Instrumental Acoustic Voice Characteristics in Adults with Type 2 Diabetes

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Summary: Objective. The objective of this study was to investigate if there are differences in acoustic parameters between diabetic patients and normal controls.

Methods. A prospective cross-sectional study was performed in 83 diabetic patients and 70 healthy controls. Voice parameters including fundamental frequency (F0), jitter, shimmer, amplitude perturbation quotient, noise-to-harmonic ratio, smoothed amplitude perturbation quotient, and relative average perturbation were analyzed using Computerized Speech Lab with the Multi-Dimensional Voice Program.

Results. F0 in female diabetic patients was significantly lower than controls (222.23 ± 27.89 Hz versus 241.08 ± 28.21 Hz, $P < 0.01$). In female diabetic subgroups with disease duration more than 10 years, poor glycemic control, or neuropathy, the F0 was still significantly lower. Multivariate analysis showed that F0 was significantly associated with diabetes after controlled for age, body mass index, presence of hypertension, and dyslipidemia. ($P = 0.022$). However, F0 was not able to predict the presence of diabetes as shown by logistic regression analysis ($P = 0.243$).

Conclusions. Voice fundamental frequency is lower in females with diabetes. However, voice fundamental frequency cannot adequately predict the presence of diabetes.

Key Words: Diabetes mellitus−Voice quality−Vowel−Voice diagnostics−Acoustic parameters−Glucose metabolism.

INTRODUCTION

Problems with diabetes

Diabetes is a major public health problem. In Thailand, the prevalence of diabetes has risen sharply over the past 18 years.[1,2] Diabetes is the cause of death for 6% of the Thai population.[3] Poor glycemic control contributes to diabetes-related morbidity and mortality through micro- and macrovascular complications, particularly retinopathy, nephropathy, and neuropathy.[4] Current diagnostic criteria for diabetes[5] depends on blood sampling for the determination of plasma glucose levels. This invasive technique is a painful, cumbersome, and may cause a delayed diagnosis.[6] Although urine testing is easier to perform than blood testing, urine glucose levels do not readily reflect blood glucose levels at the time of testing. More noninvasive methods are therefore needed. In fact, certain noninvasive methods are under development, including hair analysis[7], facial expressions analysis,[8] and voice acoustic analysis.[9,10]

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Conflict of interest: Sittichai Pinyopodjanard, Pichatorn Suppakitjanusant, Prangorn Lomprew, Nittaya Kasemkosin and Boonsong Ongphiphadhanakul declare that they have no conflict of interest.

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Voice acoustic analyses in diabetes

Diabetic complications such as diabetic myopathy and neuropathy[9−14] can have a significant impact on acoustic function. The acoustic apparatus is a musculoskeletal hanging organ whose function depends on adequate innervation and interplay between various laryngeal and respiratory muscles. There are data showing differences in acoustic parameters between patients with diabetes and controls. For example, when analyzed using Multi-Dimensional Voice Program (MDVP), acoustic parameters including fundamental frequency, jitter, shimmer, noise-to-harmonic ratio (NHR) have been shown to differ significantly between diabetic patients and nondiabetic controls.[9,10] These differences are believed to be caused by several factors associated with diabetes[15] which may include xerostomia from autonomic neuropathy,[16] compensatory higher pitched speech for sensorineural hearing loss,[17] and laryngopharyngeal reflux disease.[18]

Objective

Studies with regard to voice characteristics in patients with type 2 diabetes are scarce. Moreover, to our knowledge, voice characteristics have not been investigated in Asian patients with type 2 diabetes compared to controls. As the vocal characteristics may be different among ethnicities, it is therefore the purpose of the present study to investigate various acoustic voice characteristics using Computerized Speech Lab (CSL) in an Asian population.

MATERIALS AND METHODS

Participants

A total of 83 diabetic patients were recruited from the Endocrinology Clinic at Ramathibodi Hospital. The study was

approved by the local Institutional Review Board and all participants provided signed informed consent before participating in the study. The diagnosis of diabetes was based on an HbA1c $\geq$ 6.5% and/or fasting blood sugar (FBS) $\geq$ 126 mg/dL. The exclusion criteria included pregnancy, breastfeeding, uncontrolled hypertension (systolic blood pressures >160 mmHg or diastolic blood pressure >100 mmHg), acute myocardial infarction or stroke within 6 months, history of substance abuse, neurological disorders, active mental disorders, active smoking or having stopped smoking for not more than 6 months, alcohol consumption of more than 7 drinks per week, speech disorders, history of abnormal voice such as hoarseness of voice, upper respiratory tract infection within the previous 2 weeks.

