 21-hydroxylase deficiency was carried out in 2009 by Nygren *et al.* (28). In this research, a study group consisted of

Table 1 The summary of studies concerning voice changes in polycystic ovary syndrome.

Author	Study group size	The speech sample used in the study	Parameters assessed		The crucial findings in the PCOS group
Hannoun *et al.* (25)	17	Not applicable	Self-assessment of vocal symptoms	Throat clearing, deepening of the voice, loss of voice, lump in the throat and difficulty being heard	Increased incidence of throat clearing, lump in the throat, deepening of voice, difficulties being heard
		The vowel 'ah' sustained for 2 s	Acoustic parameters	Average fundamental frequency, relative average perturbation (RAP), shimmer, noise-to-harmonic ratio, voice turbulence index, maximum phonation time	Increased RAP, decreased maximum phonation time
		Not applicable	Laryngeal abnormalities	Vocal fold masses or lesions	No differences
Gugatschka *et al.* (26)	24	Not applicable	Self-assessment of vocal symptoms	Voice Handicap Index	No differences
		The standardized text read by the participants and the vowel sustained for 4 s	Acoustic parameters	Fundamental frequency, highest and lowest pitches, jitter, shimmer, noise-to-harmonics ratio, soft phonation index	No differences
Aydin *et al.* (27)	30	Not applicable	Self-assessment of vocal symptoms	Voice Handicap Index-10 (VHI-10), Glottal Function Index (GFI), Reflux Symptom Index (RSI)	No differences
		The vowel 'a' sustained for 500 ms	Acoustic parameters	Mean fundamental frequency, minimum F0, maximum F0, jitter, shimmer, noise-to-harmonic ratio, maximum phonation time, s-to-z ratio	No differences
		Not applicable	Laryngeal abnormalities	Supraglottic hyperfunction, glottal closure configuration, the regularity of vocal fold edge, the vocal fold amplitude, mucosal wave	Increased incidence of supraglottic hyperfunction, incomplete glottal closure configuration, impaired vocal fold vibration

38 women with CAH, recruited from the Swedish national follow-up project, among which 17 were diagnosed with salt-losing type, 15 were non-salt-losing form and 6 were non-classical mutation. The women affected by CAH were compared to a group of healthy counterparts. All participants evaluated their voice function rating the occurrence and intensity of hoarseness, voice darkness, voice problems in everyday life and vocal fatigue. Perceptual voice evaluation comprised the assessment of voice darkness coming of its timbre. In terms of acoustic analysis, the mean, minimum and maximum fundamental frequencies were measured. The results revealed the questionnaire statement 'my voice is a problem in my daily life' was rated significantly higher by patients with CAH than the control group; however, three remaining assessed symptoms did not differ between the two groups. The perceptual evaluation and acoustic parameters measurement revealed significantly darker voice timbre in diseased women and significantly lower mean, minimum and maximum fundamental frequency in a study group. What is more, the group of CAH-diagnosed women with a 'darker voice' was characterized by significantly higher BMI and lean body mass in comparison to the rest of diseased females with a normal voice, as well as comparison to their healthy matches. Neither subjective symptoms nor objective measurements did differ among three different types of CAH.

Another research assessing the voice changes in women with CAH due to 21-hydroxylase deficiency in comparison to healthy subjects was carried out by Nygren *et al.* in 2013 (29). In this investigation, the study group counted 42 CAH-affected women, recruited together with a control group from the previously mentioned follow-up project. The different number of both study groups and both control groups, as well as the different age range, indicates that the analogous cohorts were not identical, though. The author examined the female participants towards their subjective complaints, using the VHI and the additional questions concerning vocal changes due to virilization. After classifying the VHI scores as 'no/mild', 'moderate' and 'severe', the study indicated significantly more 'severe' scores in CAH-diagnosed females. In terms of the additional voice complaints, the patients diagnosed with CAH reported significantly more frequent darkness of voice, as well as the fact of being perceived as a man when speaking on the phone. After matching the participants by age, the results showed that the diseased women rated significantly higher the questions concerning hoarseness and being perceived as a man in comparison to their healthy counterparts. The research revealed the significant dependence of voice darkness and the period without proper treatment, counting from the time of the first clinical symptoms of CAH.

