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ORIGINAL ARTICLE

Clinical Value of Assessing Serum Free Thiol Levels Based on HbAc1 Variability in Patients with Microvascular Complications of T2DM

LiChao Xie [1], JiaHua Wu [2], LuoYu Fu [1], ManYi Jin [1]

[1] *Department of Neurology, The First People's Hospital of Xiaoshan Hangzhou, Hangzhou City, Zhejiang Province, China*
[2] *Department of Endocrinology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou City, Zhejiang Province, China*

ABSTRACT

Background: **Patients with type 2 diabetes mellitus (T2DM) often experience microvascular complications like retinopathy, nephropathy, and neuropathy. HbA1c variability has been recognized as being strongly associated with the risk of microvascular complications in diabetes. Serum thiols (SH), on the other hand, maintain redox homeostasis and reduce oxidative stress. Therefore, the present study attempted to assess the relationship between HbA1c variability and SH levels and its correlation with microvascular complications in patients with T2DM.**
Methods: **219 patients with T2DM were included and grouped according to tertiles of HbAc1 variability (HbAc1-SD). Patients' clinical data were collected. Free SH (R-SH) levels were measured in these patients. Univariate and multifactorial logistic analyses were performed to analyze the correlation between HbAc1-SD and R-SH as a risk of microvascular complications in patients with T2DM. The value of HbAc1-SD and R-SH in differentiating microvascular complications from T2DM alone was assessed using ROC and area under the curve.**
Results: **Ninety-eight of 219 patients with T2DM had microvascular lesions, 75 had macrovascular lesions and 46 had T2DM alone. Patients with higher HbAc1-SD (≥ 0.85%) had a longer duration of T2DM and had a higher proportion of microvascular complications (51.02%), as well as more pronounced urinary protein. Patients with higher HbAc1-SD had the lowest R-SH levels (155.88 ± 60.81 μmol/L). HbAc1-SD ≥ 0.85% and R-SH < 173.64 μmol/L were independent risk factors for microvascular complications in patients with T2DM. The combination of R-SH and HbAc1-SD improved the discriminatory value of the separate indexes to distinguish microvascular complications among T2DM patients.**
Conclusions: **Elevated HbAc1 variability and decreased serum R-SH are associated with microvascular complications in T2DM. Prolonged glycemic fluctuations may increase the risk of microvascular complications by affecting the antioxidant defense system.**
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Correspondence:
ManYi Jin
Department of Neurology
The First People's Hospital of Xiaoshan Hangzhou
No. 199, Shixin South Road
Xiaoshan District
Hangzhou City
Zhejiang Province, 311200
China
Email: jmymanyi@outlook.com

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KEYWORDS

HbAc1, HbAc1 variability, free thiols, type 2 diabetes mellitus, microvascular complications

INTRODUCTION

According to the International Diabetes Federation, diabetes mellitus (DM) is a widespread chronic condition affecting 463 million adults globally, with a prevalence rate of 9.3%. The number of cases is projected to rise by over 50% by 2045 [1]. China now leads the world in diabetes prevalence and is projected to maintain this posi-

tion for the next decade, with type 2 DM (T2DM) being the most common form [2]. The persistent rise in disability and mortality in DM patients is mainly due to chronic complications. The main chronic complications include microvascular, macrovascular, and neurological lesions, with microvascular and macrovascular lesions being especially prominent in T2DM patients.

Diabetic retinopathy (DR) is a characteristic fundopathy that often occurs in the middle to late stages of DM [3]. In 2019, a systematic review indicated that DR's yearly complication rate might be as high as 12.7% [4]. Diabetic neuropathy (DN) is a chronic kidney disease caused by DM, characterized by persistent proteinuria and/or decreased glomerular filtration rate [5]. DN has become a cause of slow-acting nephropathy worldwide, and is the leading cause of end-stage renal disease [6]. Diabetic peripheral neuropathy (DPN), encompassing both autonomic and somatic neuropathy, is a crucial microvascular complication of DM [7]. These significant complications result in a decreased quality of life for DM patients. Many of these conditions arise from prolonged inadequate glycemic control. Chronic hyperglycemia produces reactive oxygen species (ROS) and can cause oxidative damage to pancreatic β-cells, mitochondrial dysfunction, and impaired endothelial function [8]. Reports have shown that impaired endothelial function causing thickening or hypertrophy of the microvascular basement membrane is an early pathological hallmark of microvascular complications of DM [9]. In addition, an imbalance in the redox balance of the organism leads to increased microvascular permeability, extravasation of macromolecular proteins and their deposition on the wall, which in turn triggers microthrombosis and wall occlusion [10].

