A study of factors influencing long-term glycemic variability in patients with type 2 diabetes: a structural equation modeling approach

Yuqin Gan[1,2†], Mengjie Chen[1†], Laixi Kong[1], Juan Wu[3], Ying Pu[3], Xiaoxia Wang[1], Jian Zhou[4], Xinxin Fan[1], Zhenzhen Xiong[1*‡] and Hong Qi[1,2*‡]

[1]School of Nursing, Chengdu Medical College, Chengdu, China, [2]Clinical Medical College of Chengdu Medical College, First Affiliated Hospital, Chengdu, China, [3]Department of Endocrinology and Metabolism, The First Affiliated Hospital of Chengdu Medical College, Chengdu, China, [4]Department of Rheumatology and Immunology, The First Affiliated Hospital of Chengdu Medical College, Chengdu, China

Aim: The present study aims to utilize structural equation modeling (SEM) to investigate the factors impacting long-term glycemic variability among patients afflicted with type 2 diabetes.

Method: The present investigation is a retrospective cohort study that involved the collection of data on patients with type 2 diabetes mellitus who received care at a hospital located in Chengdu, Sichuan Province, over a period spanning from January 1, 2013, to October 30, 2022. Inclusion criteria required patients to have had at least three laboratory test results available. Pertinent patient-related information encompassing general demographic characteristics and biochemical indicators was gathered. Variability in the dataset was defined by standard deviation (SD) and coefficient of variation (CV), with glycosylated hemoglobin variation also considering variability score (HVS). Linear regression analysis was employed to establish the structural equation models for statistically significant influences on long-term glycemic variability. Structural equation modeling was employed to analyze effects and pathways.

Results: Diabetes outpatient special disease management, uric acid variability, mean triglyceride levels, mean total cholesterol levels, total cholesterol variability, LDL variability, baseline glycated hemoglobin, and recent glycated hemoglobin were identified as significant factors influencing long-term glycemic variability. The overall fit of the structural equation model was found to be satisfactory and it was able to capture the relationship between outpatient special disease management, biochemical indicators, and glycated hemoglobin variability. According to the total effect statistics, baseline glycated hemoglobin

and total cholesterol levels exhibited the strongest impact on glycated hemoglobin variability.

Conclusion: The factors that have a significant impact on the variation of glycosylated hemoglobin include glycosylated hemoglobin itself, lipids, uric acid, and outpatient special disease management for diabetes. The identification and management of these associated factors can potentially mitigate long-term glycemic variability, thereby delaying the onset of complications and enhancing patients' quality of life.

KEYWORDS

type 2 diabetes mellitus, glycated hemoglobin, glycemic variability, influential factors, structural equation modeling

1 Introduction

The prevalence of diabetes has increased threefold over the past 30 years (1), making it one of the most prevalent and rapidly growing illnesses. By 2045, it is projected that diabetes will affect 12.2% of the population (783.2 million) worldwide (2). In China, the prevalence rate of diabetes has reached 11.2% since 2015-2017, with type 2 diabetes accounting for over 90% of cases (3). Globally, diabetes is the ninth leading cause of mortality (1), accounting for 4.2 million deaths in 2019 alone (4), which is 2-3 times higher than in non-diabetic individuals (5). Morbidity and mortality in diabetes are mainly caused by cardiovascular disease, diabetic nephropathy, retinopathy, and neuropathy (6). Hospitalization costs for diabetic patients vary widely across different Asian countries and can range from 11% to 75% of per capita income, with three times higher costs for patients with complications (7). In 2019, the global cost of direct treatment for diabetes was estimated to be $760 billion, with China alone spending $109 billion (8). Moreover, hospitalization costs were found to be three times higher for diabetic patients with complications than for those without complications (7).

Glycosylated hemoglobin (HbA$_{1c}$) is widely used as the benchmark for glycemic control and treatment of diabetic patients in clinical settings (3). The primary therapeutic goal for diabetic patients is to maintain blood glucose levels to prevent complications (9). However, diabetes experts agree that the extent of glycemic fluctuations among diabetic patients with similar HbA$_{1c}$ management may affect their risk of complications (10). Numerous studies have established a correlation between glycemic variability (GV) and diabetic complications (11–13), and it has been established that GV is a more clinically significant glycemic control indicator than HbA$_{1c}$ (14). Bergenstal et al. (15) demonstrated that GV refers to the fluctuations in blood glucose levels, primarily reflecting a decline in pancreatic β-cell function and is more detrimental to diabetic patients than persistent and stable hyperglycemia; it encompasses short-term and long-term glycemic variability, with short-term GV being characterized by intra-day or inter-day fluctuations in blood glucose that ultimately result in an increase in HbA$_{1c}$ (16). Long-term glycemic variability refers to the inconsistency of HbA$_{1c}$ values as they fluctuate between peaks and troughs (11). Therefore, optimal glycemic control for diabetic patients involves targeting HbA$_{1c}$ levels while also minimizing HbA$_{1c}$ fluctuation as much as possible (10).

In recent years, long-term glucose variability has garnered considerable attention from experts and clinicians (17). An increasing number of studies utilize it as a primary determinant of glycemic control quality (18). The glucose standard deviation (SD) and coefficient of variation (CV) are currently the most commonly employed measures (18). Recently, novel research has proposed a new metric, the HbA$_{1c}$ variability score (HVS), which calculates the proportion of HbA$_{1c}$ variations exceeding 0.5% from the previous measurement, divided by the total number of HbA$_{1c}$ measurements, to evaluate long-term glucose fluctuations (19, 20).