In another study, Nygren *et al.* (30) investigated the voice self-assessment in patients with disorder of sex development, including 207 females affected by all subtypes of CAH. Among the group of women affected by this endocrinopathy, 66.8% emphasized dissatisfaction with their voice (with a similar percentage for each CAH type). The women were also asked about the incidence of being misrecognized as a male during a phone conversation. When considered together, 16.8 and 5.6% of CAH-affected females were misidentified 'a few times' and ' very often', respectively. The highest percentage of women mistaken as men, that was 25%, was observed in patients with salt-losing CAH, as well as 23% in women with non-salt-losing CAH. Among the subgroup of non-classical CAH, 12% of individuals were misidentified as men (Table 2).

Thyroid disorders

Mohammadzadeh *et al.* (31) compared multiple voice parameters, speech disorders and subjective pharyngolaryngeal complaints between the symptomatic hypothyroid patients, stratified by gender, with healthy individuals. The research showed a significant decrease in F0, minimum F0 and voice turbulence index, as well as a significant increase in peak to peak amplitude variation, shimmer, noise-to-harmonic ratio, soft phonation index and amplitude tremor intensity values in both genders of hypothyroid patients compared to the control group. On the other hand, the study revealed a significant decrease in maximum F0 and an increase in the standard derivation of fundamental frequency and fundamental frequency variation only in a group of hypothyroid females. What is more, the research analysis revealed a positive correlation between TSH and voice changes, as well as fundamental frequency variation, with the absence of correlations between TSH and other assessed parameters. In speech disorders assessment, the voice disorders were recognized in 81% of all hypothyroid patients. In terms of the patients' complaints, the authors point to a high prevalence of dryness in the larynx or pharynx, dyspnea and sensation of a lump in throat in hypothyroid patients, which occurred in 53.3, 49.2 and 43.3%, respectively.

In another research paper, Ersoz Unlu *et al.* (32) analysed the vocal differences between a group of 26 females affected by overt hypothyroidism, 26 females with subclinical hypothyroidism and a group of healthy individuals. In this research, the assessed parameters included the voice self-assessment by VHI-10 questionnaire, the perceptual evaluation with the use of GRBAS scale and the acoustic variables. The results revealed the significantly lower mean, highest and lowest fundamental frequency, as well as higher VHI-10 index in the group of patients with overt hypothyroidism in comparison to the control group. No significant differences were found in any assessed parameters between overt and subclinical hypothyroidism, as well as between subclinical hypothyroidism and healthy individuals. What is more, in the group of overt hypothyroidism patients, a positive correlation between fundamental frequency and fT4 concentrations was found.

There are several studies assessing the impact of hormonal replacement therapy in hypothyroidism. Birkent *et al.* (33) conducted prospective research, where the acoustic parameters were assessed in women with thyroidectomy-related hypothyroidism, before and after levothyroxine treatment. The results revealed a significant post-treatment increase in fundamental frequency, coexisting with a weak but statistically significant negative correlation between this parameter and a change in TSH level. However, other acoustic features did not show a significant change after reaching the euthyroid status.

In a similar analysis, Junuzović-Žunić *et al.* (34) compared the acoustic and perceptual parameters in a pre- and post-treatment period of female patients with hypothyroidism, as well as women with hyperthyroidism. Concerning acoustic parameters, in hypothyroid patients, as opposed to Birkent's results, this research did not reveal the significant change in a value describing fundamental frequency after treatment. Nevertheless, the results showed a statistically significant decrease in shimmer and jitter and a significant increase in harmonics-to-noise ratio after 6 months of levothyroxine replacement. On the other hand, in a hyperthyroid group, the significant difference

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Table 2 The summary of studies concerning voice changes in congenital adrenal hyperplasia.

