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Analysis of Breath from Diabetic Patients Based on a One-chip-type Sensor Array

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Abstract

Based on the results of studies on acetone excretion in diabetic patients, a one - chip sensors array was fabricated by combining acetone-selective sensor materials and volatile-organic-compound sensitive sensor materials. An electonic-nose was implemented using a sensor array and confirmed selectivity for five gases. In this system, the excretion of diabetic patients and controls was sampled with solid phase microextraction fiber and transferred to the sensor array. Although the control and diabetic patients were distinct, several samples failed. In the control group, the results of blood tests were normal, but patients were highly obese. In addition, the gas chromatography mass spectrometry results for the subjects revealed chemicals that are external factors

Keywords: One-chip sensor array, Exhaled breath, SPME fiber, GC-MS, Diabetics

1. INTRODUCTION

The gases released by respiration are composed of nitrogen, oxygen, carbon dioxide, water and volatile organic compounds (VOCs). Most VOCs result from food or environmental influences. Endogenous substances in the body metabolism have been founded be associated with disease.. For a long time, doctors have noticed the specific smell of patients' breath. Recently, researchers have used gas chromatography mass spectrometry (GC-MS) to analyze disease-related compounds [1,2]. People with diabetes smelled like acetone and the presence of Helicobacter bacteria in the stomach increased the ammonia content of their breath. In addition, large amounts of VOCs are released through exhalation, and chemical components related to body metabolism have been studied [3-6]. The number of people with diabetes increased from 108 million in 1980 to 422 million in 2014. Diabetes is a major cause of blindness, kidney failure, heart attack, stroke, and gum disease. [7]

Diabetics often take blood samples and analyze blood sugar very often. Many diabetics dislike this process of collecting blood. Therefore, noninvasive blood glucose monitoring is one of the most important techniques for diabetics. In this study, a patient's condition was monitored by measuring acetone in the breath using an electronic nose system equipped with a metal oxide sensor capable of measuring acetone or similar gases from the exhalation of a patient with diabetes.

2. EXPERIMENTAL

2.1 Implementation of the electronic nose system

The electronic nose system consisted of a sensor array, a data acquisition and processing system, and classification. The sensor array used in the system consists of three oxides of SnO_2, NiO_2, and In_2O_3 and eight sensors using Au, Pt and Pd as catalytic materials. Sensory materials and catalysts have been selected to increase the sensitivity and selectivity to acetone in the breath, and the selectivity to VOCs and NO in the breath is also configured. The sensor array was fabricated on a single chip by using the glancing angle deposition method at the Korea Institute of Science Tchnology(KIST)[8,9]. A chamber was used to maintain a stable operating temperature of the sensor array, and solid phase microextraction (SPME) fibers were used to transfer the measuring gas. The use of SPME fiber allows selective extraction of the collected gas and eliminates the influence of humidity. The SPME fiber used for aerobic sampling was 75-μm carboxen/polydimethylsiloxane (CAR/PDMS). Measurement and analysis

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of the exhalation gas were performed using a microcontroller and a 10-bit analog-to-digital converter, and the data were collected and analyzed. Degassing of the sensor array uses a filter to provide clean air and uses an additional mechanism to clean the SPME fiber.

2.2 Exhalation collection and analysis

Subjects for collection of exhalation gas were selected as diabetic patients and normal persons based on diagnosis from physicians. The study group comprise 11 normal subjects and 11 diabetic patients. Breath gas was collected in the morning after subjects maintained at least 8 h of fasting. Subjects rinsed their mouths with drinking water before collection and two 3-L Tedlar bags were filled by each subject. One sample was measured with an electronic nose system and the other was subjected to GC-MS analysis. In the electronic nose system measurement, the exhalation gas was sampled by being exposed to SPME fiber at 25°C for 20 min to adsorb the gas in the Tedlar bag. The exhalation gas adsorbed on the SPME fiber was desorbed in the chamber of the electronic nose system. GC-MS analysis was possible within 4 h, and breath gas was analyzed using the same type of SPME fiber. Measurement and analysis of exhalation gas were conducted after Dongsan Hospital's Institutional Review Board approval.