The degree of fluctuation in HbA$_{1c}$, as opposed to absolute blood glucose levels, is strongly associated with unfavorable outcomes (21). Among diabetic patients, HbA$_{1c}$ variability is a risk factor for mortality and death due to cardiovascular disease (22, 23), and it is independent of HbA$_{1c}$ levels (24). In addition, numerous observational and randomized clinical trial studies have demonstrated that HbA$_{1c}$ variability is linked to the risk of both microvascular and macrovascular complications in diabetes patients, as well as increased occurrences of hypoglycemia (12, 19, 25–27). Furthermore, a meta-analysis revealed that HbA$_{1c}$ variability is connected with the incidence of dementia among diabetic patients (28). Therefore, the degree of HbA$_{1c}$ fluctuation may play a crucial role in the clinical assessment of risks related to complications and mortality.

Given the well-established connection between HbA$_{1c}$ variability and diabetic complications and mortality, reducing HbA$_{1c}$ variability should be a target of glycemic management for diabetic patients (29). To effectively reduce HbA$_{1c}$ variability in

clinical practice, it is crucial to comprehend the factors that impact it in order to more successfully control HbA$_{1c}$ variability, delay the onset of complications, lower mortality rates in diabetic patients, and improve disease prognosis and quality of life. However, there is a dearth of trustworthy literature on the factors that influence HbA$_{1c}$ variability. Consequently, the purpose of this study is to perform a retrospective analysis to investigate the present status of HbA$_{1c}$ variability and its influencing factors, as well as to establish a reference basis for clinical concepts on strategies to decrease HbA$_{1c}$ variability in later stages.

2 Methods

2.1 Study design and participants

Clinical data of patients were obtained from the outpatient system of the Department of Endocrinology at a tertiary care hospital located in Chengdu for the purpose of collecting data from type 2 diabetes mellitus patients who were managed in the outpatient clinic from 2013 to 2022. Inclusion criteria were as follows: (1) meeting the diagnostic and classification criteria for type 2 diabetes according to the 1999 version of the World Health Organization (WHO); (2) age at the time of initial diagnosis was 18 years or older; and (3) at least three laboratory test findings were available. Exclusion criteria comprised: (1) the presence of other serious chronic diseases affecting the heart, liver, kidneys, brain, and lungs at the time of inclusion; (2) missing laboratory test data; (3) missing general data; and (4) presence of other endocrine diseases, such as thyroid, pituitary, and adrenal diseases, at the time of initial diagnosis.

2.2 Data collection

The medical records of patients receiving outpatient care at a tertiary hospital in Chengdu's endocrinology department were reviewed to extract clinical data, including demographic variables such as gender and age, as well as uric acid levels, and other variables including triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), blood glucose levels, and glycated hemoglobin (HbA$_{1c}$). The patients were also categorized based on their enrollment in the Outpatient Special Disease Management program, which involved regular HbA$_{1C}$ measurements, health education, medication prescriptions, and timely adjustments by a diabetes specialist. By organizing and analyzing the data, the variability and correlation values of each variable were determined.

2.3 Statistical analysis

The study data were exported from the EpiData (Chinese version) management software and subjected to analysis using IBM SPSS 26.0 and IBM SPSS AMOS 28.0 software. The Origin 2022 software was utilized for graphing purposes. Quantitative data were expressed in terms of mean ± standard deviation, while qualitative data were expressed as count and percentage (%). Linear regression analysis was employed to evaluate the impact of type 2 diabetes data on long-term glycemic variability. Additionally, structural equation modeling using AMOS 28.0 software was performed to identify the factors influencing long-term glycemic variability, and analyzed the power with power4SEM program. The goodness of fit index (GFI), incremental fit index (IFI), comparative fit index (CFI), standardized fit index (NFl), relative fit index (RFI), and non-normalized fit index (TLI) were used to evaluate the model fit. The values of IFI, CFI, NFI, RFI, and TLI were all greater than 0.9, while root mean square error of approximation (RMSEA) was less than 0.08, and χ2/df was less than 3 (30). Statistical significance was set at P<0.05.

2.4 Ethical considerations

The study was approved by the Ethics Committee of First Affiliated Hospital of Chengdu Medical College (approval no. 2021-07), and it was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

3 Result

3.1 Participant characteristics

This study comprised 369 subjects, the majority of whom were 40 years of age or older (95.7%). They had a follow-up duration of at least 4 years for diabetes mellitus management (69.6%), and were treated as outpatient special diseases (69.9%). A considerable

TABLE 1 Sociodemographic characteristics of the study subjects (N=369).

Variables	Category	Sample n (%)
Gender	Man	190 (51.5%)
	Woman	179 (48.5%)
Age	≤40years	16 (4.3%)
	41-60years	162 (43.9%)
	61-80years	176 (47.7%)
	≥81years	15 (4.1%)
Follow-up time	1-3years	112 (30.4%)
	4-6years	124 (33.6%)
	≥7years	133 (36.0%)
Outpatient special disease management	Yes	258 (69.9%)
	No	111 (30.1%)

TABLE 2 Descriptive statistics of HbA$_{1c}$ variants in T2DM patients.

	Mean	Standardized	Skewness	Peakedness
HbA$_{1C}$-HVS	0.529	0.285	0.016	-0.702
HbA$_{1c}$-SD	0.833	0.712	2.235	5.969
HbA$_{1C}$-CV	0.109	0.079	1.977	4.411

proportion of subjects had comorbidities (83.7%) and multiple complications (85.1%). Table 1 provides a comprehensive summary of the findings.

3.2 HbA$_{1c}$ variant distribution characteristics

In this study, the mean and standard deviation of HbA$_{1C}$-HVS were 0.529 ± 0.285, HbA$_{1C}$-SD were 0.833 ± 0.712, and HbA$_{1C}$-CV were 0.109 ± 0.079. Detailed results can be found in Table 2. Specifically, 64.50% of HbA$_{1C}$-HVS values ranged from 25.00% to 75.00%, 69.11% of HbA$_{1c}$-

SD values ranged from 0.35 to 1.50, and 58.14% of HbA$_{1c}$-CV values were between 0.05 and 0.15. The distribution of each data type among different patients is illustrated in Figure 1.

