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ORIGINAL RESEARCH

Dynamic Changes in Exhaled Breath Glucose by Condensate Collection During Oral Glucose Tolerance Testing in Healthy Adults

Wen Xu[1], Qingping Zhang[1], Yilian Hong[1], Zhenjun Mao[2]

[1]Department of Internal Medicine, University Campus, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang, People's Republic of China

Correspondence: Wen Xu, Department of Internal Medicine, University Campus, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, 310012, People's Republic of China, Email zjxuwen1982@zju.edu.cn

Purpose: Invasive blood glucose monitoring is associated with pain and suboptimal patient adherence, creating a need for non-invasive alternatives. In this study, we investigated the dynamic relationship between glucose levels in exhaled breath and blood during an oral glucose tolerance test (OGTT) in healthy adults, to assess the feasibility of using exhaled breath glucose as a non-invasive marker for glycemic monitoring.

Methods: Twenty healthy volunteers (12 males, 8 females; mean age 23.1 ± 2.4 years) underwent a standardized OGTT test. Exhaled breath condensate (EBC) and blood samples were collected simultaneously at fasting (0h) and at 0.5h, 1h, 2h, and 3h post-glucose load. EBC glucose concentration was measured using ion chromatography. The temporal profiles of both parameters were analyzed, and the correlation between the rate of change in exhaled breath glucose and blood glucose at each time point was assessed using Pearson or Spearman correlation test.

Results: Both blood glucose and exhaled breath glucose exhibited similar temporal patterns, peaking within 0.5–1 h after glucose administration and returning to baseline by 3h. Exhaled breath glucose increased from a fasting level of 0.49 ± 0.11 ng/L to a peak of 4.07 ± 1.44 ng/L at 1h. A statistically significant positive correlation between the rate of change in exhaled breath glucose and blood glucose was observed at 1h ($r = 0.84$, $p < 0.000$), whereas the correlation at 0.5h was not significant after correction for multiple comparisons ($\rho = 0.45$, adjusted $p = 0.196$). No significant correlations were detected at 2h or 3h. The changes in exhaled breath glucose were not associated with baseline pulmonary function—as measured by forced vital capacity ($p > 0.05$).

Conclusion: Exhaled breath glucose levels dynamically track blood glucose changes during the early postprandial phase in healthy adults, demonstrating strong concordance during periods of rapid glycemic excursion. These findings support the feasibility of EBC as a non-invasive tool for monitoring glycemic trends. Further validation in larger cohorts and diabetic patients is required to establish its clinical utility.

Keywords: exhaled breath condensate, EBC, oral glucose tolerance testing, OGTT, invasive blood monitor

Introduction

Diabetes mellitus is among the most prevalent chronic diseases worldwide, accounting for approximately 1.5 million deaths annually.[1] International Diabetes Federation (IDF) data indicate that diabetes is increasingly among the most prevalent noncommunicable diseases worldwide, with projections estimating a 46% rise in the number of people living with diabetes by 2045.[2] Monitoring of blood glucose levels plays an important role in the diagnosis and treatment of diabetes. The American Diabetes Association (ADA) recommends that patients receiving multiple insulin injections daily or using an insulin pump measure their blood glucose at least before meals and snacks, occasionally after meals, at bedtime, before exercise.[3] The conventional method for checking blood glucose level is the finger-prick method. Despite its high accuracy, this method remains inconvenient for many patients who are required to perform multiple daily measurements, as finger-pricking is mildly painful and the test strips are costly and single-use.[4] Other minimally invasive

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technologies, like continuous glucose monitoring (CGM) are expensive, relatively complex to use, and exhibit lower accuracy compared with the reference finger-prick method.[4] These drawbacks significantly impact the effective glycemic management. In China, Only 13% of patients with diabetes perform glucose self-testing daily and 59.2% of diabetic patients reported that they occasionally, rarely, or never self-monitor blood glucose.[5] To address the adverse factors caused by invasive blood glucose monitoring, we sought to find a new non-invasive approach for tracking dynamic changes in glucose concentration.

