ECRONICON OPEN ACCESS

EC DIABETES AND METABOLIC RESEARCH
Short Communication

Assessment of Clinical Aspects and Exhaled Breath Hydrogen Gas Originated from Intestinal Bacteria in Patients with Type 2 Diabetes

Yuji Aoki[1]* and Masato Aoki[2]

[1]*Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center, Matsumoto, Japan*

[2]*Matsumoto University Graduate School of Health Science, Matsumoto, Japan*

***Corresponding Author:** Yuji Aoki, Department of Internal Medicine, National Hospital Organization Matsumoto Medical Center, Matsumoto, Japan.

Received: September 24, 2018; **Published:** October 30, 2018

Abstract

Since reports on exhaled breath hydrogen gas in diabetes are scarce, its concentrations in relation to clinical aspects were assessed in 33 patients with type 2 diabetes (70 ± 13 years old) and 15 healthy controls (39 ± 19 years old). In 20 diabetic patients, serum malondialdehyde-modified low-density lipoprotein (MDA-LDL), an oxidized LDL, were measured by an enzyme-linked immunosorbent assay. Breath hydrogen gas concentration was significantly correlated with age in diabetic patients (33 ± 65 ppm; rs = 0.531, p = 0.001) and in healthy controls (25 ± 31 ppm; rs = 0.541, p = 0.037). Six patients had been treated with α-glucosidase inhibitors, and one of them showed an extremely high value (265 ppm). When the diabetic patients were divided into two groups by the median value of their breath hydrogen gas concentrations, there were no significant differences between two groups for gender, body mass index, diabetic treatment, HbA1c level, or the existence of retinopathy or nephropathy. It appears that serum MDA-LDL levels were reduced in patients with higher hydrogen gas concentrations, but there was no significant correlation between them (rs = 0.086, p = 0.719). As a recent report demonstrated remarkably beneficial results by subcutaneous injection of hydrogen gas in an animal model, it would be worthy of paying attention to hydrogen gas produced by intestinal bacteria in patients with type 2 diabetes.

Keywords: *Type 2 Diabetes; Breath Hydrogen Gas; Intestinal Bacteria; Oxidized LDL*

Introduction

Exhaled breath hydrogen gas is originated from the bacterial metabolism with undigested carbohydrates in the intestine. Hydrogen gas in the exhaled breath is commonly measured to detect functional gastrointestinal disorders, including carbohydrate malabsorption and small intestinal bacterial overgrowth [1]. Thus far, we have demonstrated increased hydrogen gas in the body of Japanese centenarians and the possibility of its antioxidant bioactivity [2,3]. Through such antioxidant bioactivity, it was hypothesized that the cardiovascular benefits of α-glucosidase inhibitors [4] were partially provoked by increasing the amount of undigested carbohydrates [5]. Since reports on exhaled breath hydrogen gas in diabetes are scarce, its concentrations in relation to clinical aspects, including serum levels of an oxidized low-density lipoprotein (LDL), in patients with type 2 diabetes are presented in this report.

Subjects and Methods

Fifteen healthy controls and 33 patients with type 2 diabetes were studied in accordance with the Declaration of Helsinki ethical guidelines. Their clinical characteristics are shown in Table 1. Six patients had been treated with α-glucosidase inhibitors (voglibose in one, acarbose in two and miglitol in three). Since inter-individual variations of breath hydrogen gas concentrations became larger in the post-

absorption period after a breakfast meal, exhaled breath hydrogen concentrations were measured between 11:00 and 18:00, or more than 4 hours after breakfast using a portable breath hydrogen gas analyzer (HYDlyzer, TAIYO, Osaka, Japan) [2]. In 20 diabetic patients, serum malondialdehyde-modified LDL (MDA-LDL), an oxidized LDL [6], were measured by an enzyme-linked immunosorbent assay at a referee laboratory (SRL, Inc., Tokyo, Japan).