For controls, 70 healthy subjects were recruited from individuals working at Ramathibodi Hospital who had blood tests at annual checkup for less than 6 months showing FBS < 100 mg/dL and no other underlying disease except hypertension and dyslipidemia.

Study protocol

The study was conducted from January 2017 to January 2018. Participants who met the criteria for screening were interviewed using a predefined questionnaire to collect demographic data, degree of glycemic control, duration of the disease, and the presence or absence of diabetic macro/micro vascular complications. Duration of disease was stratified as less than 10 years and more than 10 years. The glycemic control was described as good, average, or poor based on HbA1c level (HbA1c < 7% is good, HbA1c between 7% and 9% as average, and above 9% as poor). Neuropathy was assessed with a 10-g monofilament according to established standard.[19] For blood sample collection, participants had to abstain from food for at least 8 hours prior to blood collection. FBS was analyzed using the hexokinase/glucose-6-phosphate dehydrogenase method on an automated random access chemistry analyzer Architect c8000 (Abbott Laboratories, Abbott Park, IL). Hemoglobin $A1_C$ ($HbA1_C$) was assayed using turbidimetric inhibition immunoassay (Tinaquant Hemoglobin A1c Gen.3 kit) on a cobas c502 modules (Roche Diagnostics GmbH, Mannheim, Germany). Patients underwent acoustic analysis using CSL to collect MDVP acoustic parameters including fundamental frequency (F0), jitter, shimmer, amplitude perturbation quotient (APQ), NHR, smoothed APQ (sAPQ), and relative average perturbation RAP.

Voice acoustic assessment

Acoustic parameters were analyzed using CSL model 4500. CSL is considered to be the gold standard system for acoustic analysis and has been validated to assess voice pathology in many controlled trials.[20–23] The MDVP, a computerized voice analysis system, in conjunction with CSL[24–27] is a versatile voice-processing and spectrographic analysis software package ideally suited for use in determining acoustic parameters. Voice recording was conducted in the voice laboratory of the Department of Communication Sciences and Disorders, Faculty of Medicine, Ramathibodi hospital, Mahidol University, Bangkok, Thailand. The minimum signal-to-noise ratio of the laboratory environment was 42 dB. The voice recording was performed according to CSL operation manual. The voice recording procedure on the volunteers was as follows. (1) History taking was performed to ascertain the absence of upper respiratory tract infection. (2) Training of subjects for diaphragmatic breathing was provided before voice recording. (3) The recording microphone was securely placed in a stable position about 10 cm from the mouth of subject. Subject was then asked to voice the vowel sound "ah" for about 5 seconds at a comfortable pitch and loudness on one exhalation, without straining.

The following acoustic parameters were extracted and examined: F0 (Hz), jitter (%), shimmer (%), APQ (%), NHR, sAPQ (%), and relative average perturbation (%). F0 is acoustic measure of the perceptual judgment of pitch (Hz). Jitter refers to pitch perturbation that is the minute involuntary variations in the frequency of adjacent vibratory cycles of the vocal folds. The quality of the recording of each patient's sound, namely the sustained /ah/, was blindly evaluated by a speech therapist.

Statistical analysis

All study data were checked for normality and presented as mean (SD) if they were normally distributed or median (interquartile range, IQR) if they were not normally distributed. The independent *t* test or Mann-Whitney *U* test was used to all compare continuous variables in this between those with and without diabetes. Chi-square test was used to compare categorical variables between diabetes and control in Table 1. Multivariate analysis and logistic regression analysis were performed to identity independent variables associated with diabetes. A two-tailed *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using Stata version 15 (StataCorp, Texas).

RESULTS

Demographic data of all subjects

A total of 83 diabetic patients and 70 healthy controls were enrolled in this study. The mean age in the diabetic group was 54 $\pm$ 6 years which is higher than that of the control group (48 $\pm$ 7 years, $P < 0.05$). In the diabetic group, 42% were men and 39% of diabetic participants had an average diabetic duration of more than 10 years. Of these, 14% had poor glycemic control and 42.17% had diabetic neuropathy (Table 1).