Exhaled breath condensate(EBC) is collected by cooling aerosol exhaled in a calm breathing state. It consists predominantly of water (99%) and contains a small amount of airway surface liquid[6,7.] EBC analysis has been widely applied in clinical studies on various respiratory diseases, including asthma, chronic obstructive pulmonary disease, acute lung injury, and lung cancer.[8–11] Compared with traditional lung biomarker collection methods, such as bronchoalveolar lavage and sputum induction, the collection and analysis of EBC is a completely non-invasive, painless, easily repeatable, and poses minimal risk to subjects.[12] More recently, glucose detection in EBC has gained attention as a potential non-invasive approach for diabetes monitoring.[13] In the lungs, glucose is actively removed from airway surface liquid by sodium-glucose transporter pumps, which is hypothesized to occur more rapidly between blood plasma and the pulmonary compartment than in other tissues.[14] This rapid glucose exchange that occurs between the respiratory fluid and plasma makes EBC a promising indicator of blood glucose levels.[14] During hyperglycemia, increased plasma glucose levels lead to elevated glucose concentrations in respiratory fluid, which can be captured in EBC.[15] Nevertheless, research on glucose detection in EBC is still in the early stages.

In a preliminary study, we designed an EBC collection device and optimized various parameters to establish a robust, reproducible EBC collection process[16.] We further developed a sensitive ion chromatography method capable of quantifying glucose in exhaled breath and saliva samples.[17] However, the dynamic relationship between exhaled breath glucose and blood glucose during a standardized metabolic challenge has not been systematically characterized. Specifically, it remains unknown how closely exhaled breath glucose levels track blood glucose fluctuations over time, particularly during the rapid glucose metabolism stage.

In this study, we enrolled healthy individuals as the subjects to investigate the dynamic changes in exhaled breath glucose concentration during an oral glucose tolerance test (OGTT). Our objectives were: (1) to characterize the temporal profile of exhaled breath glucose in parallel with blood glucose following a standardized glucose load; (2) to quantify the correlation between the rate of change in exhaled breath glucose and blood glucose at multiple time points. These analyses will provide an experimental foundation for future investigations of EBC glucose monitoring in diabetic populations.

Materials and Methods

Participants

Twenty healthy volunteers including 12 males and 8 females, with an average age of 23.05 ± 2.44. Inclusion criteria: (1) age>18 years; (2) No history of chronic diseases (diabetes, hypertension, cardiovascular disease, pulmonary diseases, severe liver and kidney dysfunction, infectious diseases, autoimmune diseases, malignant tumors and blood system diseases); (3) No acute illness within the past months; (4) No family history of diabetes; (5) No regular use of medications affecting glucose metabolism; (6) Body mass index within the normal range (18.5–24.0 kg/m^2).

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (Approval No.: 2023–0557). All participants were informed about the purpose and procedures of the study, and written informed consent was obtained from each participant prior to enrollment. The privacy and confidentiality of participant data were maintained throughout the study.

Collection and Preservation of EBC

The EBC acquisition device was customized for the laboratory, and its internal structure is shown in Figure 1. Based on preliminary experimental conditions, the EBC collection device can achieve the most efficient glucose collection rate at an expiratory flow rate of 15L/min and a cooling temperature of −15 °C.[18]

In this experiment, the subjects were required to maintain a constant expiratory flow rate of 15 L/min until a total gas volume of 50 L has been collected. The instrument was capable of collecting approximately 2 mL of breath condensate in a dedicated condensate collection tube maintained at −15 °C. The collected sample was sealed, protected from light, stored in a −20 °C refrigerator until subsequent ion chromatography analysis for glucose contest in the EBC. The intra-day and inter-day precision of glucose detections indicated excellent reproducibility of this collection method, indicating stable analyte preservation.[17,18]