Glycemic variability (GV) is a term used to describe impaired glycemic control. The variability of glycated hemoglobin (HbA1c), a major indicator of long-term glycemic control in DM patients, has received much attention in recent years [11,12]. It quantifies blood glucose fluctuation and provides an important basis for clinical resolution. Several studies have demonstrated that HbAc1 variability is associated with microvascular complications of DM, and that the greater the degree of glycemic fluctuation, the higher the risk of complications in patients [13,14]. Thus, it was determined that HbA1c variability is strongly associated with diabetic vascular disease. These studies then considered only general clinical features and HbA1c variability and did not take into account the effect of redox balance on disease caused by blood glucose fluctuations. Redox balance depends on ROS production and antioxidant defenses, and oxidative stress occurs when the former predominates. Thiols are compounds with free sulfhydryl group (R-SH) [15]. The oxidation of free thiols by ROS and sulfur substances is rapid, so their presence in the bloodstream could directly represent the systematic redox state [16]. Several studies have shown an association between serum R-SH and the prognosis of diseases related to oxidative stress, such as chronic heart failure [16] and coronary artery disease [17]. Additionally, SH/disulfide metabolite homeostasis is recognized as a sign of oxidative stress in DM ketoacidosis [18].

Based on these findings, we believe that R-SH levels and redox status in patients with T2DM can be indirectly assessed by monitoring under HbA1c variability. Therefore, by investigating HbA1c variability in T2DM patients, measuring serum R-SH in these patients, and analyzing serum R-SH levels and the incidence of microvascular complications based on HbA1c variability, the present study provides new ideas for antioxidant therapy.

MATERIALS AND METHODS

Study subjects

The study included T2DM patients at The First People's Hospital of Xiaoshan Hangzhou from March 2022 to September 2024. T2DM was diagnosed based on the World Health Organization's standards for DM diagnosis and classification [19]. All individuals were above the age of 18 and had DM for over a year. Exclusion criteria were as follows: 1) peripheral neuropathy not due to DM; 2) arteriovenous vascular disease (venous thrombosis or lymphadenopathy); 3) advanced renal failure (serum creatinine greater than 180 μmol/L or estimated glomerular filtration rate [eGFR] of less than 30 mL/minute/1.73 m^2); 4) pregnant or lactating women; 5) any serious disease that may limit life expectancy, such as advanced heart failure and advanced cancer; 6) incomplete information; and 7) both macrovascular and microvascular lesions. Fifty subjects were excluded from the study, of whom 15 had peripheral neuropathy not due to diabetes, 4 were pregnant women, 10 had a serious disease, 5 had advanced diseases (including 2 with advanced renal failure and 3 with heart failure) and 16 had incomplete information. A general clinical data survey and an extensive clinical examination were conducted for all patients. The study was approved by the institutional review board of The First People's Hospital of Xiaoshan Hangzhou. Informed consent was obtained from all participants.

Data collection

Patients, age, gender, height, weight, duration of DM, and comorbidities (macrovascular disease and microvascular lesions) at the patient's last follow-up or e-return visit were recorded. Electronic medical records were reviewed to collect patients' use of glucose-lowering medications. Body mass index (BMI) was calculated as weight divided by the square of height. At the last follow-up visit, after overnight fasting, patients' blood specimens and urine specimens were collected the following day for measurement of total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL-C), low-density lipoproteins (LDL-C), fasting blood glucose (FBG), HbAc1, serum creatinine (SCr), urinary creatinine, and urinary protein. Macrovascular compli-

cations of DM include cerebrovascular disease, coronary artery disease, and peripheral artery disease. Microvascular complications of DM include DR, DN and DPN. The participants were diagnosed with DR by specialized ophthalmologists and endocrinologists according to Diagnosis and Treatment of Diabetic Retinopathy in China (2022). DN diagnosis was based on the Clinical guideline for the prevention and treatment of diabetic kidney disease in China (2021 edition). DPN diagnosis was based on A Position Statement by the American Diabetes Association [20]. eGFR = 186 × [SCr (mmol/L) × 0.011] - 1.154 × [age] - 0.203 × [0.742 for females] × 1.233, where 1.233 is an adjustment factor for Chinese patients [21]. UACR = urine albumin/Creatinine.