	Healthy Control	Type 2 Diabetes
N	15	33
Male/Female	8/7	11/22
Age (years)	39±19	70 ± 13
Body Mass Index	20.4 ± 1.8	25.0 ± 4.1
Duration of Diabetes (years)	-	39 ± 19
Diet/OHA/OHA + Insulin (n)	-	5/23/5
HbA1c (%)	-	7.5±1.4

Table 1: *Clinical characteristics of subjects.*
Mean ± SD; OHA: Oral Hypoglycemic Agent.

The data are expressed as the mean ± SD. Statistical analysis was performed using the Yates χ^2 test, unpaired t test, Mann-Whitney U-test or Spearman's rank correlation, where appropriate, with a significant level at $p < 0.05$.

Results

Figure 1 shows individual hydrogen gas concentrations of their exhaled breath in 15 healthy controls and 33 patients with type 2 diabetes (25 ± 31 and 33 ± 65 ppm). Six patients treated with α-glucosidase inhibitors are depicted as an open circle. The kind of α-glucosidase inhibitors was miglitol for the highest hydrogen gas concentration, acarbose for the second and third, voglibose for the fourth, and miglitol for the fifth and the lowest. This indicates that breath hydrogen gas concentrations were not necessarily increased by taking α-glucosidase inhibitors.

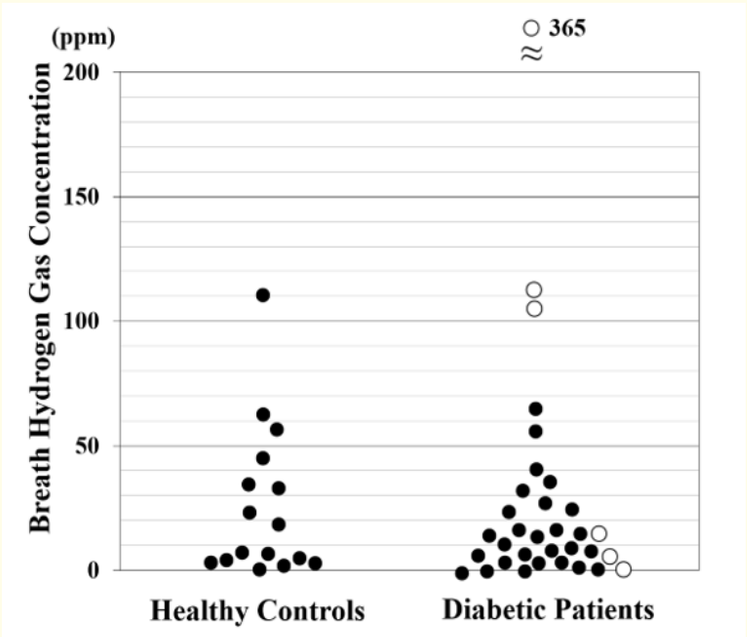

Figure 1: *Individual hydrogen gas concentrations of their exhaled breath are depicted in 15 healthy controls and 33 patients with type 2 diabetes (open circle, treated with α-glucosidase inhibitors). There was no significant difference (Mann-Whitney U-test) between two groups (25 ± 31 vs 33 ± 65 ppm).*

When the diabetic patients were divided into two groups by the median value (14.5 ppm) of their breath hydrogen gas concentrations, clinical aspects of each group are shown in Table 2. Patients with higher hydrogen gas concentrations were significantly ($p < 0.01$) older and had significantly ($p < 0.05$) longer duration of diabetes, while there were no significant differences between two groups for gender, body mass index, diabetic treatment, HbA1c level, or the existence of retinopathy or nephropathy. Breath hydrogen gas concentration was significantly correlated with age in total diabetic patients ($rs = 0.531$, $p = 0.001$) and also in healthy controls ($rs = 0.541$, $p = 0.037$).