Chromatographic Conditions

According to the early experimental conditions,[17] the specific parameters were as follows. Chromatography column: Dionex CarboPac MA1 column (250mm × 4mm); mobile phase: 0.8 mmol/L sodium hydroxide solution, pump flow rate: 0.4mL/min; column temperature: 30°C; injection volume: 100 μL; detection method: Pulse amplification detection method, with quadruple pulse waveform as shown in Table 1. The validation of the measurement has been described in details.[16–18]

OGTT Test

The subjects rinsed their mouths with purified water before sampling, and forced vital capacity (FVC) data were collected for pulmonary function testing. Fasting EBC samples were collected after fasting and water deprivation for 8h, and fasting blood glucose levels were measured. Each subject received 75g of glucose solution orally, and EBC was collected at 0.5h, 1h, 2h, and 3h after the OGTT test, while blood glucose levels were measured at the corresponding time points.

The collected EBC was filtered through a 0.22 μm PTFE membrane and analyzed under the chromatographic conditions described in section 2.3. After deducting the blank background, the glucose concentration directly measured in EBC was defined as C1 (mg/L). To account for inter-individual variability in exhaled breath volume, the glucose

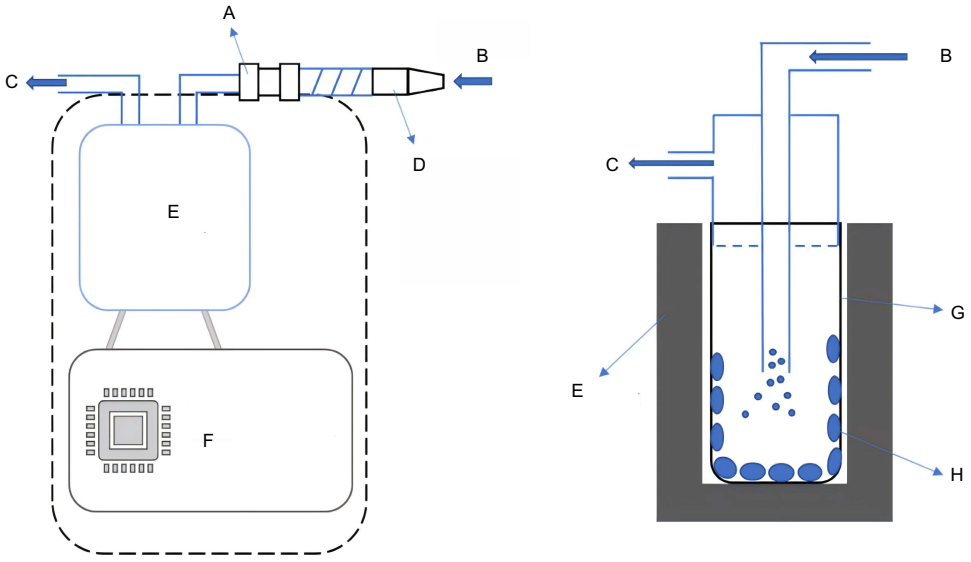

Figure 1 Schematic diagram of the customized exhaled breath condensate (EBC) collection device. The device consists of a disposable mouthpiece, a one-way valve with an integrated flow meter, a semiconductor refrigeration module surrounding a cold trap, and a disposable collection tube. Subjects exhaled at a controlled flow rate of 15 L/min. The exhaled breath passed through the one-way valve and was cooled in the cold trap maintained at -15°C. The exhaled breath condensate (EBC) was collected in the disposable tube at the bottom for subsequent ion chromatography analysis. (**A**): One-way valve and flow meter (**B**): Exhale breath in (**C**): Gas outle (**D**): Disposable mouthpiece (**E**): Cold trap (**F**):Semiconductor refrigeration module (**G**): Disposable collection tube (**H**): Exhaled Breath Condensate.