3. RESULTS AND DISCUSSION

The selectivity of the sensor array used for the electronic nose was verified by selecting nitrogen dioxide, acetone, ethanol, and VOC gases. The operating temperature of the sensor during measurement was 300°C. The concentration of the measurement gas was 2 ppm of standard gas and 1 ppm of ethanol was used. The sensitivity of the sensor array is shown in Fig. 1. The values shown in Fig. 1 are the result of normalizing the sensitivity of the sensor. Among the eight sensors, S1 - S4 are sensors using tin oxide and a catalyst and are designed to have selectivity for VOC and acetone gas. S5 and S6 are indium sensors and have high selectivity for NO_2 and acetone in high-temperature and high-humidity environments. To increase the selectivity to acetone, S7 and S8 used nickel, which has high sensitivity to nitrogen monoxide and toluene. Sensitivity to acetone is high in S1-S4. S7 and S8 showed high sensitivity to nitrogen monoxide. The concentration of acetone gas emitted during the exhalation increases to several ppm, and because VOC concentrations are several tens or several ppb, the exhalation can be measured.

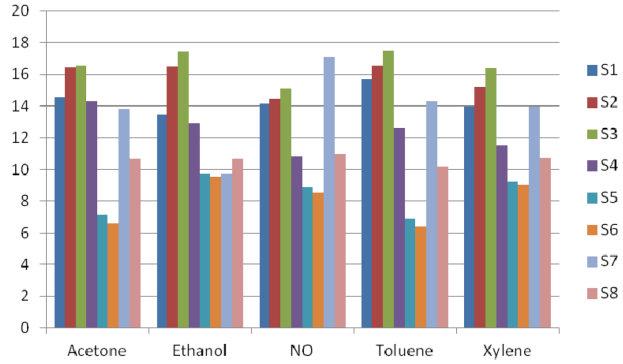

Fig. 1. Graph normalizing the sensitivity for each gas: acetone, ethanol, NO, toluene, and xylene

The results of the blood analysis of the subjects given in Table 1. The mean blood sugar test (BST) index for diabetic patients was 140 mg/dl, whereas the BST index for normal subjects was 99mg/dl. BST is a marker of diabetes mellitus with a diagnosis of >126mg/dl. BSTs can detect short-term blood glucose levels, but the glycated hemoglobin(HbA1c) concentration represents an average of about three months of blood glucose levels.

If the value of HbA1c is ³6.5%, the patient is diagnosed as diabetic, and, if it is < 6%, the patient is diagnosed as normal person. HbA1C was 5.89% in the control group and 7.4% in the diabetic group.

The results of the expiration measurements on these subjects are shown in Fig. 2. Sensor S2 shows differences between diabetic patients and normal subjects, and S7 and S8 show a slightly higher sensitivity in the expiration of normal subjects. S7 and S8 are sensors that show a high response to VOC and nitrogen monoxide, which are slightly higher for normal subjects.

The expiration breath samples from the subjects were analyzed by GC-MS, as shown in Fig. 3. GC-MS analysis of normal subjects and diabetic patients showed that concentrations of

Table 1. Blood analysis of normal and diabetic patients

	Age (years)	BMI	BST (mg/dl)	Glucose (mg/dl)	HbA1C (%)
Control N(11)	56±6.4	23±2	99±10.2	98.3±9.1	5.89±0.36
Diabetes N(11)	60±8.6	26±3	140±38	145±49.7	7.59±1.34

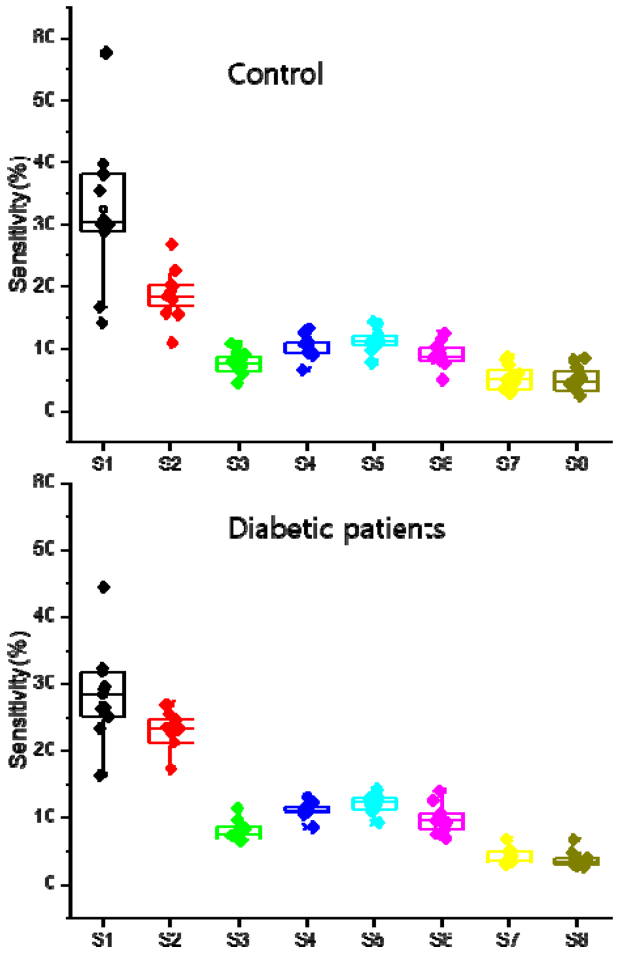

Fig. 2. Normalization of sensitivity for control and diabetic patients measured by the sensor array