Author	Study group size	The speech sample used in the study	Parameters assessed		The crucial findings in the CAH group
Nygren *et al.* (28)	38	Not applicable	Self-assessment of vocal symptoms	Hoarseness, voice darkness, voice problems in everyday life, vocal fatigue	More frequent rating of the statement 'my voice is a problem in my daily life'
		The standardized text read by the participants	Perceptual evaluation	Voice darkness coming of its timbre	Darker voice timbre
			Acoustic parameters	Mean, minimum and maximum fundamental frequencies	Lower mean, minimum and maximum fundamental frequencies
Nygren *et al.* (29)	42	Not applicable	Self-assessment of vocal symptoms	Voice Handicap Index	More 'severe' scores
				Additional questions concerning vocal changes due to virilization	More frequent report of darkness of voice, the fact of being perceived as a man when speaking on the phone
Nygren *et al.* (30)	207 CAH-affected women: 109 salt-losing CAH (SW CAH), 65 non-salt-losing CAH (SV CAH), 33 non-classical CAH (NC CAH)	Not applicable	Self-assessment of vocal symptoms	Satisfaction with the voice	'Very satisfied'/'satisfied': 10% CAH-affected women SW CAH: 10.3% | SV CAH: 9.8% | NC CAH: 9.4% 'Neutral': 23.2% CAH-affected women SW CAH: 22.7% | SV CAH: 24.6% | NC CAH: 21.9% 'dissatisfied'/'very Dissatisfied': 66.8% CAH-affected women SW CAH: 67.1% | SV CAH: 65.6% | NC CAH: 68.8%
				Being perceived as a man during the phone conversation	'A few times'/'very often': 22.4% CAH-affected women SW CAH: 25% | SV CAH: 23% | NC CAH: 12%

in post-treatment measurements was noted only in MPT prolongation. In terms of perceptual parameters, measured in the use of GRBAS scale, the pre-treatment hypothyroid, as well as hyperthyroid women, was characterized by significantly different roughness, breathiness and strain in comparison to post-treatment period, whereby in a group of hyperthyroid females, the additional difference was noticed also in asthenia. The lack of detailed statistical analysis disenables unequivocal determination of whether perceptual parameters have increased or decreased after the treatment, though.

Another paper describing voice characteristics in thyroid gland disorders is a research conducted by Hamdan *et al.* (35), where the acoustic and perceptual parameters were compared between the patients with thyroiditis and healthy subjects. In this research, a study group comprised patients affected by subacute thyroiditis and autoimmune chronic thyroiditis, that is Hashimoto disease. As a result, no significant difference in any voice assessments between the study and the control group was seen (Table 3).

Type 2 diabetes mellitus

Hamdan *et al.* (36) were the first who made an attempt to compare voice perturbations connected with type 2 DM with the healthy control group, in a relation to its duration, glycaemic control and neurological complications. The study assessed the subjects' voice in terms of acoustic parameters, as well as perceptual features using the GRBAS score. The results detected no significant differences in an acoustic evaluation between the patients and a control group in general and after stratifying the study group into the three mentioned subgroups, as well as stratifying it by gender. Nevertheless, the study found several differences in perceptual variables. Although the comparison between the patients in general and the controls did show no significant differences, the two diabetic subgroups, with poor glycaemic control and neuropathy, were recognized as having significantly higher G overall grade in comparison to the controls. What is more, the patients with uncontrolled diabetes had significantly more strain.

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Table 3 The summary of studies concerning voice changes in thyroid disorders.