Acoustic analysis of diabetic patients and controls

The F0 in diabetic patients was significantly lower than in controls (190.93 $\pm$ 50.66 Hz versus 215.35 $\pm$ 51.02 Hz, $P = 0.004$). The sAPQ in diabetic patients was significantly

TABLE 1.
Baseline Characteristics of Diabetic Patients and Controls

Variables	DM (n = 83)	Controls (n = 70)	*P* Value
Age in years (mean ± SD)	54 ± 6	48 ± 7	<0.05
Gender (%)			
Male	35 (42.17%)	18(25.71%)	<0.05
Female	48 (57.83%)	52 (74.29%)	<0.05
Height (cm) (mean ± SD)	161 ± 9	159 ± 8	0.17
Weight (kg) (mean ± SD)	71 ± 15	62 ± 14	<0.05
BMI (kg/m^2) (mean ± SD)	27± 4	25 ± 5	<0.05
Duration of disease (%)			
<10 y	51 (61.45%)	N/A	N/A
≥10 y	32 (38.55%)	N/A	N/A
Hypertension (%)	46 (55.42%)	11 (15.71%)	<0.05
Dyslipidemia (%)	66 (79.52%)	34 (48.57%)	<0.05
FBS (mean ± SD)	149 ± 56	90 ± 6	<0.05
Glycemic control (%)			
Good HbA1C <7	36 (38.3%)	N/A	N/A
Average HbA1C 7-9	45 (47.87%)	N/A	N/A
Poor HbA1C>9	13 (13.83%)	N/A	N/A
Microvascular complication			
Nephropathy (%)	24 (28.92%)	N/A	N/A
Retinopathy (%)	12 (14.46%)	N/A	N/A
Neuropathy (%)	35 (42.17%)	N/A	N/A
Macrovascular complication			
CAD (%)	4 (4.82%)	N/A	N/A
PAD (%)	1 (1.2%)	N/A	N/A
Number of DM drugs (mean ± SD)	3 ± 1	N/A	N/A
Insulin use (%)	30 (36.14%)	N/A	N/A

higher than in controls (5.38 ± 1.89% versus 4.78 ± 1.57%, $P = 0.037$).

When stratified by gender, female diabetic patients still had significantly lower fundamental frequency compared with controls (222.23 ± 27.89 Hz versus 241.08 ± 28.21 Hz, $P < 0.01$). In male diabetic patients, no significant difference was observed in any acoustic parameters when compared with controls (Tables 2).

When analyzing diabetic patients with a duration of disease of more than 10 years versus controls, there was still a significantly lower fundamental frequency in diabetic females compared with controls, but there were no statistical differences in any other acoustic parameters compared with controls. Similar results were found for the subgroup with poor glycemic control versus controls, and the neuropathy group versus controls (Table 3,4).

To determine fundamental frequency as an independent variable significantly associated with diabetes, we performed multivariate linear regression analysis. Results showed that fundamental frequency still differed significantly among the diabetic and control groups ($P = 0.022$, Table 5), independent of relevant variables including age, body mass index (BMI), hypertension, and dyslipidemia.

To assess fundamental frequency as a tool for the prediction of diabetes, we performed a logistic regression analysis with diabetes as an outcome and patient characteristics including age, sex, BMI, hypertension, dyslipidemia, and fundamental frequency as relevant variables. Data showed that fundamental frequency did not significantly predict diabetes when other factors were taken into account ($P = 0.243$, Table 6).

DISCUSSION

Diabetes is associated with lower fundamental frequency in females

Using CSL[20–23] to obtain MDVP acoustic parameters,[24–26,28] we found that there were no significant differences in any of the acoustic parameters compared with controls in males. In contrast, in females, fundamental frequency was significantly lower in diabetic female patients compared with controls and in the subgroups with a disease duration more than 10 years, poor glycemic control, and neuropathy. Moreover, fundamental frequency was demonstrated to be significantly associated with diabetes when controlled for age, BMI, presence of hypertension, and dyslipidemia. However, fundamental frequency *per se* was not able to predict the presence of diabetes as shown by the logistic regression analysis in the present study. There are a number of underlying mechanisms, which may explain the lower fundamental frequency in females with diabetes. Fundamental frequency is a function of mass, tension, and length of

TABLE 2.
Mean and Standard Deviation of Acoustic Parameters Among Diabetic Patients and Controls, Categorized by Sex (Male/Female)