3.3 Biochemical index variability in T2DM patients: descriptive statistics

In this investigation, the mean values and standard deviations for the variability of biochemical markers were determined as follows: UA-SD (51.509 ± 33.448), UA-CV (0.160 ± 0.106), TG-SD (0.977 ± 2.774), TG-CV (0.382 ± 0.349), TC-SD (0.677 ± 0.483),

FIGURE 1
Characteristics of HbA$_{1c}$ variant distribution in T2DM patients.
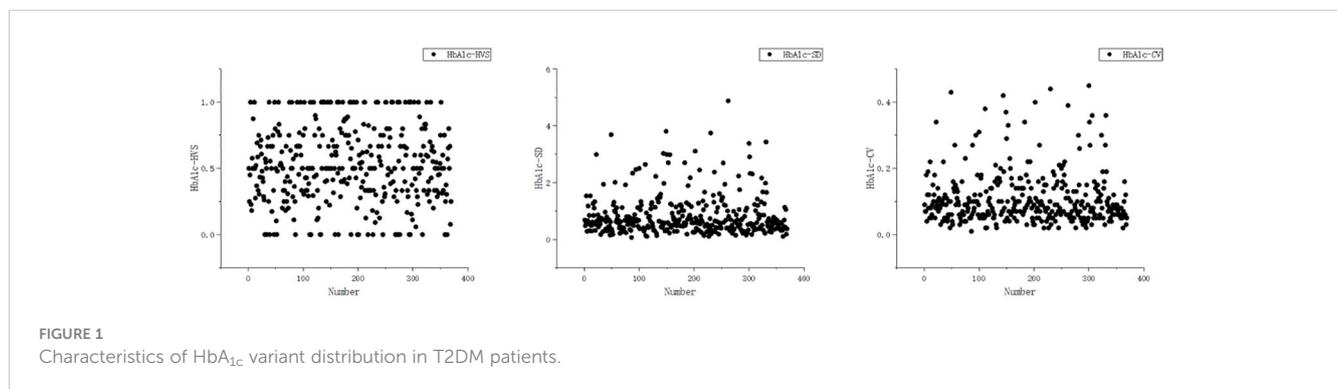
TABLE 3 Biochemical index variability in T2DM patients: descriptive statistics.

	Mean	Standardized	Skewness	Peakedness
UA-SD	51.509	33.448	2.361	8.288
UA-CV	0.160	0.106	3.342	17.902
TG-SD	0.977	2.774	10.457	141.382
TG-CV	0.382	0.349	4.647	29.899
TC-SD	0.677	0.483	3.639	21.709
TC-CV	0.165	0.088	1.433	3.354
LDL-SD	0.578	0.548	10.017	145.566
LAL-CV	0.268	0.154	2.964	19.933
HDL-CV	0.139	0.196	12.419	186.634
HDL-SD	0.354	3.509	19.136	367.086

TC-CV (0.165 ± 0.088), LDL-SD (0.578 ± 0.548), LAL-CV (0.268 ± 0.154), HDL-CV (0.139 ± 0.196), HDL-SD (0.354 ± 3.509). Further elaboration of the results can be found in Table 3.

3.4 One-way logistic regression analysis of factors influencing HbA$_{1c}$ variants in T2DM patients

In this investigation, it was observed that specific outpatient disease management, changes in uric acid levels, average triglyceride and total cholesterol levels, variability of total cholesterol and LDL, as well as baseline and recent glycation, were significant contributing factors to the variation in HbA$_{1C}$ among patients with type 2 diabetes (P<0.05). The results of the study are presented in Table 4, while Table 5 provides the details of the variable assignments.

3.5 Structural equation model

Drawing on the literature on variability in HbA$_{1C}$ levels, the variables that demonstrated a significant impact on such variability were integrated into a structural equation model while taking into account the study's objectives and domain-specific knowledge. The resulting model incorporated five observed variables - namely, outpatient-specific disease management, mean triglyceride, mean total cholesterol, baseline HbA$_{1C}$, and recent HbA$_{1C}$- along with four latent variables: uric acid variability, total cholesterol variability, LDL variability, and HbA$_{1c}$ variability. The final structural equation model is illustrated in Figure 2. The goodness-of-fit indices, which included a χ2/df of 2.698:3, RMSEA of 0.068:0.08, GFI of > 0.9, AGFI of 0.9, NFI of > 0.9, RFI of > 0.9, IFI of > 0.9, TLI of > 0.9, and CFI of > 0.9, revealed a good fit for the model. The model specific fits are detailed in Table 6. The power4SEM program and calculated the study efficacy of 0.969 for this study based on the study results RMSEA=0.068, DF=39, N=369, α=0.05. Further details are available in Figure 3.

3.6 Effect analysis of structural equation model variables

The present investigation discovered that TC-mean exerted a negative direct impact on HbA$_{1c}$ variability (β=-0.600, P=0.028). Baseline HbA$_{1C}$ exhibited the strongest positive direct influence on HbA$_{1C}$ variability (β=0.644, P=0.001), while TG-mean had a positive direct effect on HbA$_{1C}$ variability (β=0.176, P=0.042) and outpatient specific disease management had a positive direct effect on HbA$_{1C}$ variability (β=0.071, P=0.039). Further details are available in Table 7.

4 Discussion

In this study, the aim was to investigate the association between HbA$_{1C}$ variability and outpatient special disease management,

uric acid, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, and other relevant variables in patients with type 2 diabetes. The results indicated that each of the aforementioned variables had a varying degree of impact on HbA$_{1C}$ variability. This provides theoretical support for healthcare professionals to implement effective strategies to improve HbA$_{1C}$ variability in diabetic patients, thereby aiding in reducing the detrimental health outcomes associated with this disease and improving the quality of life of patients and their families, as well as minimizing the economic burden on society.