HbAc1 variability

Data on HbA1c (minimum of 6 visits) were gathered from 24 months before and 12 months after the program began. The accuracy of variability might be influenced by the number of individual visits, and HbA1c variability was measured using the adjusted standard deviation (SD) of HbA1c. The mean and SD were obtained based on multiple HbAc1 values, and the adjusted SD was subsequently divided by [n/(n-1)] 0.5 and labeled as HbAc1-SD [13], where n is the number of HbAc1 measurements.

R-SH measurement

The serum specimens were preserved at -80°C pending the measurement of R-SH. The serum samples were diluted in a ratio of 1 to 4 using Tris buffer and then moved onto microplates with a plate marker (PerkinElmer, Boston, MA, USA). Utilizing 630 nanometers (nm) for calibration, the absorption wavelength reached 412 nm. Following this, 10 μL of 3.8 mM 5,5'-dithiobis-2-nitrobenzoic acid (Sigma-Aldrich, MO, USA) was introduced into the specimen. Following a 20-minute incubation at ambient temperature, the absorption measurements were reassessed. By concurrently measuring the calibration curve of L-cysteine (Fluka Biochemika, Buchs, Switzerland) in a solution of 0.1 M Tris/10 mM EDTA (pH 8.2), the ultimate concentration of R-SH was ascertained.

Statistical analysis

The statistical evaluations were conducted utilizing the SPSS 20.0 software. Data normality was assessed using the Shapiro-Wilk test. In the case of a normal distribution, the data was presented as mean ± standard deviation, with the ANOVA test applied for comparisons; for a skewed distribution, the data were displayed as the median (IOR), and the Kruskal-Wallis H test was utilized for comparing between groups. Count data were presented in terms of frequency (n) and rate (%) and underwent testing using either the chi-squared test or Fisher's exact test. To compare R-SH, the Kruskal-Wallis H test followed by Dunnett's multiple comparisons test was employed. Univariate analysis was employed to examine elements linked to microvascular complications in T2DM patients, while multivariate logistic analyses incorporated factors of statistical significance to identify independent risk factors influencing these complications in T2DM patients. The effectiveness of HbAc1-SD and R-SH alone or in combination in differentiating microvascular complications from DM, was evaluated through the receiver operating curve (ROC) curve and area under the curve (AUC). No artificial intelligence-assisted technologies were used in the production of this manuscript.

RESULTS

Clinical characterization of T2DM patients based on HbAc1 variability

The study ultimately included 219 T2DM patients, with 98 having microvascular lesions, 75 having macrovascular lesions, and 46 having only T2DM at the end of the follow-up. The tertile values of HbAc1 variability (HbAc1-SD) in these patients were 0.51, 0.67, and 0.84, respectively. Three groups were classified based on HbAc1 variability: HbAc1-SD ≤ 0.51%, HbAc1-SD 0.52 - 0.84%, and HbAc1-SD ≥ 0.85%. Table 1 shows the baseline characteristics of the above three groups of patients. Patients with higher HbAc1-SD had a longer duration of DM and a higher proportion of microvascular complications, as well as more pronounced urinary proteins, compared with patients with lower variability. Patients with higher HbAc1-SD used insulin more frequently for glycemic control, and these patients had higher TG levels. Patients with higher HbAc1-SD had higher FBG and HbAc1 levels.

