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A Negative Correlation Between Blood Glucose and Acetone Measured in Healthy and Type 1 Diabetes Mellitus Patient Breath

Artur Rydosz, PhD[1]

Abstract

Background: Exhaled acetone analysis has long been recognized as a supplementary tool for diagnosis and monitoring diabetes, especially type 1 diabetes. It is essential, therefore to determine the relationship between exhaled acetone concentration and glucose in blood. Usually, a direct linear correlation between this both compounds has been expected. However, in some cases we can observe a reverse correlation. When blood glucose was increasing, breath acetone declined.

Methods: The breath analysis as a supplementary tool for diagnosing and monitoring diabetes makes sense only in case of utilization of portable analyzers. This need has created a market for gas sensors. However, commercially available acetone gas sensors are developed for measuring samples at several tens part per million. The exhaled acetone concentration was measured using commercial acetone gas sensor (TGS 822, 823 Figaro, Arlington Heights, IL, USA Inc) with micropreconcentrator in low temperature cofired ceramics. The reference analyzer–mass spectrometry (HPR-20 QIC, Hiden Analytical, Warrington, UK) was used.

Results: Twenty-two healthy volunteers with no history of any respiratory disease participated in the research, as did 31 patients diagnosed with type 1 diabetes. Respectively, 3 healthy volunteer and 5 type 1 diabetes mellitus subjects with reverse trend were selected. The linear fitting coefficient various from 0.1139 to 0.9573. Therefore, it is necessary to determine the correlation between blood glucose concentrations and under different conditions, for example, insulin levels, as well as correlate the results with clinical tests, for example, Hb1Ac.

Conclusions: It is well known that the concentration of acetone is strongly influenced by diet, insulin treatment, and so on. Therefore, much more complex analysis with long-term measurements are required. Thus, presented results should be regarded as tentative, and validation studies with the analysis of clinical test and in a large number of patients, including control groups, need to be carried out.

Keywords

acetone sensor, breath acetone detection, micropreconcentrator, type 1 diabetes mellitus patient

Breath analysis would provide a convenient and safe method for diagnosing and monitoring several diseases, for example, diabetes.[1-6] In general, diabetes is diagnosed on the basis of the glucose concentration in blood. A noninvasive and painless method for diagnostic, preventive, and monitoring diabetes is still expected. The detection of acetone in the human breath is promising for noninvasive diagnosis of diabetes. Recent, studies show that test based on breath gas acetone alone cannot be reliable. Greiter et al[7] have presents investigation results on breath samples measured from 21 patients with insulin-treated type 2 diabetes and 26 healthy controls. The present results showed that, if acetone alone was used to identify diabetes, 5 false-positive and 5 false-negative test results were obtained. The authors suggested to use at least 8 endogenous volatile organic compounds present in the exhaled breath, such as acetone, isoprene, butanol, pyridine, dimethyl sulfide to separate between patients and controls. Moreover, enhanced acetone levels can be inducted by fasting[8] or eating a specific products, such as garlic or fruits, as well as by intense exercise.[9] Therefore, it has to be underlined that

[1]Department of Electronics, AGH University of Science and Technology, Krakow, Poland

Corresponding Author:
Artur Rydosz, PhD, Department of Electronics, AGH University of Science and Technology, Krakow, Poland, Av Mickiewicza 30, Krakow, 30-059 Poland.
Email: artur.rydosz@agh.edu.pl