Author	Study group size and characteristics	The speech sample used in the study	Parameters assessed		The crucial findings
Mohamma-dzadeh *et al.* (31)	120 primary hypothyroid patients (106 symptomatic females and 14 symptomatic males)	No information	Acoustic parameters	Fundamental frequency (F0), intensity variation, jitter, shimmer, maximum phonation time	Both genders (vs *control group)***:** lower F0, min. F0, voice turbulence index, higher peak to peak amplitude variation, shimmer, noise-to-harmonic ratio, soft phonation index, amplitude tremor intensity; Only females (vs *control group)***:** lower max. F0 higher the standard derivation of fundamental frequency, fundamental frequency variation
		Not applicable	Self-assessment of pharyngolaryngeal symptoms	Dryness in larynx and pharynx, dyspnea, sensation of lump in the throat, globus, oropharyngeal dysphagia, vague pain, itching, burn in the larynx	Both genders: 53.3%: dryness in the larynx or pharynx 49.2%: dyspnea 43.3%: sensation of a lump in throat
Ersoz Unlu *et al.* (32)	26 females with primary overt hypothyroidism	Not applicable	Self-assessment of vocal symptoms	Voice Handicap Index-10	Overt hypothyroid patients *(vs control group)*: higher VHI-10; Subclinical hypothyroid patients *(vs control group)***:** no differences
	26 females with subclinical hypothyroidism	The standardized text read by the participants	Perceptual evaluation	GRBAS scale	Overt hypothyroid patients *(vs control group)*: no differences; Subclinical hypothyroid patients *(vs control group)***:** no differences
		The vowel 'a' sustained for 3 s	Acoustic parameters	Mean, highest and lowest fundamental frequencies, jitter, shimmer, noise-to-harmonics ratio	Overt hypothyroid patients *(vs control group)*: lower mean, highest and lowest fundamental frequency; Subclinical hypothyroid patients *(vs control group)***:** no differences
Birkent *et al.* (33)	24 females with thyroidectomy-related hypothyroidism: pre- and post-treatment period assessment	The vowel 'a' sustained for 3 s	Acoustic parameters	Fundamental frequency, jitter, shimmer, amplitude perturbation quotient, pitch perturbation quotient, noise-to-harmonics ratio, maximum phonation time	Higher fundamental frequency in post-treatment assessment, negative correlation between fundamental frequency and a change in TSH level

Junuzović-Žunić *et al.* (34)	20 females with hypothyroidism: pre- and post-treatment period assessment	The vowel 'a' sustained for at least 2 s	Acoustic parameters	Fundamental frequency, jitter, shimmer, harmonics- to-noise ratio, maximum phonation time	Hypothyroid patients in post-treatment period: lower shimmer, jitter higher harmonics-to-noise ratio; Hyperthyroid patients in post-treatment period: maximum phonation time prolongation
	27 females with hyperthyroidism: pre- and post-treatment period assessment	The standardized text read by the participants	Perceptual evaluation	GRBAS scale	Hypothyroid patients in post-treatment period: different roughness, breathiness, strain; Hyperthyroid patients in post-treatment period: different roughness, breathiness, strain, asthenia
Hamdan *et al.* (35)	17 patients with thyroiditis	Sustained vowel 'a' and count to 10	Acoustic parameters	Fundamental frequency, shimmer, relative average perturbation, noise-to-harmonic ratio, voice turbulence index, maximum phonation, habitual pitch	No differences
		Sustained vowel 'a' and count to 10	Perceptual evaluation	GRBAS scale	No differences

In their next research paper (37), Hamdan *et al.* completed the assessment of voice changes in type 2 DM with the analysis of the affected patients' self-evaluation. In this work, the participants were asked to self-report the phonatory symptoms and mark a VHI-10 questionnaire. The study group was again subdivided into three groups in terms of duration of the disease, glycaemic control and neuropathy. The results revealed a significantly higher incidence of hoarseness and vocal strain in diabetic patients in comparison to the healthy controls. Among the diseased subjects, hoarseness was reported significantly more often in individuals with poor glycaemic control and neuropathy. What is more, the neurological complications of diabetes were also associated with vocal strain and aphonia/loss of voice. There was no correlation between the diabetes duration and any of the analysed vocal symptoms.

A study conducted by Chitkara & Sharma (38) analysed the differences in acoustic parameters between type 2 DM patients and healthy individuals, stratifying both groups by gender. The research showed a statistically significant reduction in all analysed parameters in diabetic women. In diabetic men, the results were similar, except for an absolute jitter and RAP, which did show no decrease after comparing to the healthy individuals.

Pinyopodjanard *et al.* (39) studied the impact of type 2 DM on the acoustic parameters. The study group was also stratified by disease duration, glycaemic control and the occurrence of diabetic neuropathy. In contrast to the research by Chitkara & Sharma (38), and in accordance to the study by Hamdan *et al.* (36), no significant differences were found in any analysed parameter in a male diabetic group in comparison to their healthy counterparts. Moreover, the only parameter which differed the diseased women between the controls was fundamental frequency, which was lower not only in a general group of diabetic females but also in its subgroups with a disease history longer than 10 years, poor glycaemic control or neuropathy. Taking into consideration a whole study group, the study showed that the fundamental frequency was statistically lower and the smoothed amplitude perturbation quotient (sAPQ) higher in comparison to the control group. What is more, the study emphasizes that fundamental frequency differs significantly in the general population of diabetics, without stratifying by gender, after comparison to healthy individuals, regardless of age, BMI, hypertension or dyslipidemia.