R-SH levels in patients with T2DM

In these patients, we first analyzed R-SH concentrations in patients with microvascular complications based on HbAc1 variability, as shown in Figure 1. The results showed that patients with higher HbAc1-SD had the lowest R-SH levels (155.88 ± 60.81 μmol/L vs 200.77 ± 66.35 μmol/L, 246.09 ± 53.21 μmol/L). Subsequently, we also investigated the serum R-SH concentrations in patients with these different types of microvascular complications (DR, DN, and DPN), macrovascular lesions, and DM alone, as shown in Figure 2. Serum R-SH concentrations in patients with macrovascular lesions and DM alone were 241.65 ± 51.03 μmol/L and 249.18 ± 57.12 μmol/L, respectively, and there was no statistically significant difference between the two groups ($p > 0.05$). Although patients with DPN had the lowest median R-SH (187.43 ± 77.12 μmol/L), no significant difference was observed from the DR group (190.37 ± 66.99 μmol/L) and the DN group (195.66 ± 63.30 μmol/L) ($p > 0.05$). Notably, R-SH levels were significantly lower in patients with all types of microvascular complications than in patients with macrovascular lesions and those with DM alone (both $p < 0.05$). Value of HbAc1 variability and serum R-SH in predict-

Table 1. General clinical characteristics of the patients.

	HbAc1-SD ≤ 0.51% (n = 73)	HbAc1-SD 0.52 - 0.84% (n = 73)	HbAc1-SD ≥ 0.85% (n = 73)	p-value
Age, years	65.0 ± 7.2	71.6 ± 10.2	74.5 ± 7.6	0.157
Male, n (%)	31	28	29	
BMI (kg/m^2)	28.9 ± 4.2	28.2 ± 4.5	29.2 ± 4.8	0.842
DM duration, years	6.2 [1.5, 10.2]	8.2 [3.3, 15.9]	8.8 [5.0, 19.6]	< 0.001
Comorbidities, n (%)				
Cerebrovascular disease	5 (6.85)	6 (8.22)	6 (8.22)	0.938
Coronary artery disease	7 (9.59)	8 (10.96)	10 (13.70)	0.729
Peripheral arterial disease	8 (10.96)	10 (13.70)	15 (20.55)	0.249
DR	6 (8.22)	12 (16.44)	18 (24.66)	0.028
DN	5 (6.85)	10 (33.33)	15 (24.66)	0.055
DPN	5 (6.85)	10 (33.33)	17 (20.55)	0.019
Glucose-lowering medication				
Insulin + OHA	0	0	0	< 0.001
Only OHA	66 (90.41)	56 (76.71)	42 (57.53)	
Only insulin	5 (6.85)	15 (20.55)	30 (41.1)	
No treatment	2 (2.74)	2 (2.74)	1 (1.37)	
TC (mg/dL)	180.5 ± 30.2	178.6 ± 35.6	184.6 ± 31.7	0.109
TG (mg/dL)	152.5 ± 36.9	166.0 ± 41.2	180.6 ± 58.2	0.008
HDL-C (mg/dL)	43.9 ± 12.8	46.8 ± 15.2	47.2 ± 14.2	0.542
LDL-C (mg/dL)	98.5 ± 38.6	105.2 ± 40.2	102.2 ± 38.9	0.224
FBG (mmol/L)	6.92 ± 1.56	7.56 ± 1.85	9.15 ± 2.56	< 0.001
HbAc1 (%)	7.0 ± 1.2	7.6 ± 1.6	8.9 ± 1.8	< 0.001
eGFR (mL/min/1.73 m^2)	83.5 [72.3, 110.5]	78.6 [70.9, 99.6]	72.1 [66.2, 88.5]	0.327
UACR (mg/g)	20.2 [19.6, 86.5]	26.3 [18.6, 119.6]	32.6 [24.6, 256.7]	< 0.001

Categorical variables are shown as n (%) using the chi-squared test or Fisher's exact test; continuous variables are shown as X ± S or median [IQR] using the ANOVA test or the Kruskal-Wallis H test. p < 0.05 was statistically significant. BMI: Body mass index, DM: diabetes mellitus, DR: diabetic retinopathy, DN: diabetic nephropathy, DPN: diabetic peripheral neuropathy, OHA: oral hypoglycemic agents, TC: total cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, UACR: urinary microalbumin to creatinine ratio.

ing microvascular complications in patients with T2-DM.