breath acetone has been mostly considered as a biomarker of type 1 diabetes. The exhaled acetone is usually in the range of 300-900 ppb for healthy humans and over 1800 ppb for diabetic patients.[10,11] Costello et al[12] have presented a first compendium of volatile organic compounds reported from the healthy human body. Until today, 1840 different VOCs have been assigned from breath. The total number of VOCs is still unknown due to various differences, such as age, diet, sex, height, body fat, metabolism of individuals, and so on. Acetone and other volatiles in breath are present in nanomolar quantities. To measure such low gas concentrations in breath the laboratory systems such as gas chromatography–mass spectrometry,[13] proton transfer reaction–mass spectrometry (PTR-MS),[14] selected ion flow tube–mass spectrometry[15] are used. Repeatedly, a kind of sample preconcentration process is still necessary before the analysis for the sensitive and accurate determination of the acetone in exhaled breath.[16-18] Recently, Kim et al[19] have reviewed technical developments in breath analysis and its applications in clinical diagnosis, including diabetes. The authors concluded that increased concentration of acetone in the blood can be exchanged with an alveolar air and represented the metabolic products of diabetes. The development of small, cheap, and real-time measurement of acetone in breath is desirable. For the past 20 years, many types of acetone sensors have been developed, for example, semiconductor sensors,[20] optical-fiber sensors.[21] However, the commercial available acetone gas sensors have still a low gas sensitivity and selectivity.[22] Therefore, the researchers around the world have tried to fabricate a novel sensors with improved 3-S parameters (sensitivity, selectivity and stability). Wang et al[23] have reported an acetone sensor developed by using a lead foil electrode in sodium tartrate solutions. It has a linear relationship between response current and acetone concentration in the range from 50 to 250 ppm. Liu et al[24] have reported the acetone sensor developed by a sol-gel method. A novel sensing material, $SmFe_{1-x}Mg_xO_3$ was applied. The highest response to 300 ppm acetone gas was reached 353 at 260°C. Recently, Righettoni et al[25] have reported a portable acetone sensor consisting of flame-deposited and in situ annealed Si-doped WO_3 nanostructured films. The sensor response was around 1.8 to 500 ppb dry acetone at 350°C. These sensors were applied to breath acetone monitoring of 5 different tests persons and were in agreement (>98%) to high-sensitivity PTR-MS measurements. However, the maximum response to acetone was at 350°C, requiring about 9 W to heat up the substrate. These indicators are still too high to be applied to sensors in hand-held breath analyzers. Braun et al[26] have reviewed the recent state of clinical breath analysis from perspectives to routine clinical practice. The review is a starting point for better understanding of the 2 interest groups: researchers and practitioners. Therefore, it is widely agreed that clinical breath analysis needs a strong multidisciplinary effort to realize its potential.[26]

In this study, the commercial available acetone gas sensors (TGS 822, TGS 823 Figaro, Arlington Heights, IL, USA Inc) with micropreconcentrator made in low temperature cofired ceramics (LTCC) technology[14] filled with different adsorbent materials such as Carboxen-1018, Carboxen-1021, Carboxen-569 (Sigma-Aldrich, St. Louis, MO, USA) were applied to the detection of acetone in healthy volunteer (HV) and type 1 diabetes mellitus (T1DM) patients' breath. Figure 1 shows a schematic view of the measurement system based on micropreconcentrator in LTCC technology with a gas sensor array based on Figaro sensors. Recent investigations have usually reported a direct linear correlation between blood glucose and exhaled acetone concentration.[27-30] However, some subjects can exhibit a inversely correlation.[31] Galasetti et al[32] have reported investigation results on 10 healthy volunteers during an oral glucose tolerance test. Breath acetone decreased when blood glucose increased with an average correlation coefficient of .70, and not lower than .41 in any subject.[32]

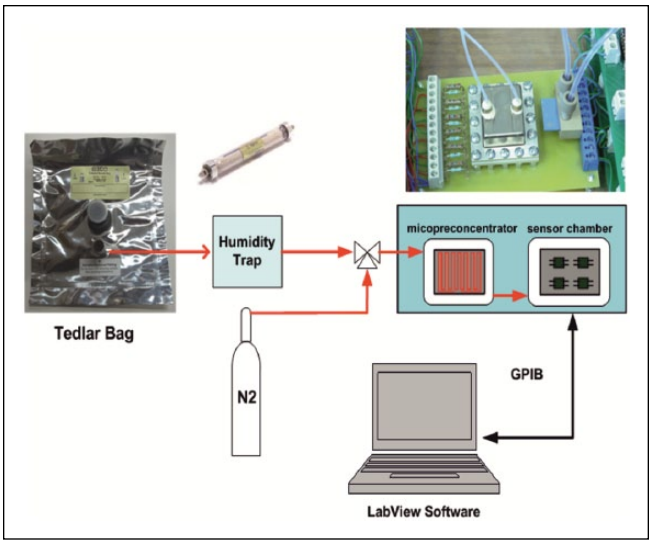

Figure 1. A schematic view of the measurement system based on micropreconcentrator in LTCC technology with gas sensor array based on Figaro sensors.

Experimental

All experiments involving human subjects were performed according to the "Declaration of Helsinki" and in accordance with Polish law. All patients and volunteers declared a written consent to participate in the investigation. The brief description of breath measurements, apparatus and experimental procedure was previously reported in.[26] During this study, 5 patients diagnosed with type 1 diabetes (3 women and 2 men with an average age of 30 and 26 years, respectively) and 3 healthy volunteers (3 men with an average age of 29) characterized by reverse trend were asked to breath into breath bags and measured glucose in blood using the commercial available glucometer Accu-Chek Active (Roche Diagnostics, Berlin, Germany). All subjects used the same device, but own lancets. Before measurement, the bags were heated to 40°C for at least 15 minutes.