4.1 Current status of long-term glycemic variability in patients with T2DM

The results of this study indicated that the HbA$_{1C}$ high variability score (HbA$_{1C}$-HVS) was below the threshold value (60%) reported in the study by Li et al. (19). This was potentially due to the majority of patients being enrolled in outpatient special disease management, which increased their compliance with treatment and resulted in a relatively low HVS. In contrast, the HbA$_{1c}$ standard deviation (HbA$_{1C}$-SD) and coefficient of variation (HbA$_{1C}$-CV) values were higher than those reported in the study by Sun et al. (31), who employed interventions to strengthen glycemic control and reduce glucose fluctuations. However, these values were lower than those reported in the study by Mo et al. (32) on the percentage of glucose variation in Chinese diabetic patients, with a coefficient (%CV) threshold value of 33%. These results suggest that the HbA$_{1C}$ fluctuations observed in this study were relatively stable, and that lower HbA$_{1C}$ variability in diabetic patients could potentially reduce or delay the occurrence of complications associated with diabetes (33). Moreover, lower levels of HbA$_{1C}$ variability in patients could potentially reduce the number of hypoglycemic events, alleviate economic and psychological stress, and improve their quality of life (27).

4.2 Risk factors for long-term glycemic variability in patients with T2DM

The present study employed structural equation modeling to investigate the predictors of long-term glycemic variation in patients with type 2 diabetes mellitus. The results indicated that outpatient special disease management, baseline HbA$_{1c}$, mean total cholesterol (TC), and mean triglycerides (TG) had significant direct effects on long-term glycemic variation. Moreover, outpatient special disease management was found to have an indirect effect on long-term glycemic variation by influencing both baseline and recent HbA$_{1c}$. However, long-term glucose variance was not significantly predicted by variance in low-density lipoprotein (LDL), uric acid (UA), recent HbA$_{1c}$, or TC variance. Nevertheless, LDL variance and UA variance were found to have an indirect effect on long-term glucose variance through their effect on mean TC, while TC variance was also found to have an indirect effect on long-term glucose variance through its effect on mean TG.

Diabetes is a persistent, lifelong condition that necessitates frequent medication and monitoring of blood glucose levels, as well as regular assessments for worsening and complications to

TABLE 4   Linear regression analysis of risk factors for HbA$_{1C}$ variants in patients with type 2 diabetes.

Dependent variable	Independent variable	β	standardized coefficient β	t	P-Value	β Percentile95%CI		R^2
						Lower	Upper	
HbA$_{1C}$-HVS	Outpatient special disease management	13.165	0.212	4.152	<0.001	6.930	19.401	0.045
	UA-SD	0.179	0.210	4.105	<0.001	0.093	0.264	0.044
	UA-CV	58.687	0.219	4.294	<0.001	31.813	85.561	0.048
	TG-mean	2.750	0.163	3.161	0.002	1.039	4.460	0.027
	TC-mean	5.453	0.166	3.230	0.001	2.133	8.772	0.028
	TC-CV	52.975	0.164	3.179	0.002	20.206	85.744	0.028
	TC-SD	12.713	0.215	4.222	<0.001	6.792	18.635	0.046
	LDL-SD	6.886	0.132	2.555	0.011	1.586	12.187	0.017
	Baseline HbA$_{1C}$	5.915	0.383	7.950	<0.001	4.452	7.378	0.147
	Recent HbA$_{1C}$	7.795	0.337	6.865	<0.001	5.562	10.028	0.114
HbA$_{1C}$-SD	Outpatient special disease management	0.390	0.251	4.974	<0.001	0.236	0.544	0.063
	UA-SD	0.007	0.334	6.778	<0.001	0.005	0.009	0.111
	UA-CV	2.124	0.317	6.412	<0.001	1.473	2.776	0.101
	TG-mean	0.059	0.140	2.708	0.007	0.016	0.102	0.020
	TC-mean	0.116	0.141	2.737	0.006	0.033	0.199	0.020
	TC-SD	0.351	0.238	4.699	<0.001	0.204	0.498	0.057
	TC-CV	1.949	0.241	4.767	<0.001	1.145	2.753	0.058
	LDL-SD	0.251	0.193	3.77	<0.001	0.120	0.382	0.037
	LDL-CV	0.609	0.132	2.555	0.011	0.140	1.078	0.016
	Baseline HbA$_{1C}$	0.270	0.702	18.894	<0.001	0.242	0.298	0.493
	Recent HbA$_{1C}$	0.171	0.297	5.969	<0.001	0.115	0.228	0.088
HbA$_{1C}$-CV	Outpatient special disease management	0.039	0.229	4.507	<0.001	0.022	0.056	0.052
	UA-SD	0.001	0.286	5.723	<0.001	0	0.001	0.082
	UA-CV	0.182	0.247	4.884	<0.001	0.109	0.256	0.061
	TG-mean	0.006	0.127	2.453	0.015	0.001	0.011	0.016
	TC-mean	0.010	0.108	2.077	0.038	0.001	0.019	0.012
	TC-SD	0.032	0.195	3.807	<0.001	0.015	0.048	0.038
	TC-CV	0.188	0.210	4.125	<0.001	0.098	0.277	0.044
	LDL-SD	0.023	0.160	3.096	0.002	0.008	0.037	0.025
	LDL-CV	0.057	0.111	2.144	0.033	0.005	0.108	0.011
	Baseline HbA$_{1C}$	0.025	0.580	13.651	<0.001	0.021	0.028	0.337
	Recent HbA$_{1C}$	0.012	0.189	3.680	<0.001	0.006	0.018	0.036

allow for timely intervention. Patients who meet the requisite criteria for diabetes management are encouraged to participate in outpatient special disease treatment as the diabetes management system improves. The proportion of patients in this study who were enrolled in the diabetes clinic's special disease management

program (69.92%) was higher than that reported by Luo Xiaolu et al. (34) for community-based diabetic patients in Chengdu (48.94%), possibly due to patients' recognition of the importance of standardized diabetes management. Outpatient management of specific diseases can not only enhance patient health status,

TABLE 5 Assignment of factors affecting patients with T2DM.