To further analyze the value of HbAc1 variability and serum R-SH in predicting microvascular complications in patients with T2DM, we first performed a univariate logistic analysis, and those factors that were statistically significant ($p < 0.05$) were included in the multivariate analysis (Table 2). DM duration of more than 10 years was an independent risk factor for microvascular complications in patients with T2DM [OR, 95% CI 1.53 (1.20 - 2.11), p = 0.028]; for each increase in the UACR by one SD, the 1.06-fold increase in the risk of microvascular complications [OR, 95% CI 1.06 (1.00 ~ 3.36), p = 0.044]. For HbAc1 variability and R-SH levels, being above the third quartile of HbAc1-SD (0.85%) and below the first quartile of R-SH (< 173.64 μmol/L) was an independent risk factor for microvascular complications in patients with DM [OR, 95% CI 1.32 (1.03 - 2.36), p = 0.010; OR, 95% CI 1.20 (1.09 - 2.97), p = 0.025].

HbAc1 variability and R-SH concentrations in two cohorts of patients with microvascular complications and DM alone were subjected to ROC analysis (Figure 3). Both R-SH and HbAc1-SD had good discriminatory value (AUC both above 0.70). When combined, they significantly improved the discriminatory value for microvascular complications in patients with T2DM [AUC, 95% CI 0.847, (0.783 - 0.910)].

Table 2. Value of HbAc1 variability and serum R-SH in predicting microvascular complications in T2DM patients.

	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age ≥ 65 years	1.06 (1.01 - 2.36)	0.002	1.02 (0.96 - 2.05)	0.053
Male	0.85 (0.65 - 3.25)	0.527		
BMI	1.05 (0.89 - 10.25)	0.726		
DM duration ≥ 10 years	2.23 (1.02 - 3.26)	< 0.001	1.53 (1.20 - 2.11)	0.028
TC	1.26 (0.86 - 5.34)	0.429		
TG	1.06 (0.74 - 3.65)	0.229		
HDL-C	0.86 (0.25 - 1.52)	0.342		
FBG	1.02 (0.98 - 3.58)	0.095		
eGFR	1.25 (0.75 - 6.58)	0.594		
UACR	1.15 (1.00 - 10.85)	0.036	1.06 (1.00 - 3.36)	0.044
HbAc1-SD ≤ 0.51%	0.86 (0.25 - 3.25)	0.408	0.78 (0.36 - 4.25)	0.325
HbAc1-SD 0.52 - 0.84%	2.16 (1.05 - 5.20)	0.012	1.75 (0.96 - 3.25)	0.106
HbAc1-SD ≥ 0.85%	3.21 (2.02 - 4.25)	< 0.001	1.32 (1.03 - 2.36)	0.01
R-SH < 173.64 µmol/L	2.69 (1.65 - 5.32)	< 0.001	1.20 (1.09 - 2.97)	0.025
R-SH 173.65 - 219.58 µmol/L	1.36 (1.06 - 8.25)	0.045	1.25 (0.78 - 5.64)	0.254
R-SH ≥ 219.59 µmol/L	0.88 (0.65 - 2.25)	0.527	0.95 (0.78 - 3.54)	0.854

BMI: body mass index, DM: diabetes mellitus, DR: diabetic retinopathy, DN: diabetic nephropathy, DPN: diabetic peripheral neuropathy, OHA: oral hypoglycemic agents, TC: total cholesterol, TG: triglyceride, eGFR: estimated glomerular filtration rate, UACR: urinary microalbumin-to-creatinine ratio. BMI, TC, TG, HDL-C, LDL- C, FBG, eGFR, and UACR results were expressed as an increased risk of one SD. For HbAc1-SD and R-SH, HbAc1-SD ≤ 0.51% and R-SH ≥ 219.59 µmol/L were used as references. OR: odd ratio, 95% CI: 95% confidence interval. p < 0.05 was statistically significant.