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Table 1 Potential Waveform

Time/s	Potential/V	Integration
0	+0.1	/
0.20	+0.1	begin
0.40	+0.1	end
0.41	−2.0	/
0.42	−2.0	/
0.43	+0.6	/
0.44	−0.1	/
0.50	−0.1	/

Note: / null value.

concentration perliter of exhaled breath, denoted as C (ng/L), was calculated according to Equation (1):

$$C = C\ 1V1\ /\ V \tag{1}$$

C: Exhaled breath glucose (ng/L),

C1: EBC glucose (mg/L),

V1: EBC volume (L),

V: Exhaled breath volume (L)

where V1 is the collected EBC volume (L) and V is the total exhaled breath volume (L). Unless otherwise specified, "exhaled breath glucose" throughout this manuscript refers to the converted concentration C.

Glucose Change Rate (Ratio) (Equation 2)

$$\text{Ratio} = \text{Glucose (after)} / \text{Glucose (before)} \tag{2}$$

Ratio: Glucose change rate of exhaled breath or blood

Glucose (after): Exhaled breath or blood glucose concentration measured at 0.5h, 1h, 2h, and 3h after the OGTT test

Glucose (before): Exhaled breath or blood glucose concentration was measured in a fasting state for 8h before the OGTT test

Statistical Methods

All statistical analyses were performed using GraphPad Prism version 9.5.0 (GraphPad Software Inc. San Diego,CA, USA). Data are presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to assess the normality of data distribution. For normally distributed data, Pearson's correlation test was applied; for non-normally distributed data, Spearman's rank correlation test was used.

To account for multiple comparisons, Bonferroni correction was applied to the four correlation tests performed at different time points (0.5h, 1h, 2h, 3h). Statistical significance was determined using the adjusted threshold, and both raw and adjusted p values are reported in Table 2.The difference was statistically significant at $p < 0.05$.

Result

Detailed experimental data are available in the Supplementary Material.

Correlation Among Time, Blood and Exhaled Breath Glucose Measurement

In this study, the fasting blood glucose level of the healthy individuals was 5.245 ± 0.692 mmol/L (Table 3). After the OGTT test, the blood glucose reached its peak at 0.5h and 1h, and gradually decreased after 2h until it returned to fasting blood glucose level at 3h (Figure 2).

Table 2 Correlation Between the Rate of Change Inexhaled Breath Glucose and Blood Glucose at Each Time Point Post-OGTT in Healthy Adults (n=20)

Time	Correlations			Adjusted *p* value
	R/*ρ*	Testing Method	Raw *p* value	
0.5h	0.445	Spearman	0.049*	0.196
1h	0.841	Pearson	< 0.000**	< 0.000**
2h	0.232	Spearman	0.326	1.000[b]
3h	0.172	Spearman	0.469	1.000[b]

Notes: **P <0.05, **P < 0.01* . The rate of change was calculated as the ratio of glucose concentration at each time point to fasting glucose concentration (Equation 2). Normality was assessed using the Shapiro–Wilk test; Pearson's correlation was applied for normally distributed data (1h), and Spearman's rank correlation was applied for non-normally distributed data (0.5h, 2h, 3h). The Bonferroni correction was applied for multiple comparisons across four time points. b Adjusted *p* values > 1.000 are reported as 1.000. **p* < 0.05, ***p* < 0.01 indicate statistical significance in raw analysis.

Table 3 Correlation Among Time, Blood and Exhaled Breath Glucose Measurements

Measurement Time (Hour)	Blood Glucose (mmol/l)	Exhaled Breath Glucose (ng/l)	Coefficient of Variation in Exhaled Breath (CV %)
0	5.245 ± 0.692	0.494 ± 0.112	22.7
0.5	8.310 ± 1.602	1.655 ± 0.402	24.3
1	8.230 ± 2.172	4.066 ± 1.440	35.4
2	6.795 ± 1.100	0.748 ± 0.226	30.2
3	5.445 ± 0.798	0.524 ± 0.186	35.5

In the present study, the fasting exhaled breath glucose concentration in healthy individuals was 0.494 ± 0.112ng/L (Table 3). After the OGTT, it gradually increased after 0.5h and peaked at 1h. After 2h, the exhaled breath glucose levels decreased significantly and returned to baseline by 3h (Figure 2).