Breath hydrogen gas concentration (ppm)	< 14.5 6.3 ± 3.5	14.5≤ 58.4 ± 84.7	
n	16	17	P value
Male/Female	7/9	4/13	0.389
Age (years)	63 ± 14	76 ± 8	0.002
Body Mass Index	26.0 ± 4.3	24.1 ± 3.9	0.202
Duration of Diabetes (years)	8.9 ± 6.0	15.1 ± 8.2	0.019
Diet/OHA/OHA+Insulin (n)	4/10/2	1/13/3	0.605
Taking α-Glucosidase inhibitors (n)	2	4	0.712
HbA1c (%)	7.6 ± 1.4	7.5 ± 1.4	0.92
Retinopathy (-/+)	12/4	9/8	0.34
Nephropathy (-/+)	9/7	8/9	0.858

Table 2: *Clinical aspects of diabetic patients divided by the median value of their breath hydrogen gas concentrations.*

Mean ± SD; Yates χ^2 test or unpaired t test; OHA: Oral Hypoglycemic Agent.

Figure 2 shows the correlation between breath hydrogen gas concentrations and serum MDA-LDL levels in 20 diabetic patients. It appears that serum MDA-LDL levels were reduced in patients with higher hydrogen gas concentrations, but there was no significant correlation between them ($rs = 0.086$, $p = 0.719$). Considering the distribution of data in an attempt to make a difference, patients with the hydrogen gas concentrations higher than 30 ppm (n = 7) had lower serum MDA-LDL levels compared with the other patients (n = 13) (52 ± 14 vs 72 ± 34 U/L, one-sided $p = 0.079$, borderline significance).

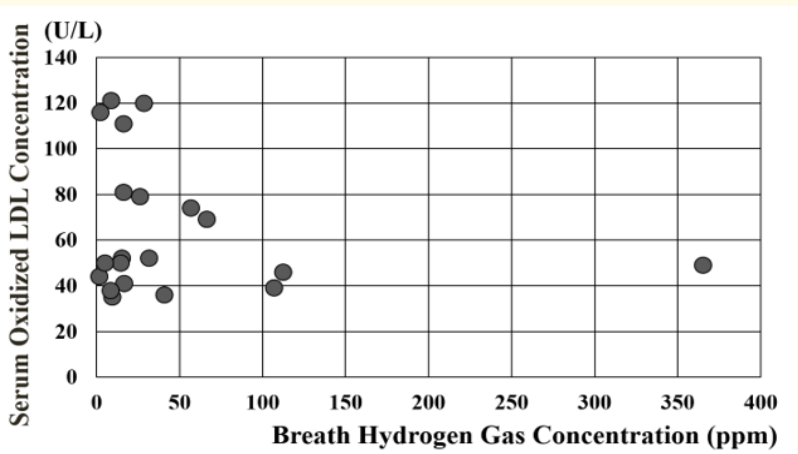

Figure 2: *Correlation between breath hydrogen gas concentrations and serum malondialdehyde-modified LDL (oxidized LDL) levels in 20 diabetic patients. There was no significant correlation between them ($rs = 0.086$, $p = 0.719$).*

Discussion

The data of exhaled breath hydrogen gas concentrations did not show a normal distribution in healthy controls or diabetic patients. There was no significant difference between them, and a few persons had considerably high hydrogen gas concentrations in both groups. One diabetic patient treated with an α-glucosidase inhibitor showed an extremely high value, but it was suggested that taking α-glucosidase inhibitors were not always associated with high breath hydrogen gas concentrations. However, it has been clearly demonstrated that bacterial production of hydrogen gas was significantly enhanced after the administration of α-glucosidase inhibitors [5]. Accordingly, breath hydrogen gas concentrations are considered to still depend on intake of foods and intestinal microbiome even after the administration of α-glucosidase inhibitors. In our study, it was found that breath hydrogen gas concentrations increased with aging in both control and diabetic groups, but were not associated with clinical aspects assessed. Increased concentrations of breath hydrogen gas in the elderly are attributable to impaired absorptive capacity for carbohydrates, small intestinal bacterial overgrowth and so on [1,7,8].