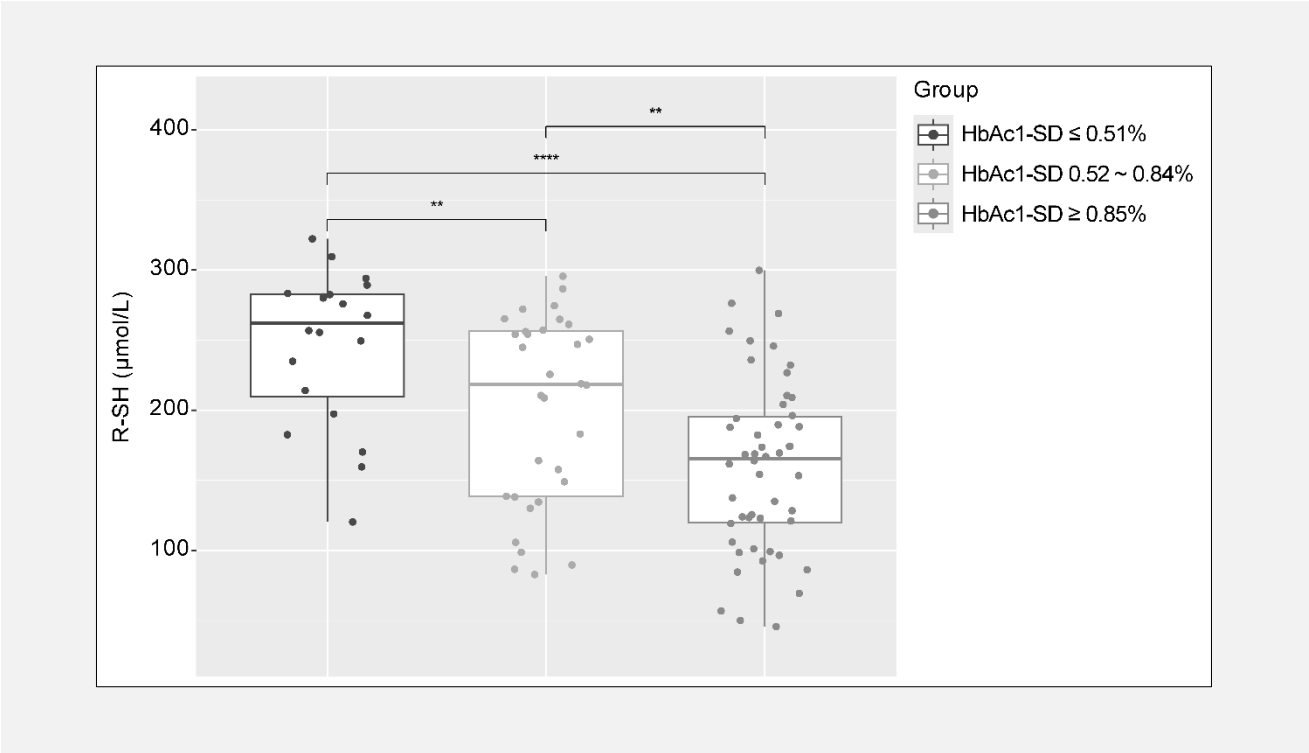


Figure 1. Serum R-SH levels in patients with microvascular complications based on HbAc1 variability.

Data were compared with Kruskal-Wallis H test with post-hoc Dunnett's multiple comparisons test. ** p < 0.01, *** p < 0.001.