Correlation Between Exhaled Breath Glucose and Blood Glucose Levels

The correlation between the rate of change in exhaled breath glucose concentration and the rate of change in blood glucose concentration was investigated. The calculation method was shown in Equation(2).As shown in Table 2, a significant positive correlation between the rate of change in exhaled breath glucose and blood glucose was observed at 1h post-OGTT (r = 0.84, p < 0.000). The correlation at 0.5h (ρ = 0.45, raw p = 0.049) did not remain statistically significant after Bonferroni correction for multiple comparisons (adjusted p = 0.196). No significant correlations were detected at 2h or 3h (Table 2, Figures 3 and 4).

Correlation Between the Rate of Change in Exhaled Breath Glucose Concentration and Lung Function

The correlation between the rate of change in exhaled breath glucose concentration and lung function – forced vital capacity(FVC) was compared at 0.5h, 1h, 2h, and 3h after OGTT. The results showed that there was no significant correlation between the two at any time point (p > 0.05). (Table 4)

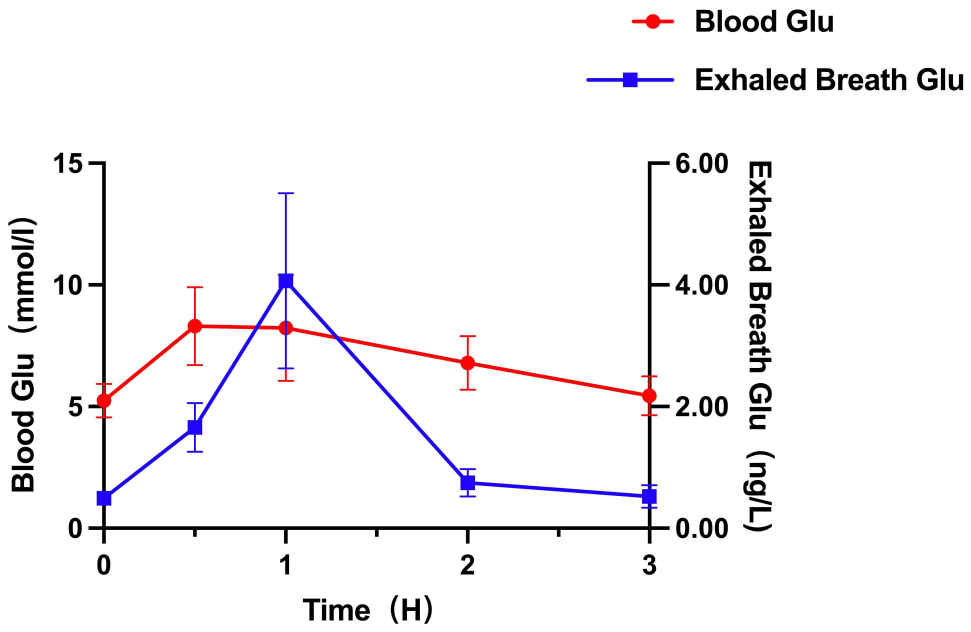

Figure 2 Time course of blood glucose and exhaled breath glucose concentrations during oral glucose tolerance test (OGTT) in healthy adults (n=20). Blood glucose (left Y-axis, mmol/L, ●—●) and exhaled breath glucose (right Y-axis, ng/L, ■—■) were measured at fasting (0h) and at 0.5h, 1h, 2h, and 3h after 75g glucose load. Data are presented as mean ± SD. Both parameters peaked at 0.5–1h and returned to baseline by 3h.Data are presented for descriptive purposes only.