Since drinking hydrogen-rich water was demonstrated to reduce serum lysine-modified or oxidized LDL levels [9,10], the correlation between breath hydrogen gas concentrations and serum MDA-LDL levels in diabetic patients was assessed. Drinking such water briefly increases breath hydrogen gas concentrations, which are within the range of daily intra- or inter-individual variations [2,9,11]. No significant correlation was seen between them in the present study, but it is of note that serum MDA-LDL levels appeared to be reduced in patients with high hydrogen gas concentrations. The mentioned study [9] demonstrated that intake of hydrogen-rich water significantly decreased electronegative charge-modified (that is, lysine-modified) LDL*s* caused by acetylation, carbamylation, glycation, glycoxidation or oxidation. MDA-LDL is an oxidized LDL formed by the reaction of MDA or malondialdehyde, a peroxidative end product, with lysine residues of apolipoprotein B-100, the major protein present in LDL particles, during lipid peroxidation releasing F2-isoprostanes [12,13]. It is inferred that hydrogen gas would rather protect lipids from oxidative stress as shown with urine F2-isoprostanes [3].

Thus, it seemed that breath hydrogen gas concentrations just increased with aging and were not associated with clinical aspects of type 2 diabetes. However, antioxidant bioactivity of hydrogen gas in the body was expected in diabetic patients with high concentrations of breath hydrogen gas. As a most recent report [14] demonstrated remarkably beneficial results by subcutaneous injection of hydrogen gas (1 ml/mouse/week for 4 weeks) in an animal model of type 2 diabetes, it would be worthy of paying attention to hydrogen gas produced by intestinal bacteria in patients with type 2 diabetes.

Conflict of Interest Statement

The authors have indicated no potential conflict of interest.

Bibliography

1. Simren M and Stotzer P-O. "Use and abuse of hydrogen breath tests". *Gut* 55.3 (2006): 297-303.

2. Aoki Y. "Increased concentrations of breath hydrogen gas in Japanese centenarians". *Anti-Aging Medicine* 10.5 (2013): 101-105.

3. Aoki Y. "Antioxidant bioactivity of molecular hydrogen gas produced by intestinal bacteria with undigested carbohydrates". *Acta Scientific Nutritional Health* 2.9 (2018): 23-25.

4. Chiasson JL., *et al*. "Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial". *Journal of the American Medical Association* 290.4 (2003): 486-494.

5. Suzuki Y., *et al*. "Are the effects of α-glucosidase inhibitors on cardiovascular events related to elevated levels of hydrogen gas in the gastrointestinal tract?" *Federation of European Biochemical Societies Letters* 583.13 (2009): 2157-2159.

6. Ohira M., *et al*. "Metformin reduces circulating malondialdehyde-modified low-density lipoprotein in type 2 diabetes Mellitus". *Clinical and Investigative Medicine* 37.4 (2014): E243-E251.

7. Feibusch JM., *et al*. "Impaired absorptive capacity for carbohydrate in the aging human". *Digestive Diseases and Sciences* 27.12 (1982): 1095-1100.

8. Mac Mahon M., *et al*. "Are hydrogen breath tests valid in the elderly?" *Gerontology* 42.1 (1996): 40-45.

9. Kajiyama S., *et al*. "Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance". *Nutrition Research* 28.3 (2008): 137-143.

10. Song G., *et al*. "Hydrogen-rich water decreases serum LDL-cholesterol levels and improves HDL function in patients with potential metabolic syndrome". *Journal of Lipid Research* 54.7 (2013): 1884-1893.

11. Shimouchi A., *et al*. "Breath hydrogen produced by ingestion of commercial hydrogen water and milk". *Biomarker Insights* 4 (2009): 27-32.

12. Haberland ME., *et al*. "Malondialdehyde-altered protein occurs in atheroma of Watanabe heritable hyperlipidemic rabbits". *Science* 241.4862 (1988): 215-218.

13. Lynch SM., *et al*. "Formation of non-cyclooxygenase-derived prostanoids (F2-isoprostanes) in plasma and low density lipoprotein exposed to oxidative stress in vitro". *Journal of Clinical Investigation* 93.3 (1994): 998-1004.

14. Zhang X., *et al*. "Subcutaneous injection of hydrogen gas is a novel effective treatment for type 2 diabetes". *Journal of Diabetes Investigation* 9.1 (2018): 83-90.

Volume 2 Issue 2 November 2018