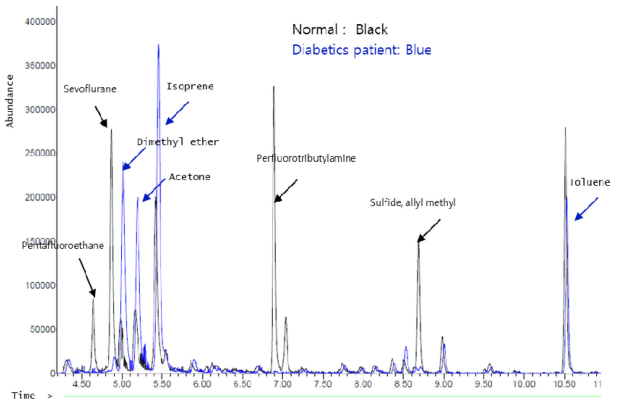

Fig. 3. GC-MS analysis of breath of normal and diabetic patients

dimethyl ether, acetone, and isoprene were higher in diabetic patients. Other VOC concentrations were similar or slightly different.

The results of a principal components analysis (PCA) for the data measured with the electronic nose are shown in Fig. 4. As

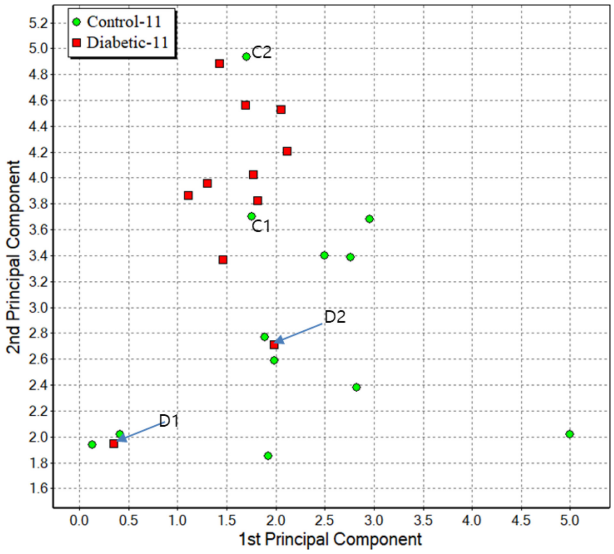

Fig. 4. PCA results by expiration of diabetic patients and control group

shown in Fig. 4, diabetic patients and controls were well differentiated. Two of the control samples were included in the patient group. C1 has a normal BST index, but the HbA1c index is 6% and the BMI is 33.27. Toluene, benzene and acetone were detected in normal subject C1. In addition, a large amount of N, N-dimethylacetamide was detected. Sevoflurane was detected in C2, but sevoflurane is not a chemical substance produced in the body, and there is the possibility of it being supplied from medicine. Acetone was not detected in patients with D1 and D2 included in normal subjects. Also, their blood glucose level was that of diabetic patients, and acetone was not detected in GC-MS analysis. The diabetic patient, D1, had a low glucose of 67mg/dl, and HbA1c was 7%, which is value that can be classified as that of diabetic. In addition the BMI index was 22.8, suggesting that diabetes treatment will be effective. In patients D2, 1,3-butadiene and 2-propanol were detected.

For C1, acetone is detected in GC-MS analysis, and electronic nose measurement gives an accurate classification of acetone form the patient. However, normal people may develop acetone in the metabolic process caused by exercise. The possibility of exposure to medicines or contaminated environments should also be taken into account.

4. CONCLUSIONS

In this study, we implemented an electronic nose system by fabricating a one-chip sensor array using a gas-selective sensor.

Before measuring exhalations, acetone, nitrogen monoxide and VOC were measured to confirm the selectivity of each sensor in the sensor array.

We investigated the possibility of determining whether or not diabetic patients could be distinguished from their exhaled breath. The two groups were distinguishable by measurement of the breath of diabetic patients and the control group using an electronic nose. However, when the subject was exposed to a contaminated living environment, the accumulated gas was discharged and judged to be an error. Therefore, to diagnose diabetes using exhalation, it is necessary to find metabolites other than acetone as a chemical marker of diabetes. In addition, solutions to the effects of other diseases or drugs or the environment will be discussed in the next study.

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