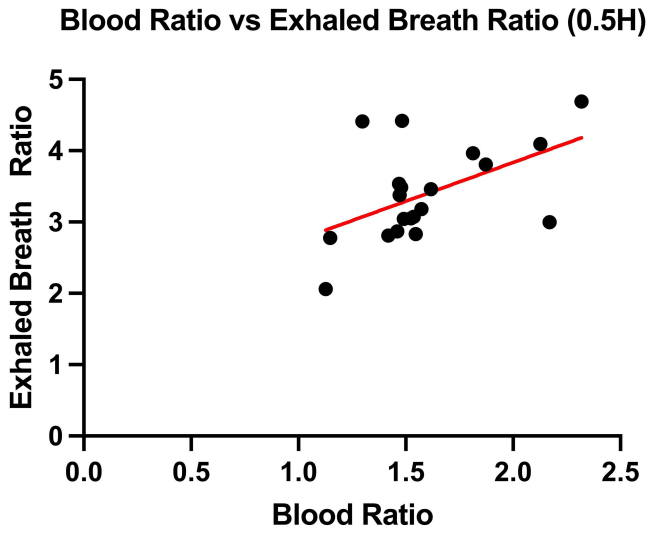

Figure 3 Correlation between the rate of change in blood glucose and exhaled breath glucose at 0.5h post-OGTT. The rate of change was calculated as the ratio of glucose concentration at 0.5h to fasting glucose concentration. A moderate positive correlation was observed (Spearman's ρ = 0.45, raw p = 0.049). However, after Bonferroni correction for multiple comparisons across the four time points, this correlation did not remain statistically significant (adjusted p = 0.196). Therefore, this result should be interpreted with caution.

Discussion

Diabetes mellitus is a chronic disease and metabolic disorder resulting in elevated blood glucose levels. The prevalence of diabetes has been increasing annually. For instance, among US adults aged 60 years and older, the prevalence reached 27.3% in 2021–2023[19]. Effective blood glucose control can significantly reduce serious complications of diabetes, such as retinopathy, peripheral neuropathy, and cardiovascular and cerebrovascular diseases[20]. The American Diabetes Association (ADA)recommends that patients receiving insulin treatment should monitor their blood glucose levels up to six to ten times daily.[21] However, conventional blood glucose monitoring is often an invasive technique, associating

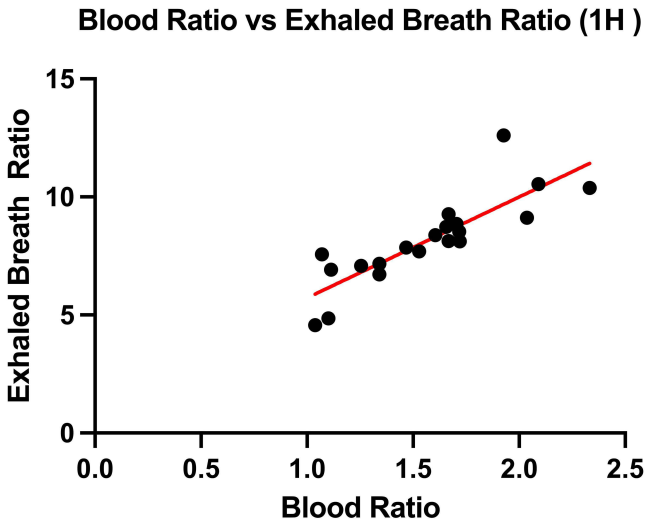

Figure 4 Correlation between the rate of change in blood glucose and exhaled breath glucose at 1h post-OGTT. A strong positive correlation was observed (Pearson's $r = 0.84$, $p < 0.000$, n=20).

with pain, infection risk, and inconvenience, which studies have shown that up to 67% of patients fail to regularly monitor blood glucose.[22–24] These limitations underscore the urgent need for non-invasive alternatives.