	DM (mean ± SD)		Control (mean ± SD)		*P* Value	
Variables	Male (n = 35)	Female (n = 48)	Male (n = 18)	Female (n = 52)	Male	Female
F0 (Hz)	146.63 ± 40.26	222.23 ± 27.89	141.01 ± 17.41	241.08 ± 28.21	0.576	0.002
Jitter (%)	0.64 ± 0.36	0.49 ± 0.28	0.57 ± 0.49	0.62 ± 0.43	0.591	0.083
RAP (%)	0.37 ± 0.23	0.29 ± 0.17	0.33 ± 0.29	0.37 ± 0.26	0.607	0.071
Shimmer (%)	4.35 ± 1.68	3.31 ± 1.15	3.89 ± 1.35	3.39 ± 1.52	0.317	0.772
APQ (%)	3.62 ± 1.32	2.67 ± 0.85	3.26 ± 0.92	2.63 ± 1.15	0.310	0.844
sAPQ (%)	5.67 ± 2.23	5.16 ± 1.59	4.9 ± 1.14	4.73 ± 1.70	0.178	0.195
NHR	0.15 ± 0.02	0.12 ± 0.01	0.14 ± 0.02	0.12 ± 0.02	0.660	0.947

Abbreviations: F0: fundamental frequency, RAP: relative average perturbation, APQ: amplitude perturbation quotient (APQ), sAPQ: smoothed amplitude perturbation quotient, NHR: noise-to-harmonic ratio.

TABLE 3.
Subgroup Analysis of Female Diabetic Patients Compared with Female Control Group According to Duration of Diabetes, Glycemic Control, and the Presence of Neuropathy

Variables	Controls (N = 52)	DM>10 y (N = 16)	*P* Value	Poor Glycemic Control (HbA1c > 9) (N = 10)	*P* Value	Neuropathy (N = 21)	*P* Value
F0(Hz)	241.077 ± 28.207	223.039 ± 22.072	0.022	218.414 ± 22.711	0.02	223.129 ± 29.088	0.017
Jitter (%)	0.615 ± 0.430	0.549 ± 0.321	0.572	0.551 ± 0.281	0.653	0.473 ± 0.175	0.147
RAP (%)	0.372 ± 0.264	0.329 ± 0.196	0.549	0.332 ± 0.179	0.652	0.282 ± 0.107	0.135
Shimmer (%)	3.386 ± 1.519	3.208 ± 0.688	0.652	3.673 ± 1.340	0.58	3.288 ± 1.120	0.789
APQ (%)	2.632 ± 1.145	2.613 ± 0.559	0.951	2.814 ± 0.795	0.633	2.682 ± 0.852	0.856
sAPQ (%)	4.734 ± 1.701	5.250 ± 1.315	0.27	5.281 ± 1.007	0.331	5.413 ± 1.660	0.125
NHR	0.125 ± 0.023	0.123 ± 0.114	0.844	0.123 ± 0.015	0.78	0.123 ± 0.011	0.716

Abbreviations: F0: fundamental frequency, RAP: relative average perturbation, APQ: amplitude perturbation quotient (APQ), sAPQ: smoothed amplitude perturbation quotient, NHR: noise-to-harmonic ratio.

TABLE 4.
Subgroup Analysis of Male Diabetic Patients Compared With Male Control Group According to Duration of Diabetes, Glycemic Control, and the Presence of Neuropathy

Variables	Controls (N = 18)	DM>10 y (N = 16)	*P* Value	Poor Glycemic Control (HbA1c > 9) (N = 3)	*P* Value	Neuropathy (N = 14)	*P* Value
F0(Hz)	141.011 ± 17.412	139.724 ± 31.769	0.883	151.661 ± 56.085	0.495	146.747 ± 41.483	0.599
Jitter (%)	0.573 ± 0.487	0.659 ± 0.470	0.605	0.767 ± 0.449	0.526	0.623 ± 0.358	0.749
RAP (%)	0.333 ± 0.291	0.383 ± 0.289	0.62	0.459 ± 0.281	0.494	0.361 ± 0.223	0.769
Shimmer (%)	3.887 ± 1.345	4.393 ± 1.763	0.35	3.917 ± 1.279	0.972	4.477 ± 1.543	0.257
APQ (%)	3.259 ± 0.919	3.674 ± 1.464	0.325	2.973 ± 0.913	0.623	3.800 ± 1.400	0.198
sAPQ (%)	4.897 ± 1.144	5.833 ± 2.849	0.208	4.775 ± 0.728	0.862	6.300 ± 2.849	0.066
NHR	0.144 ± 0.022	0.147 ± 0.023	0.715	0.140 ± 0.009	0.75	0.153 ± 0.027	0.312