The most recent study, conducted by Gölaç *et al.* (40), assessed the acoustic parameters in diabetic population, stratified by disease duration, glycaemic

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control, neurological complications and voice complaint, in comparison to the healthy control group. The results showed a statistically significant increase of absolute jitter in the whole population of diabetic patients in comparison to healthy individuals. Moreover, in the subgroup of diabetic neuropathy, a significant decrease of MPT and the increase of shimmer local were observed, while in a subgroup of patients with a voice complaint, the study refers to the significant increase of both shimmer local and decibel (Table 4).

Discussion

To date, only some authors have made an attempt to analyse the voice changes in hormonal disorders. Unfortunately, the vast majority of presented results differ between the individual studies. An important limitation of comparing the aforementioned research results and possibly one of the most significant causes of their inconsistency might be the way of collecting the speech samples. In the vast majority of the studies describing acoustic parameters, the authors have analysed a short recording of sustained vowel 'a', lasting only several seconds, which can pose a crucial problem with acoustic data validation. Some authors, including Nygren *et al.* and Gugatschka *et al.* (28, 26), conducted the analysis of some acoustic parameters using the recording of the standardized text read by participants, which seems to be much more meaningful data source.

Another possible reason for such incompatible conclusions between the studies might be a relatively small number of participants in the majority of analysed groups (e.g. 17 PCOS-affected females in the study by Hannoun *et al.* (25)) or subgroups (e.g. 12 patients with diabetic neuropathy in the study by Gölaç *et al.* (40)).

Out of three articles analysing voice changes in PCOS, only the research by Hannoun *et al.* (25) reported significant differences between PCOS patients and healthy controls in both, subjective complaints and acoustic parameters. Notwithstanding, it is important to note that self-evaluation of the patients in this study was performed with no use of any standardized questionnaire. Another important difference between the studies mentioned above is the phase of the menstrual cycle in which the patients were examined. For instance, only in the study by Aydin *et al.* (27), the women were examined in the follicular phase, which in the context of voice changes during the menstrual cycle (1, 10, 11) can pose a problem for comparing the described results with conclusions from other studies. The important problem can be the lack of information concerning androgens concentration in study groups of some research, as it was for example in a study carried out by Hannoun *et al.* (25), in which the testosterone concentrations were evaluated only in some participants.

Among the reproductive disorders group, the vocal changes including the self-assessed vocal complaints, perceptual evaluation and acoustic measurements seem to be more strongly expressed in women with CAH, especially in the salt-losing subtype of CAH, which was proved inthree research papers by Nygren *et al.* (28, 29, 30). Taking into consideration, some studies (1, 41) suggesting the possibility of voice masculinization in both sexes providing certain threshold of androgen concentrations, the findings in CAH-affected groups might be explained by higher average androgens levels in women with CAH in comparison to patients affected by PCOS (42, 43). What is more is the studies by Nygren *et al.* (28, 29, 30) reasonably highlight the need for the medical staff to be aware of vocal changes in CAH-affected women and the possibility to refer those patients to vocal training in order to improve their quality of life.