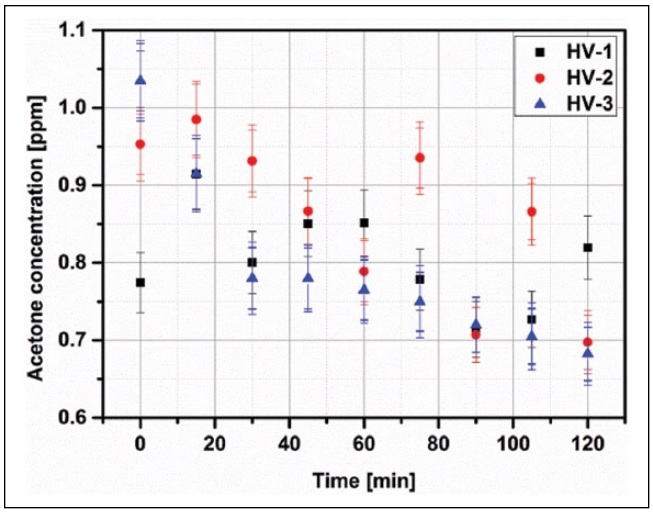

Figure 2. Breath acetone concentrations for healthy volunteers characterized with reverse trend before and after consumption of 75 g of glucose with 15-min interval.

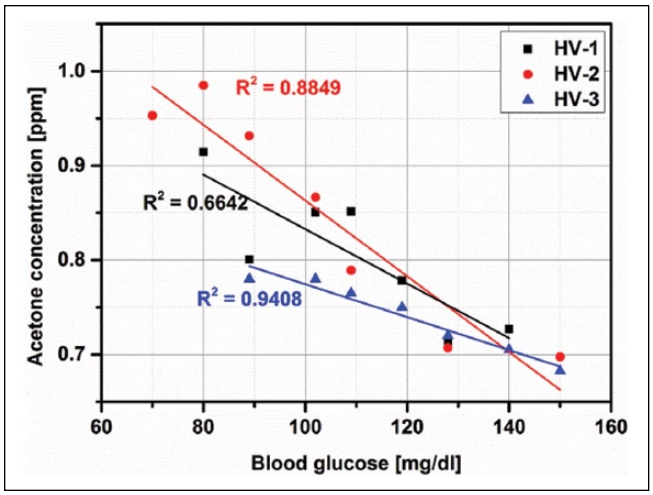

Figure 3. Relations between breath acetone concentration and blood glucose for HV subjects with reverse trend.

Results and Discussion

Based on literature review, we expect a linear relationship between breath acetone and blood glucose concentration for both investigated groups: T1DM and healthy volunteers.[27-30] The exhaled acetone concentration as well as glucose in blood for HV were measured before and after, following the consumption of 75 g of glucose with 15-minute interval (Figure 2). Figure 3 shows the correlation between exhaled acetone concentration and blood glucose for 3 investigated HV before and after glucose consumption. Figure 4 shows the correlation between exhaled acetone concentration and blood glucose for 5 investigated T1DM subjects. The measurements were performed at different time of the day, however, the subjects had the same individual diet and resisted taking any drugs, drinking alcohol, and taking any psychoactive substances. Each measurement

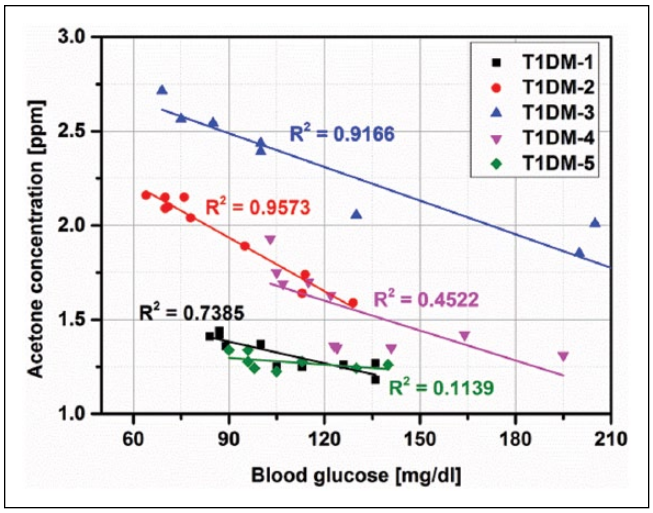

Figure 4. Relations between breath acetone concentration and blood glucose for T1DM subjects with reverse trend.

was performed at least 3 times to avoid incidental results. The measurements were compared to that of mass spectrometry (HPR-20 QIC, Hiden Analytical, UK).