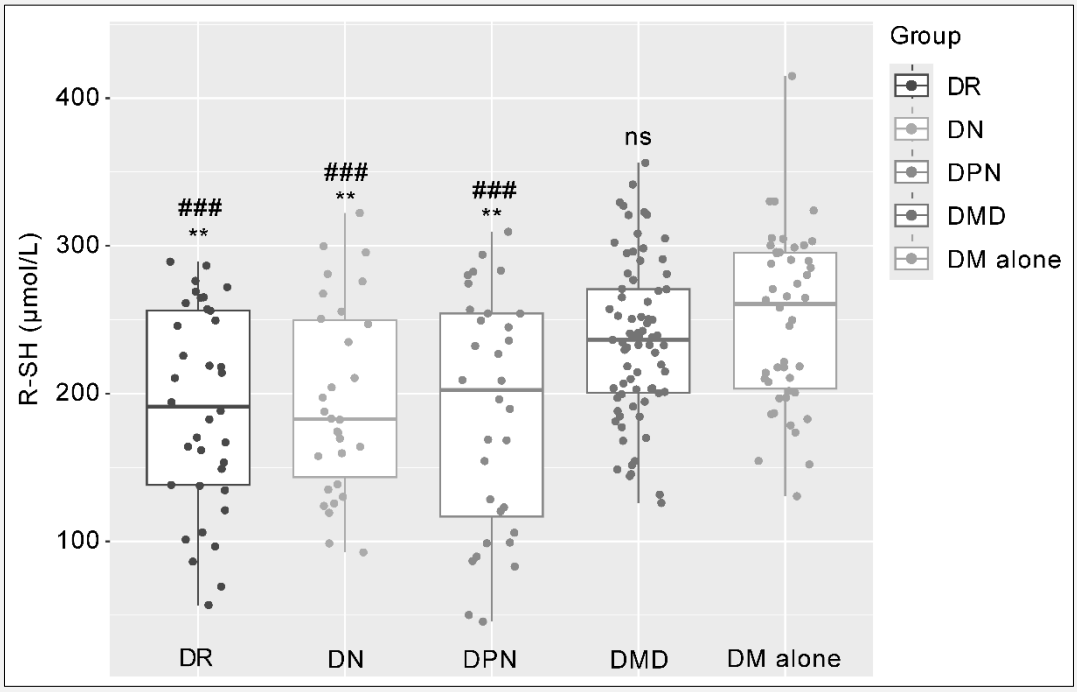


Figure 2. Serum R-SH levels in patients with different types of microvascular disease, macrovascular disease, and DM alone.

Data were compared with Kruskal-Wallis H test with post-hoc Dunnett's multiple comparisons test. p < 0.01 compared to DMD ** p < 0.01 and ### p < 0.001 compared to DM alone.

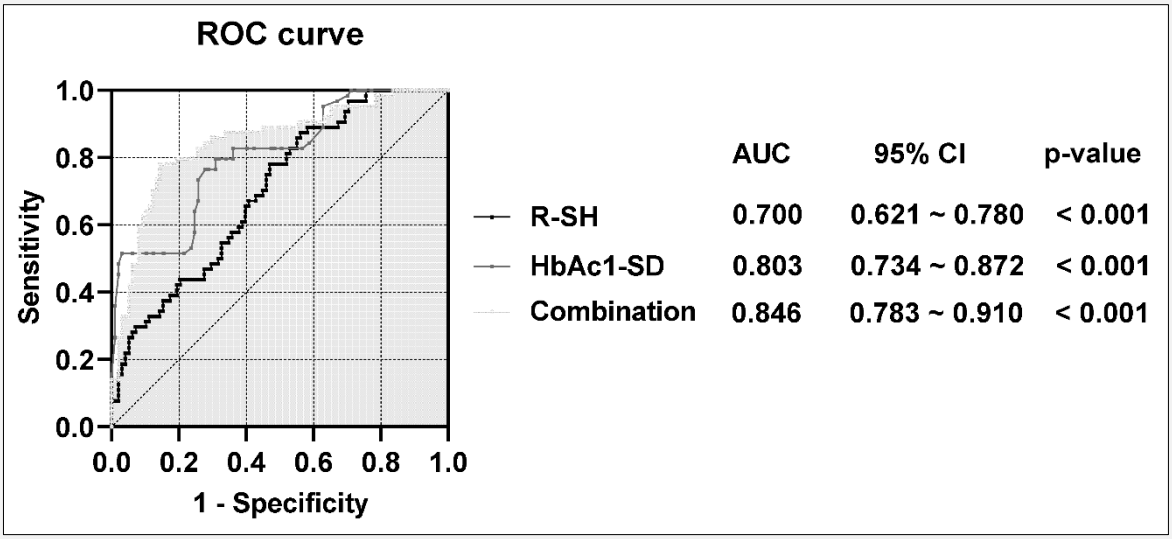


Figure 3. ROC curves for differentiation of HbAc1-SD and R-SH for microvascular complications.

p < 0.05 was statistically significant.

DISCUSSION

To date, this is the first study to assess the risk of microvascular complications in patients with T2DM based on HbA1C variability focusing on serum R-SH. The main findings of this study were that patients with higher HbAc1-SD (third quartile value) had a longer duration of DM and a higher proportion of microvascular complications and had lower serum R-SH levels. HbAc1-SD ≥ 0.85% (third quartile value) as well as R-SH < 173.65 μmol/L were independent risk factors for microvascular complications in patients with T2DM.