The articles describing voice changes in thyroid disorders also show a few dissonant conclusions. Due to a pronounced female preponderance in both hypo- and hyperthyroidism (18), many authors have withdrawn from collecting a male study group. Mohammadzadeh *et al.* (31) were the only ones who conducted the research that compared acoustic parameters between hypothyroid and euthyroid individuals, stratifying both groups by gender. On the other hand, the research conducted by Ersoz Unlu *et al.* (32) compared the healthy participants not only to the group of overtly hypothyroid but also subclinically hypothyroid females. What is interesting is the studies conducted by Birkent *et al.* and Junuzović-Žunić *et al.* (33, 34) also compared acoustic parameters in the hypo- and euthyroid group, with the difference that the study and control group concerned the same patients before and after the proper treatment. The common finding in studies carried out by Mohammadzaneh *et al.*, Ersoz Unlu *et al.* and Birkent *et al.* (31, 32, 33) was significantly lower fundamental frequency in a state of hypothyroidism. This important result can be explained by the decreased number of vocal fold vibrations in a time unit due to the vocal fold oedema and muscle weakness, which occur typically in a state of insufficient thyroid hormones secretion. Reversely, the remission of described symptoms in the post-treatment period leads to the higher fundamental frequency, as it was proved in the research by Birkent *et al.* (33). However, the analysis presented by Junuzović-Žunić *et al.* (34)

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Table 4 The summary of studies concerning voice changes in type 2 diabetes mellitus.

Author	Study group size and characteristics	The speech sample used in the study	Parameters assessed		The crucial findings
Hamdan *et al.* (36)	82 patients stratified by - Disease duration - Glycaemic control - Neuropathy	Sustained vowel 'a' nd count to 10	Acoustic parameters	Fundamental frequency, shimmer, relative average perturbation, harmonic-to-noise ratio, voice turbulence index, maximum phonation time, habitual pitch	No differences
		Sustained vowel 'a' and count to 10	Perceptual evaluation	GRBAS scale	Study group vs control group in general: no differences subgroup of poor glycaemic control vs control group: higher G overall grade, more strain subgroup of neuropathy occurrence vs control group: higher G overall grade
Hamdan *et al.* (37)	105 patients stratified by - Disease duration - Glycaemic control - Neuropathy	Not applicable	Self-assessment of vocal symptoms	Voice Handicap Index-10	No differences
				Additional questions concerning presence or absence of hoarseness, vocal tiring or fatigue, vocal strain, aphonia or complete loss of voice	Study group vs control group in general: higher incidence of hoarseness and vocal strain subgroup of poor glycaemic control vs control group: higher incidence of hoarseness subgroup of neuropathy occurrence vs control group: higher incidence of hoarseness, vocal strain, aphonia/loss of voice
Chitkara & Sharma (38)	177 voice samples stratified by gender	The vowel 'a' sustained for 4 s	Acoustic parameters	Jitter, shimmer, amplitude perturbation quotient, noise-to-harmonic ratio, relative average perturbation, smoothed amplitude perturbation quotient	Diabetic females vs control group: all parameters were lower diabetic males vs control group: lower shimmer, amplitude perturbation quotient, noise-to-harmonic ratio, smoothed amplitude perturbation quotient
Pinyopodjanard *et al.* (39)	83 patients stratified by - Disease duration - Glycaemic control - Neuropathy - Gender	The vowel 'ah' sustained for 5 s	Acoustic parameters	Fundamental frequency (F0), jitter, shimmer, amplitude perturbation quotient, noise-to-harmonic ratio, relative average perturbation, smoothed amplitude perturbation quotient (sAPQ)	Study group vs control group in general: lower fundamental frequency higher sAPQ diabetic males vs control group: no differences diabetic females vs control group: lower fundamental frequency lower fundamental frequency in subgroups of a disease history longer than 10 years, poor glycaemic control and neuropathy in diabetic females

(Continued)

Table 4 Continued.

Author	Study group size and characteristics	The speech sample used in the study	Parameters assessed		The crucial findings
Gölaç *et al.* (40)	51 diabetic patients stratified by - Disease duration - Glycaemic control - Neuropathy - Voice complaint	The vowel 'a' sustained for 3 s	Acoustic parameters	Mean fundamental frequency, maximum phonation time, jitter local, jitter absolute, shimmer local, shimmer decibel, harmonics-to-noise ratio	Study group vs control group in general: higher absolute jitter subgroup of neuropathy occurrence vs control group: lower maximum phonation time higher shimmer subgroup of voice complaints vs control group: higher shimmer local and shimmer decibel

surprisingly did not confirm this hypothesis. Another difference concerning study group characteristics occurs in the analysis carried out by Birkent *et al.* (33), where the cause of hypothyroidism in all patients was a thyroidectomy due to thyroid carcinoma, which was an exclusion criterion in other studies. Although the analysed study group consisted of patients after uncomplicated thyroidectomy, some articles indicate possible vocal changes even in well-performed surgery (44, 45, 46). Moreover, the participants of the research by Birkent *et al.* (33) had a relatively short history of hypothyroidism spanning 6 weeks between the surgery and pre-treatment voice assessment, which might be a too short period to observe vocal changes due to insufficient thyroid hormones concentration. Furthermore, the post-treatment assessment of vocal parameters in this study was performed after 2 months of hormonal replacement therapy, while in research by Junuzović-Žunić *et al.* (34), the evaluation took place after 6 months of treatment.