It is well known that the concentration of acetone is strongly influenced by diet and by how hungry the individual is.[31] It was found that after fasting, when blood glucose was low, acetone tended to be relatively high (Figure 2). Following the consumption of 75 g glucose, blood glucose increased, and breath acetone declined. Therefore, it was characterized as a reverse trend because we usually expect that when blood glucose increased, breath acetone increased as well. However, reverse trend was also observed for 5 T1DM patients without taken any glucose. The coefficient of determination (R^2) various from .1139 to .9573. Therefore, it is necessary to determine the correlation between blood glucose concentrations and under different conditions, for example, insulin levels as well as correlate the results with clinical test, for example, Hb1Ac. Validation studies in large number of patients are needed to be carried out. Nevertheless, acetone concentration in the breath are not simply related to glucose levels in the blood and additional research is necessary to make it a viable marker compound for clinical routine.

Conclusions

In the present study the reverse correlations between blood glucose and breath acetone concentration for healthy and type 1 diabetic patients were presented. The breath samples were further determined using commercial available gas sensor and micropreconcentrator structure filled with a different adsorbent material. The effect of the concentration factor changes for acetone samples at different experimental condition was briefly discussed in the previous work.[14] Therefore, it was crucial to investigate whether it is possible to utilize commercial gas sensor with micropreconcentrator to analyze exhaled acetone from diabetic and nondiabetic breath. The author focused on patients with reverse trend as a potentially

excluded from a noninvasive breath measurements. However, much more complex analysis that includes suites of compounds (rather than single acetone), repeated measurements (eg, for 1-2 years) are required. Thus, presented results should be regarded as tentative, and validation studies with the analysis of clinical test and in large number of patients, including control groups, need to be carried out.

Abbreviations

HV, health volunteer; LTCC, low temperature cofired ceramics; T1DM, type 1 diabetes mellitus.