	Variables	Variable assignment
X1	Gender	Man=1,Woman=2
X2	Age	≤40years=1;41-60years=2;61-80years=3;≥81years=4
X3	Follow-up time	1-3years=1;4-6years=2;≥7years=3
X4	Outpatient special disease management	YES=1;NO=2

functional mobility, and combat obesity (35), but also improve glycemic control and reduce negative outcomes (36), shorten patient stays (37), and reduce medication usage and expenses (38), thereby reducing the financial burden on patients. Additionally, outpatient special disease management can improve patients' blood glucose control, adherence to treatment, and decrease the incidence of adverse events (39). Greater adherence by patients results in better blood glucose control and timely detection of abnormal values, leading to timely intervention and hence reducing blood glucose fluctuations, ultimately leading to lower HbA$_{1c}$ levels (40), and in turn, reducing long-term bloating. Long-term blood glucose fluctuation can be minimized as a result. A study by Gill et al. (41) on the connection between healthcare expenses and glycemic control in diabetic patients revealed that diabetic patients managed by an endocrinologist specialist had lower healthcare costs, particularly those linked to microvascular and macrovascular complications, and improved HbA$_{1c}$ levels (41). Thus, eligible patients should be encouraged to participate in outpatient special disease care, which will not only minimize treatment expenses and family and societal obligations, but also

improve glycemic control and diabetes outcomes, thereby improving patients' quality of life.

Diabetes is a progressive and insidious condition, which may persist for a period of 4 to 6 years before its initial diagnosis (42). The presence of one or more complications highlights the urgency of early detection and management of glycemic aberrations, which can potentially minimize the severity and incidence of these complications. The baseline level of glycated hemoglobin (HbA$_{1c}$) serves as a pivotal determinant of glucose-lowering therapies (43) and strongly correlates with HbA$_{1c}$ variability (44). Elevated baseline HbA$_{1c}$ levels significantly augment HbA$_{1c}$ decline following therapeutic interventions, precipitating increased variability (45). This variability escalates the risk of patient-related complications and mortality (46). Hence, it is imperative to fortify diabetes education programs and emphasize routine blood glucose monitoring, aimed at detecting and intervening early to minimize blood glucose fluctuations and improve HbA$_{1c}$ variability, thereby impeding the progression of complications and enhancing diabetes-related outcomes.

The present investigation also determined that lipid variability was strongly associated with HbA$_{1c}$ variability. Increased lipid oscillations
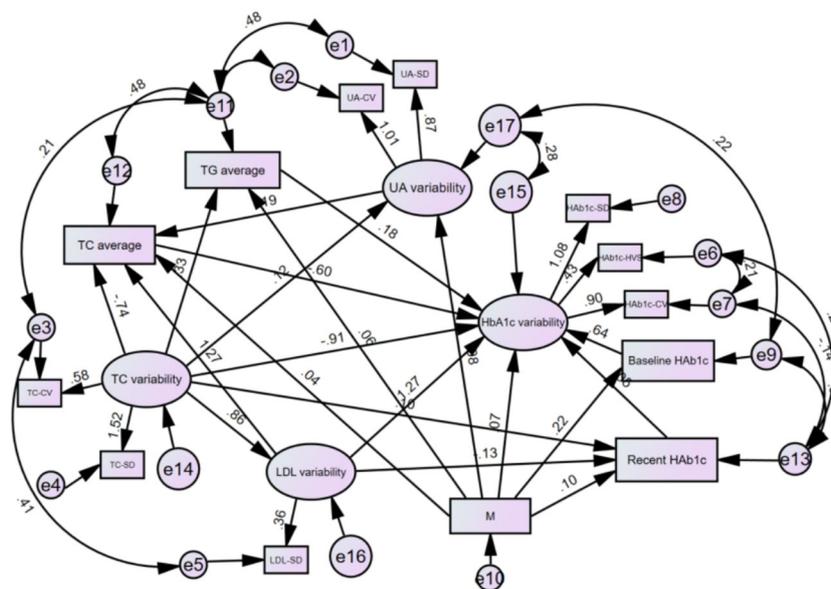
FIGURE 2
Modified model of structural equations for HbA$_{1c}$ variants in T2DM patients. M.Outpatient sppecial disease management. HbA$_{1c}$ Glycated hemoglobin; UA, Uric acid; TG, Triglycerides; TC, Total cholesterol; LDL, Low-density lipoprotein; CV, Coefficient of Variation; SD, Standard Deviation; HVS, HbA$_{1c}$ variability score.