In terms of perceptual evaluation, in the research conducted by Mohammadzaneh *et al.* (31), the participant's speech disorders were assessed with no standardized questionnaire, which enables comparing this analysis to the results obtained by Junuzović-Žunić *et al.* (34) and Ersoz Unlu *et al.* (32), where the GRBAS scale was used. However, the results of those two latter studies also differ from each other, since Ersoz Unlu *et al.* (32) did not describe any differences between the two study groups and the healthy individuals and Junuzović-Žunić *et al.* (34) found some changes in the perceptual evaluation of hypothyroid patients' voice. Unfortunately, the study by Junuzović-Žunić *et al.* (34) does not demonstrate the detailed statistical analysis of the data devoted to perceptual evaluation, describing the trend of each parameter with the word 'different' instead of explaining whether the discussed perceptual feature decreased or increased.

To date, there are only two studies, the first conducted by Junuzović-Žunić *et al.* and the second by Hamdan *et al.* (34, 35), which included hyperthyroid patients. However, only the first one enables concluding about voice changes in thyroid hormones excess, due to the independent analysis of both hypo- and hyperthyroid participants. The limitation of research by Hamdan *et al.* (35) is a non-homogeneous study group of thyroiditis patients, combining hyperthyroid, euthyroid and hypothyroid patients, where hypothyroid and hyperthyroid individuals counted only 11.8 and 17.6%, respectively.

As it was in the case with reproductive and thyroid disorders, there is a limited number of papers describing voice changes in type 2 DM. The analysis concerning acoustic parameters in diabetic subjects revealed several conflicting results. While Hamdan *et al.* (35) did not show any differences in acoustic features comparing diabetic and healthy individuals, even after stratifying the study group into three subgroups relevant to glycaemic control, the disease duration and the occurrence of diabetic neuropathy, Chitkara & Sharma, Pinyopodjanard *et al.*, as well as Gölaç *et al.* (38, 39, 40) suggested some changes of assessed traits in the diabetic population. What is worth noting, the acoustic parameters analysed in the four aforementioned research differed from each other, for example, in a work by Chitkara & Sharma (38), there was no measurement of the fundamental frequency, which in the study conducted by Pinyopodjanard *et al.* (39) constituted the important change. Furthermore, the lack of precise methodology and statistical data given in the study conducted by Chitkara & Sharma (38) significantly disrupted gathering information from this research and disenables alleging it in further discussion. What is more, some studies suggest that the vocal parameters can change depending on the age (47, 48, 49) or BMI (50, 51, 52). Thus, another possible cause of some contrary conclusions might stem from the fact that

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in some research, the study and the control groups were not matched with BMI and age, as is the case in a study conducted by Pinyopodjanard *et al.* (39), or only in BMI, as in both research by Hamdan *et al.* (36, 37).

Conclusions

The vast majority of studies analysing voice changes in PCOS, thyroid disorders and type 2 DM present conflicting results. On the contrary, all the studies concerning CAH, conducted by Nygren *et al.* (28, 29, 30), pose the exception, confirming correspondingly the significant voice changes in the affected women, especially in terms of voice self-evaluation. The speech assessment in all discussed endocrinopathies still requires further investigations; however, all researchers planning to explore this problem should take care of the methodology of their future studies. What is more, we suggest the implementation of the standardized questionnaire to assess the symptoms self-reported by the affected individuals, since in the era of patient-centered medicine, it is important to focus on the patients' everyday problems connected with a particular disease. We believe it would help the health professionals to understand the patient better and offer them the best possible support.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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