Abbreviations: F0: fundamental frequency, RAP: relative average perturbation, APQ: amplitude perturbation quotient (APQ), sAPQ: smoothed amplitude perturbation quotient, NHR: noise-to-harmonic ratio.

acoustic apparatus. A decrease in the strength of the intrinsic laryngeal muscles can result in a decrease in fundamental frequency. Studies have shown that patients with diabetes have reduced muscular strength, as a result of diabetic myopathy and neuropathy.[9,10] However, in our study, the presence of laryngeal myopathy/neuropathy was not assessed and the contribution of such impairments to the lower fundamental frequency cannot be readily determined.

TABLE 5.
Multivariate Linear Regression Analysis with Fundamental Frequency as an Outcome

	Fundamental Frequency	
Variables	B	*P* Value
Age	−0.211	0.762
Body mass index	−0.378	0.704
Hypertension	−3.339	0.763
Dyslipidemia	−0.482	0.960
Patient Groups (Diabetic/ Nondiabetic)	23.214	0.022
Adjusted R^2	0.024	

TABLE 6.
Logistic Regression Analysis of Fundamental Frequency and Relevant Variables on Diabetic Status

	Diabetic Status	
Variables	B	*P* Value
Age	1.119	0.001
BMI	1.144	0.006
SEX	0.862	0.831
Hypertension	0.551	0.230
Dyslipidemia	0.403	0.038
F0	0.993	0.243
Adjusted R^2	0.277	

Abbreviations: BMI: body mass index, F0: fundamental frequency.

Lack of predictive power of fundamental frequency

One possible explanation for the lack of predictive power of fundamental frequency may be related to the relatively minor influence of fundamental frequency compared with other well-established risk factors for type 2 diabetes and also the co-variation of fundamental frequency with such factors. In our study, diabetic patients had more advanced age, higher body mass index, higher hypertension and dyslipidemia. These are known factors that affect fundamental frequency. Females aged in their 60s showed clearly lower frequencies than those in their 40s. Across all age groups, until the 80s, fundamental frequency tended to decrease in step with aging, but males exhibited only small changes through the first six decades of their lives.[29,30] The relation between body weight and voice has been researched in some studies in which it was found that obese individuals tend to have a lower fundamental frequency. A possible explanation is the interference of excessive body weight in abdominal breathing resulting in a reduction of this parameter.[31–33] Hypertension and dyslipidemia may also influence fundamental frequency through a myo-neuropathy process like diabetes.[34–36]

Other voice parameters in the study

Diabetes can also potentially cause alterations in other voice acoustic parameters through diabetic myo-neuropathy resulting in the loss of fine motor muscles control leading to an increase in the cycle-to-cycle variation in frequency and loudness.[37–39] Such alterations can result in abnormalities in RAP, APQ, and sAPQ.[40] However, in our study, there were no significant differences in any of these acoustic parameters in the diabetic patients compared with controls which may be due to the presence of multiple confounding variables and co-variations among parameters as mentioned above.

In addition, the course of voice changes may have arisen from a circadian rhythm. This is the nature of physiology and results from metabolic events and muscle coordination. However, it is important to evaluate vocal folds function in diabetes (DM) and control groups.

Limitations

There are a number of limitations in the present study. First, is the lack of laryngeal examination, which would have helped in better interpreting the results of our investigation. Second, baseline characteristics between diabetic patients and controls were different due to limitations in the recruiting process. Multivariate analyses were therefore used to control for relevant confounders where appropriate. Third, the sample size was small in both groups, this was especially the case for males. Lastly, speech pressure level data were not available in the present study which might affect to some extent the validity of the measured parameters in the study. Future research studies with larger sample sizes, adequate laryngeal examinations as well as more conforming to recommended standards[41] are warranted.

CONCLUSIONS

In the present study, we found that voice F0 was significantly associated with diabetes when controlled for age, BMI, presence of hypertension, and dyslipidemia, particularly in females. However, voice F0 alone cannot adequately predict the presence of diabetes. Future research studies with additional voice features and larger sample sizes are warranted to further investigate the feasibility of using voice as a biomarker for diabetes.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jvoice.2019.07.003.

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