Non-invasive blood glucose monitoring technology can be divided into three categories based on the following principles:1. A sample analysis method for measuring glucose concentration in body fluids such as salivary, sweat, and tears;[25] 2. Optical non-invasive blood glucose measurements using near infrared spectroscopy and other methods;[26] 3. Non-invasive blood glucose measurement methods are based on human physiological processes and are represented by the metabolic thermal integration methodsand bioimpedance methods.[27] While promising, these methods are often susceptible to environmental interference, inter-individual differences in tissue composition, and physiological variability.[28]

Compared with other non-invasive glucose monitoring methods, our technology offers some advantages. A recent systematic review and meta-analysis by Kreuter et al[29] reported a weak correlation ($r^2 = 0.05$ –0.11) between salivary and blood glucose levels, thereby limiting the clinical utility of salivary glucose as an option for blood glucose monitoring. Fathimal et al reported a near-infrared optical system achieved a strong correlation of ($r = -0.95$) and a mean absolute

Table 4 Correlation Between the Rate of Change in Exhaled Breath Glucose and Forced Vital Capacity (FVC) in Healthy Adults (n=20) During OGTT

Time(h)		Correlations	
	R/ρ	Testing Method	p value
0.5	0.019	Pearson	0.936
1	0.258	Pearson	0.275
2	0.168	Pearson	0.478
3	0.395	Spearman	0.085

Notes: The rate of change was calculated as the ratio of exhaled breath glucose concentration at each time point to fasting exhaled breath glucose concentration (Equation 2). Pearson's correlation test was used for normally distributed data; Spearman's rank correlation test was used for non-normally distributed data. No significant correlations were observed between EBC glucose change rate and FVC at any time point (all P > 0.05).

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percentage error of 5.99%.[30] Although effective, near-infrared-based optical devices required complex hardware calibration and was susceptible to environmental interference.

EBC glucose testing represents a distinct non-invasive technology, which is still in its early stages. Glucose in EBC originates from plasma and crosses the alveolar–capillary membrane via passive diffusion; its concentration in EBC is maintained at low levels by active sodium–glucose transporters.[31,32] The rapid and stable equilibration between blood and respiratory fluid makes glucose detection in EBC an ideal choice for glycemic monitoring.[14] In this study, we investigated the dynamic relationship between exhaled breath glucose and blood glucose during a standardized OGTT in healthy adults, with particular emphasis on time-specific correlations and the feasibility of using EBC for longitudinal trend monitoring.

The gas exhaled by the human body contains a large amount of water vapor, inducing the glucose concentrations in generally below 10μM[14,33] A major challenge in EBC research is the measurement of solutes at extremely low concentrations. Ion chromatography is an effective method for analyzing ionic compounds, with high accuracy, good sensitivity, and ease of operation.[14] In our preliminary studies, we designed an EBC collection device[16] and established a complete standardized testing process capable of reaching the lowest detection limit[18.] Therefore, this integrated approach provides a robust and competitive methodological foundation for noninvasive measurement.

Using this established methodology, we subsequently examined the dynamic relationship between exhaled breath glucose and blood glucose during OGTT. Our results demonstrated that exhaled breath glucose concentrations changed in synchrony with blood glucose during the early postprandial phase. Both exhaled breath and blood glucose levels peaked within 0.5–1h, and returned to baseline by 3 h (Figure 2). The temporal profiles were consistent with previous reports,[34] confirming the feasibility of detecting glucose in EBC. Notably, exhaled breath glucose consistently peaked at 1 h, whereas blood glucose peaked between 0.5–1h. This slight temporal lag is physiologically plausible: tight junctions which was made up of several proteins between airway epithelial cells restrict paracellular glucose movement. Glucose must diffuse across these tight junctions, equilibrate the airway surface liquid, and then be aerosolized as droplets of exhaled air to condense into a liquid that can be collected and analyzed.[33] This multistep process inevitably introduces a minor delay. At 0.5h post-OGTT, blood glucose rises rapidly, but exhaled breath glucose may not have fully equilibrated due to the time required for diffusion and subsequent accumulation in the airway lining fluid. This temporal offset likely accounts for the moderate correlation at this early time point. By 1h, both systemic circulation and airway lining fluid have reached a steady-state-like equilibrium, resulting in stronger concordance (r = 0.84). Importantly, this lag does not diminish the utility of EBC for trend monitoring—the strong correlation at 1 h (r = 0.84) confirms that exhaled breath glucose reliably tracks dynamic changes in blood glucose, albeit with a consistent, physiologically grounded time shift. Collectively, results from our study indicate that the correlation between exhaled breath glucose and blood glucose is strongest during periods of rapid glycemic excursion—specifically, the peak phase—rather than during steady-state conditions or the early ascending phase.