FIGURE 3
Structural equation modeling study power.
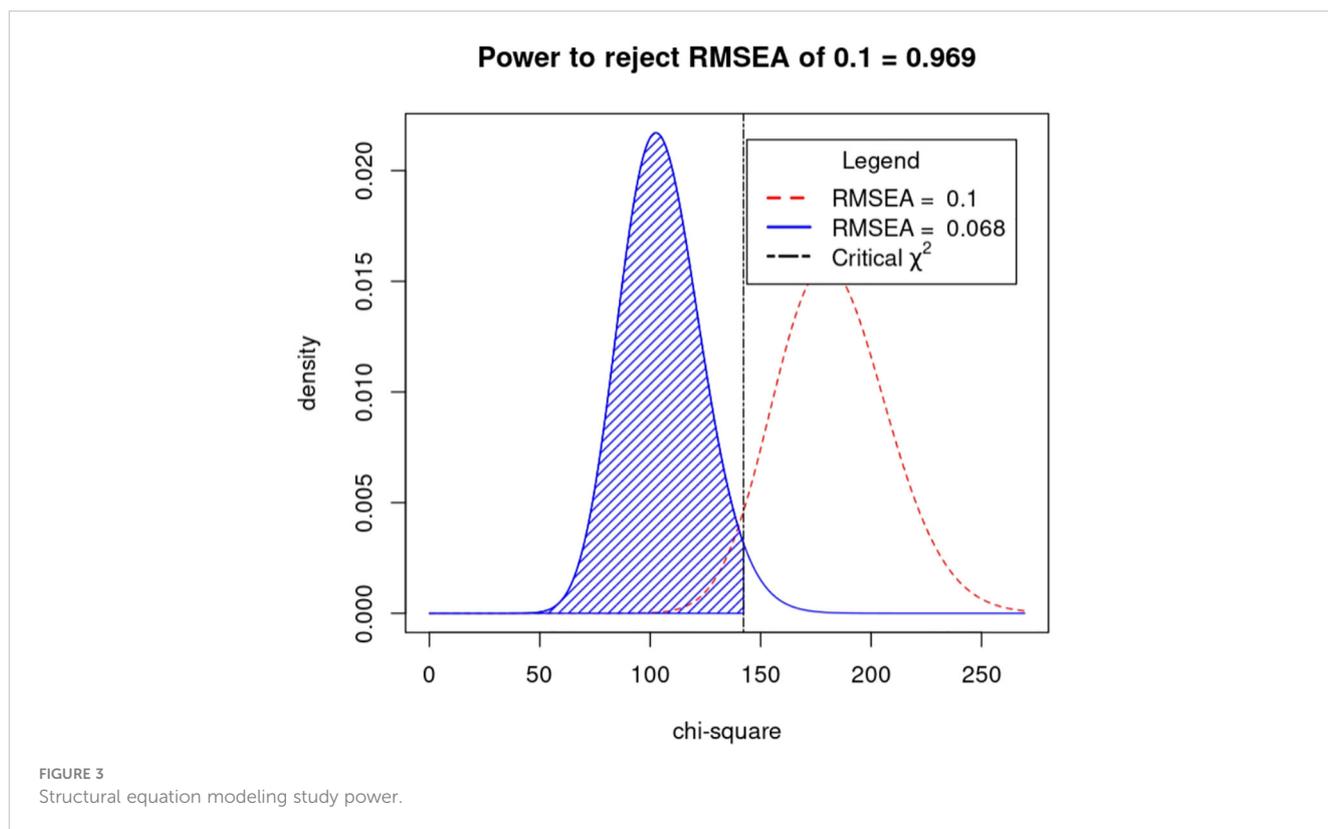
have been linked to adverse outcomes such as cardiovascular disease and all-cause mortality (47, 48), as well as diabetic complications such as retinopathy, nephropathy, and neurological disease (49, 50). Moreover, the incidence of diabetes and lipid variability were positively correlated (51), suggesting that greater lipid variability is linked to an elevated risk of HbA$_{1c}$ abnormalities. This may be due to the lipotoxic effect of lipids on beta cells, which alters the structure of glucose-activating enzymes and lipid rafts on the cell membrane, leading to beta cell apoptosis (52). Consequently, insulin secretion is reduced and glucose oxidation and utilization are increased, further exacerbating HbA$_{1c}$ variability (53). According to previous research, dyslipidemia plays a pivotal role in the etiology and pathophysiology of diabetes and is strongly positively correlated with HbA$_{1c}$ (54–57). Elevated lipid levels enhance variability by causing beta cell dysfunction and apoptosis (52), leading to reduced insulin secretion and elevated HbA$_{1c}$ levels (56, 58). In addition, uric acid fluctuations have an indirect impact on HbA$_{1c}$ variations. Uric acid is involved in lipid regulation and is positively correlated with cholesterol (59), which can cause dyslipidemia and poor glucose tolerance by inducing hypothalamic inflammation and gliosis and reducing hypothalamic endocrine capacity (60). This leads to suboptimal lipid markers and

elevated blood glucose levels, which combined contribute to poor glycemic control and HbA$_{1c}$ oscillations. Uric acid variability has been linked to diabetes (61), cardiovascular risk (62), renal function, and all-cause mortality (63). Thus, elevated levels of lipids and uric acid can impact not only HbA$_{1c}$ variability but also the severity of adverse outcomes and quality of life in diabetes patients. Improvements in the monitoring of lipid and uric acid levels in diabetic patients are necessary for early detection and management to enhance diabetes outcomes. Elevated levels of lipids and uric acid exert not only direct but also indirect effects on the variability of HbA$_{1C}$, contributing to the exacerbation of adverse outcomes and diminished quality of life in individuals with diabetes. The management strategy for glycemic control in diabetic patients revolves around addressing the three principal components of glycemic dysregulation, namely chronic hyperglycemia, hypoglycemia, and glycemic variability. Heightened variability in HbA$_{1C}$ has been associated with numerous unfavorable prognostic factors in diabetes and currently stands as the strongest indicator of diabetic outcomes, rendering it of considerable clinical significance. Hence, early intervention to regulate blood glucose levels and maintain glycemic stability is imperative to enhance patient prognosis and improve their quality of life.

TABLE 6 Evaluation results of the best fit of the optimal model.

Adaptation index	χ2/df	GFI	NFI	RFI	IFI	TLI	CFI	RMSEA
Reference value	<3.00	>0.9	>0.9	>0.9	>0.9	>0.9	>0.9	<0.08
Model test value	2.698	0.957	0.971	0.942	0.981	0.963	0.981	0.068

TABLE 7 Direct, indirect and total effects of each influencing factor on long-term blood glucose variability.