In individuals with T2DM, variations in blood glucose levels significantly contribute to the onset of microvascular complications [22]. Not only do dramatic shifts in blood glucose levels result in endothelial cell dysfunction, but they also heighten oxidative stress, contributing to diabetic complications [23]. Increased oxidative stress leads to decreased antioxidant capacity, which further exacerbates endothelial damage [24]. In diabetic patients, this cycle can result in damage to both microvascular and macrovascular systems. There is a strong connection between rapid glycemic changes and endothelial dysfunction, which is notably evident in DM patients [25]. Fluctuations in blood glucose over time have been shown to trigger oxidative stress and chronic inflammation [26]. Therefore, aggressive glycemic control is crucial in patients with T2DM to prevent microvascular and macrovascular complications. Microvascular complications of DM have been shown to range from 20 to 50% [27]. In the present study, 219 patients with T2DM were investigated and microvascular complications occurred in 44.74% (98/219) of patients, including 36 with DR, 30 with DN and 32 with DPN. Several risk factors are known to be associated with microvascular complications of DM, such as the duration of DM [28] and increased HbAc1 [28]. In the present study, 51.02% of microvascular lesions occurred in the cohort with higher variability of HbAc1. Lower eGER and higher UACR are risk factors for microvascular lesions [29]. The present study also observed increased UACR as an independent risk factor for microvascular complications of DM. The above results, we believe, are mediated by oxidative stress and endothelial dysfunction induced by fluctuating or sustained high glucose levels.

Serum R-SH acts as an antioxidant and becomes an indicator of systemic redox status. Patients with higher R-SH concentrations have higher glycemic control [30]. The present study has a similar conclusion that R-SH has lower levels in patients with poor glycemic control (higher HbAc1 variability). Mechanistically, in addition to acting as an antioxidant, R-SH may also act as a ROS buffer, helping to prevent the adverse effects of reduced insulin signaling [31]. Previous research indicated that T2DM patients with comorbidities had lower R-SH levels than those without, but it lacked clinical information, including glycemic control [32]. Also, it has been suggested that relying on a relatively simple composite indicator such as R-SH alone is not sufficient to predict the occurrence of complications in the long term. In the present study, we included glycemic variability together with R-SH in a multivariate logistic regression and utilized the combination of the two for the prediction of microvascular complications in T2DM. The results showed that in the risk model with HbAc1-SD, R-SH below the first quartile (173.64 μmol/L) was an independent risk factor for developing microvascular complications. And the combination of the two was of excellent value in differentiating DM from DM with microvascular complications. Particularly in our study, we did not observe that R-SH concentrations in patients with macrovascular diseases were lower than those with DM alone, whereas R-SH concentrations were lower in patients with microvascular complications than those with DM alone. We believe that there are some differences in the mechanisms of DM microangiopathy and macroangiopathy, and that microangiopathy is mainly associated with hyperglycemia, AGEs, oxidative stress, activation of the polyol metabolic bypass, and PKC activation [33-35]. In contrast, macrovascular lesions are associated with vascular endothelial damage, abnormalities in lipid metabolism, insulin resistance and hyperinsulinemia, and abnormalities in inflammation and immune response [36-38]. It is known that polyol metabolic bypass and R-SH metabolic pathways are interconnected intracellularly. For example, glutathione synthesis requires cysteine as a precursor, and cysteine levels may be affected by activation of the polyol metabolic bypass, although this is mostly found in cancer [39,40].

This study also has some limitations. This research is a short-term follow-up, showing a correlation between glycemic variability changes and serum F-SH and DM microvascular complications, though the causal link remains unclear. Furthermore, our research focused solely on T2DM samples, and further studies are needed to confirm if the findings apply to T1DM. Finally, given the small sample size, we converted continuous variables into dummy variables, which may have led to missing some vital information.

CONCLUSION

Elevated HbAc1 variability and decreased serum R-SH are associated with microvascular complications of T2DM. And based on elevated HbAc1 variability, serum R-SH is significantly reduced. Therefore, active control of blood glucose is significant for maintaining redox balance.

Data Available:
Data is available from the corresponding author on request.

Ethics Statement:
The present study was approved by the Ethics Committee of The First People's Hospital of Xiaoshan Hangzhou and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Declaration of Generative AI in Scientific Writing:
No artificial intelligence-assisted technologies were used in the production of this manuscript.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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