In our study, we concluded that exhaled breath glucose is better suited for tracking relative changes in blood glucose than estimating absolute glucose concentrations. We determined the variation rate as the ratio of glucose concentration after OGTT to its value before OGTT. As Karyakin et al[34] argued, a correlation in variation rates between exhaled breath and blood is sufficient to support the feasibility of a non-invasive monitoring approach—particularly when periodic calibration against reference blood measurements is acceptable, a practice already employed by commercial continuous glucose monitoring systems. The correlation analysis revealed a strong positive correlation between the rate of change in exhaled breath glucose and blood glucose at 1 h post-OGTT (r = 0.84, $p < 0.000$), indicating that exhaled breath glucose most closely tracks blood glucose during the peak glycemic excursion. Although a moderate correlation was observed at 0.5 h (ρ= 0.45, raw p = 0.049), this association did not remain statistically significant after correction for multiple comparisons (adjusted p = 0.196). This suggests that the relationship at 0.5 h may be weaker or potentially influenced by the relatively small sample size. Obtaining absolute blood glucose values from exhaled breath remains challenging due to inter-individual variability and low analyte concentrations; however, EBC glucose measurement may hold greater clinical value as a trend-monitoring tool during dynamic glucose fluctuations.

Based on the analysis of the correlation between the rate of exhaled breath glucose change and lung function (forced vital capacity, FVC), the absence of correlation between two parameters at any time point (all $p > 0.05$, Table 4) indicates

that the observed exhaled breath glucose dynamics are not confounded by baseline pulmonary function. Consistent with our study, Roberts et al[35] also reported no association between EBC glucose levels and lung function in patients with cystic fibrosis. The results suggested that EBC glucose reflects systemic glycemic status rather than individual variations in lung mechanics, supporting the validity of EBC as a noninvasive glucose monitoring tool across individuals with different baseline pulmonary function.

Several limitations should be acknowledged. First, the sample size (n = 20) was relatively small,which limits statistical power. Second, the study population exhibited a narrow age range (young adults only), and no control group comprising individuals with diabetes was included.

Based on these findings, future studies should include several directions: First, enrolling a larger and more diverse cohort, particularly older adults and individuals with diabetes, to improve the statistical power; Second, integrating continuous glucose monitoring (CGM) with EBC trend monitoring. A promising future direction is the multi-technology fusion of EBC trend monitoring with emerging CGM-derived dynamic indices and machine learning approaches.Such an integrated framework will include CGM for continuous absolute glucose and EBC for tracking short-term dynamics, thereby enhancing multimodal metabolic monitoring strategies and improving both patient adherence and clinical decision-making.

Conclusion: This study demonstrates that exhaled breath glucose levels dynamically track blood glucose changes during the early postprandial phase in healthy adults, with the strongest correlation observed during the peak glycemic excursion at 1h post-OGTT ($r = 0.84$, $p < 0.000$). The absence of correlation between exhaled breath glucose and pulmonary function suggests that exhaled breath glucose reflects systemic glycemic status rather than individual variations in lung mechanics. These findings support the feasibility of EBC as a non-invasive tool for monitoring glycemic trends, particularly during periods of rapid glucose fluctuation. However, owing to the limited sample size and exclusive enrollment of healthy individuals, validation in larger and more diverse populations—including elderly individuals and diabetic patients —is essential before clinical applications.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author, Wen Xu (zjxuwen1982@zju.edu.cn), upon reasonable request.

Ethics Statement

Ethical approval was granted by the Ethics Committee of the second Affiliated Hospital of Zhejiang University School of Medicine.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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