Influence Factors	Indirect effects	Direct effects	total effects	P-Value
Baseline HbA$_{1C}$	—	0.644	0.644	<0.001
TC-mean	—	-0.600	-0.600	0.028
LDL-Variation	-0.766	1.271	0.505	0.072
DOPD	0.128	0.071	0.199	0.039
TG-mean	—	0.176	0.176	0.042
UA-Variation	-0.112	—	-0.112	—
Recent HbA$_{1C}$	—	0.049	0.049	0.230
TC-Variation	0.927	-0.907	0.020	0.093

"–" Indicates no effect.

This study did not uncover a significant association between HbA$_{1C}$ variability and changes in follow-up duration. Upon thorough examination of the existing literature, it is evident that no study has thus far provided a specific threshold denoting the extent of risk posed by fluctuations in glycosylated hemoglobin levels for patients. While one study identified a correlation between prolonged variability in glycosylated hemoglobin and cardiovascular disease as well as mortality in individuals with diabetes, the long-term ramifications remain uncertain. Consequently, it is recommended to conduct follow-up investigations spanning a duration of 10 years or more, which may serve as a potential avenue for future research endeavors.

4.3 Limitations

This study possesses certain inherent limitations. Primarily, it is a retrospective study conducted at a single medical center, potentially resulting in an inadequate sample size. Secondly, it neglects to incorporate the influence of medications on long-term glycemic variation. It is anticipated that future investigations will employ multi-center surveys, expand the sample size, and undertake thorough exploration of the specific impact of medications on prolonged glucose variability in a prospective study. These endeavors will serve to augment the study's depth and furnish a theoretical foundation for improved clinical treatment options, thereby enhancing the quality of care provided to patients.

5 Conclusions

Using structural equation modeling, we conducted an assessment of the factors that impact HbA$_{1c}$ variability in individuals with type 2 diabetes. Our findings revealed that outpatient special disease management, baseline HbA$_{1c}$, lipids, and uric acid are significant risk factors for HbA$_{1c}$ variation. Consequently, it is recommended that health education programs be intensified for diabetic patients and those at risk, with emphasis on promoting treatment compliance and timely regulation of potential risk factors such as lipids and uric acid to maintain blood glucose stability. This approach is conducive to reducing HbA$_{1c}$ variability, improving adverse outcomes and mortality in diabetic patients, enhancing their quality of life, and reducing the economic burden on families and society.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* (2018) 14(2):88–98. doi: 10.1038/nrendo.2017.151

2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* (2022) 183:109119. doi: 10.1016/j.diabres.2021.109119

3. Society CD. Guideline for the preventon and treatment of type 2 diabetes mellitus in China(2020 edition)(part 1). *Chin J Pract Internal Med* (2021) 41(08):668–95. doi: 10.19538/j.nk2021080106

4. Demir S, Nawroth PP, Herzig S, Ekim Ü.B. Emerging targets in type 2 diabetes and diabetic complications. *Adv Sci (Weinh)* (2021) 8(18):e2100275. doi: 10.1002/advs.202100275

5. Raghavan S, Vassy JL, Ho YL, Song RJ, Gagnon DR, Cho K, et al. Diabetes mellitus-related all-cause and cardiovascular mortality in a national cohort of adults. *J Am Heart Assoc* (2019) 8(4):e011295. doi: 10.1161/JAHA.118.011295

6. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol* (2020) 16(7):377–90. doi: 10.1038/s41581-020-0278-5

7. Goldhaber-Fiebert JD, Li H, Ratanawijitrasin S, Vidyasagar S, Wang XY, Aljunid S, et al. Inpatient treatment of diabetic patients in Asia: evidence from India, China, Thailand and Malaysia. *Diabetes Med* (2010) 27(1):101–8. doi: 10.1111/j.1464-5491.2009.02874.x

8. Williams R, Karuranga S, Malanda B, Saeedi P, Basit A, Besançon S, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* (2020) 162:162108072. doi: 10.1016/j.diabres.2020.108072

9. Cardoso C, Leite NC, Moram C, Salles GF. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol* (2018) 17(1):33. doi: 10.1186/s12933-018-0677-0

10. Endocrinology CSO. Expers consensus on management of glycemic variability of diabetes mellitus. *Drug Eval* (2017) 14(17):5–814. doi: 10.3969/j.issn.1672-2809.2017.17.001

11. Škrha J, Šoupal J, Škrha JJ, Prázný M. Glucose variability, HbA$_{1c}$ and microvascular complications. *Rev Endocr Metab Disord* (2016) 17(1):103–10. doi: 10.1007/s11154-016-9347-2

12. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol* (2019) 7(3):221–30. doi: 10.1016/S2213-8587(18)30136-0

13. Martinez M, Santamarina J, Pavesi A, Musso C, Umpierrez GE. Glycemic variability and cardiovascular disease in patients with type 2 diabetes. *BMJ Open Diabetes Res Care* (2021) 9(1):e002032. doi: 10.1136/bmjdrc-2020-002032

14. Devries JH. Glucose variability: where it is important and how to measure it. *Diabetes* (2013) 62(5):1405–8. doi: 10.2337/db12-1610

15. Bergenstal RM. Glycemic variability and diabetes complications: does it matter? Simply put, there are better glycemic markers!. *Diabetes Care* (2015) 38(8):1615–21. doi: 10.2337/dc15-0099

16. Home P. Contributions of basal and post-prandial hyperglycaemia to micro- and macrovascular complications in people with type 2 diabetes. *Curr Med Res Opin* (2005) 21(7):989–98. doi: 10.1185/030079905X49662

17. Klimontov VV, Saik OV, Korbut AI. Glucose variability: how does it work? *Int J Mol Sci* (2021) 22(15):7783. doi: 10.3390/ijms22157783

18. Rodbard D. Glucose variability: A review of clinical applications and research developments. *Diabetes Technol Ther* (2018) 20(S2):S25–S215. doi: 10.1089/dia.2018.0092