Declaration of Conflicting Interests

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References

1. Tassopoulos C, Barnett D, Fraser T. Breath-acetone and blood-sugar measurements in diabetes. *Lancet*. 1969;239: 1282-1286.
2. Zhang Q, Wang P, Li J, Gao X. Diagnosis of diabetes by image detection of breath using gas-sensitive laps. *Biosens Bioelectron*. 2000;15:249-256.
3. Fleischer M, Simon E, Rumpel E, et al. Detection of volatile compounds correlated to human diseases through breath analysis with chemical sensors. *Sensors Actuators*. 2002;83:245-249.
4. Miekisch W, Schubert JK, Noeldge-Schomburg GFE. Diagnostic potential of breath analysis: focus on volatile organic compounds. *Clinica Chimica Acta*. 2004;347:25-39.
5. Amann A, Smith D. *Breath Analysis for Clinical Diagnosis and Therapeutic Monitoring*. Singapore: World Scientific; 2005.
6. Guo D, Zhang D, Zhang L, Lu G. Non-invasive blood glucose monitoring for diabetics by means of breath signal analysis. *Sensors Actuators B*. 2012;173:160-113.
7. Greiter MB, Keck L, Siegmund MD, Hoeschen C, Oeh U, Paretzke HG. Differences in exhaled gas profiles between patients with type 2 diabetes and healthy controls. *Diabetes Technol Ther*. 2010;12:455-463.
8. Smith D, Spanel P, Davies S. Trace gases in breath of healthy volunteers when fasting and after a protein-calorie meal: a preliminary study. *J Applied Physiol*. 1999;87:1584-1588.
9. Lindinger W, Hansel A, Jordan A. On-line monitoring of volatile organic compounds at PPTV levels by means of proton-transfer-reaction mass spectrometry (PTR-MS): medical applications, food control and environmental research. *Int J Mass Spectrom Ion Processes*. 1998;17(3):191-241.
10. Mohamed E, Linder R, Perriello G, Daniele N, Poeppl S, De Lorenzo A. Predicting type 2 diabetes using an electronic nose-based artificial neural network analysis. *Diabetes Nutr Metab*. 2002;15:215-221.
11. Teshma N, Li J, Toda K, Dasgupta PK. Determination of acetone in breath. *Analytica Chemica Acta*. 2005;545:189-199.
12. Costello B, Amann A, Al-Kateb H, Flynn C, Filipiak W, Khalid T, Osborne D, Ratcliffe NM. A review of the volatiles from the healthy human body. *J Breath Res*. 2014;8:014001-014030.
13. Fana GT, Yanga CL, Lina CH, Chenb CC, Shihc CH. Applications of Hadamard transform-gas chromatography/mass spectrometry to the detection of acetone in healthy human and diabetes mellitus patient breath. *Talanta*. 2014;120:386-390.
14. Moser B, Bodrogi F, Eibl G, Lechner M, Rieder J, Lirk P. Mass spectrometric profile of exhaled breath-field study by PTR-MS. *Respir Physiol Neurobiol*. 2005;145:295-300.
15. Turner C, Spaniel P, Smith D. A longitudinal study of ammonia, acetone and propanol in the exhaled breath of 30 subjects using selected ion flow tube mass spectrometry, SIFT-MS. *Physiol Meas*. 2006;27:321-337.
16. Ueta I, Saito Y, Hosoe M, et al. Breath acetone analysis with miniaturized sample preparation device: in-needle preconcentration and subsequent determination by gas chromatography-mass spectroscopy. *J Chromatogr B*. 2009;877:2551-2556.
17. Rydosz A, Maziarz W, Pisakiewicz T, Domański K, Grabiec P. A gas micropreconcentrator for low level acetone measurements. *Microelectronics Reliability*. 2012;52:2640-2646.
18. Rydosz A, Maziarz W, Pisarkiewicz T, Bartsch de Torres H, Mueller J. A micropreconcentrator design using low temperature cofired ceramics technology for acetone detection applications. *IEEE Sensors J*. 2013;13:1889-1896.
19. Kim KH, Jahan SA, Kabir E. A review of breath analysis for diagnosis of human health. *Trends Anal Chem*. 2012;33:1-8.
20. Anno Y, Maekawa T, Tamaki J, Asano Y, Hayaski K. Zinc-oxide-based semiconductor sensors for detecting acetone and capronaldehyde in the vapor of consommé soup. *Sensors Actuators B* 1995;24:623-627.
21. Bene R, Kiss G, Perczel IV, Meyer FA, Reti F. Application of quadrupole mass spectrometer for the analysis of near-surface gas composition during DC sensor-test. *Vacuum*. 1998;50:331-337.
22. Figaro TGS 822 product information datasheet. Available at: http://www.figarosensor.com/products/822pdf.pdf.
23. Wang CC, Weng YC, Chou TC. Acetone sensor using lead foil as working electrode. *Sensors Actuators B*. 2007;122:591-595.
24. Liu X, Hu J, Cheng B, Qin H, Jiang M. Acetone gas sensing properties of $SmFe_{1-x}Mg_xO_3$ perovskite oxides. *Sensors Actuators B*. 2008;134:483-487.
25. Righettoni M, Tricoli A, Gass S, Chmid A, Amman A, Pratsinisa SE. Breath acetone monitoring by portable Si:WO_3 gas sensors. *Analytica Chimica Acta*. 2012;738:69-75.
26. Braun PX, Gmachl CF, Dweik RA. Bridging the collaborative gap: realizing the clinical potential of breath analysis for disease diagnosis and monitoring-tutorial. *IEEE Sensors J*. 2012;12:3258-3270.
27. Sulway M, Malins J. Acetone in diabetic ketoacidosis. *Lancet*. 1970;296:736-740.
28. Musa-Veloso K, Likhodii SS, Rarama E, et al. Breath acetone predicts plasma ketone bodies in children with epilepsy on a ketogenic diet. *Nutrition*. 2006;22:1-8.
29. Landini BE, Bravard ST. Breath acetone concentration measured using a palm-size enzymatic sensor system. *IEEE Sensors J*. 2009;12:1802-1807.
30. Worrall AD, Bernstein JA, Angelopoulos AP. Portable method of measuring gaseous acetone concentration. *Talanta*. 2013;112:26-30.
31. Rydosz A. Micropreconcentrator in LTCC technology with mass spectrometry for the detection of acetone in healthy and type-1 diabetes mellitus patient breath. *Metabolites*. 2014;4:921-931.
32. Galasetti PR, Novak B, Nemet D, et al. Breath ethanol and acetone as indicators of serum glucose levels: an initial report. *Diabetes Technol Ther*. 2005;7:115-123.