19. Li S, Nemeth I, Donnelly L, Hapca S, Zhou K, Pearson ER. Visit-to-visit hbA(1c) variability is associated with cardiovascular disease and microvascular complications in patients with newly diagnosed type 2 diabetes. *Diabetes Care* (2020) 43(2):426–32. doi: 10.2337/dc19-0823

20. Yang CY, Su PF, Hung JY, Ou HT, Kuo S. Comparative predictive ability of visit-to-visit HbA$_{1c}$ variability measures for microvascular disease risk in type 2 diabetes. *Cardiovasc Diabetol* (2020) 19(1):105. doi: 10.1186/s12933-020-01082-9

21. Forbes JM, Fotheringham AK. Vascular complications in diabetes: old messages, new thoughts. *Diabetologia* (2017) 60(11):2129–38. doi: 10.1007/s00125-017-4360-x

22. Wan EY, Fung CS, Fong DY, Lam CL. Association of variability in hemoglobin A1c with cardiovascular diseases and mortality in Chinese patients with type 2 diabetes

mellitus - A retrospective population-based cohort study. *J Diabetes Complications* (2016) 30(7):1240–7. doi: 10.1016/j.jdiacomp.2016.05.024

23. Lee CL, Sheu WH, Lee IT, Lin SY, Liang WM, Wang JS, et al. Trajectories of fasting plasma glucose variability and mortality in type 2 diabetes. *Diabetes Metab* (2018) 44(2):121–8. doi: 10.1016/j.diabet.2017.09.001

24. Gorst C, Kwok CS, Aslam S, Buchan I, Kontopantelis E, Myint PK, et al. Long-term glycemic variability and risk of adverse outcomes: A systematic review and meta-analysis. *Diabetes Care* (2015) 38(12):2354–69. doi: 10.2337/dc15-1188

25. Hirakawa Y, Arima H, Zoungas S, Ninomiya T, Cooper M, Hamet P, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. *Diabetes Care* (2014) 37(8):2359–65. doi: 10.2337/dc14-0199

26. Zhou JJ, Schwenke DC, Bahn G, Reaven P. Glycemic variation and cardiovascular risk in the veterans affairs diabetes trial. *Diabetes Care* (2018) 41(10):2187–94. doi: 10.2337/dc18-0548

27. Long C, Tang Y, Huang J, Liu S, Xing Z. Association of long-term visit-to-visit variability of HbA$_{1c}$ and fasting glycemia with hypoglycemia in type 2 diabetes mellitus. *Front Endocrinol (Lausanne)* (2022) 13975468. doi: 10.3389/fendo.2022.975468

28. Song J, Bai H, Xu H, Xing Y, Chen S. HbA$_{1c}$ variability and the risk of dementia in patients with diabetes: A meta-analysis. *Int J Clin Pract* (2022) 2022:7706330. doi: 10.1155/2022/7706330

29. Jiaying N, Xiaojing M, Jian Z. Research progress of abnormal glycemic variability and diabetic complications. *Chin J Diabetes* (2022) 14(04):388–92. doi: 10.3760/cma.j.cn115791-20210510-00262

30. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Struct equation modeling: Multidiscip J* (1999) 6(1):1–55. doi: 10.1080/10705519909540118

31. Sun B, Gao Y, He F, Liu Z, Zhou J, Wang X, et al. Association of visit-to-visit HbA$_{1c}$ variability with cardiovascular diseases in type 2 diabetes within or outside the target range of HbA$_{1c}$. *Front Public Health* (2022) 101052485. doi: 10.3389/fpubh.2022.1052485

32. Mo Y, Ma X, Lu J, Shen Y, Wang Y, Zhang L, et al. Defining the target value of the coefficient of variation by continuous glucose monitoring in Chinese people with diabetes. *J Diabetes Investig* (2021) 12(6):1025–34. doi: 10.1111/jdi.13453

33. Scott ES, Januszewski AS, O'connell R, Fulcher G, Scott R, Kesaniemi A, et al. Long-term glycemic variability and vascular complications in type 2 diabetes: *post hoc* analysis of the FIELD study. *J Clin Endocrinol Metab* (2020) 105(10):dgaa361. doi: 10.1210/clinem/dgaa361

34. Xiaolu L, Yanli H, Shuang F, Yu S. Effect of special disease Outpatient Mangement on Prevalence and Efficacy of Statin Treament in Type 2 Diabetic Patients:a Multicenter Community-based Study. *Chin Gen Pract* (2019) 22(11):1277–82. doi: 10.12114/j.issn.1007-9572.2019.00.068

35. Lipton BJ. Association between Health Insurance and Health among Adults with Diabetes: Evidence from Medicare. *J Am Geriatr Soc* (2020) 68(2):388–94. doi: 10.1111/jgs.16238

36. Brown A, Kressin N, Terrin N, Hanchate A, Suzukida J, Kher S, et al. The influence of health insurance stability on racial/ethnic differences in diabetes control and management. *Ethn Dis* (2021) 31(1):149–58. doi: 10.18865/ed.31.1.149

37. Zhang A, Quan J, Eggleston K. Association between the quality of primary care, insurance coverage, and diabetes-related health outcomes in a cohort of older adults in China: results from the China Health and Retirement Longitudinal Study. *BMJ Open* (2022) 12(9):e059756. doi: 10.1136/bmjopen-2021-059756

38. Guo L, Zheng J, Pan Q, Zhang Q, Zhou Y, Wang W, et al. Changes in direct medical cost and medications for managing diabetes in Beijing, China 2016 to 2018: Electronic Insurance Data Analysis. *Ann Fam Med* (2021) 19(4):332–41. doi: 10.1370/afm.2686

39. Hai-Li X, Hong G, Ming Z, Meng-Jie Y, Lei X. Analysis of the influence of pharmaceutical care on the health management of diabetic patients. *Chin J Drug Appl Monit* (2020) 17(01):56–9. doi: CNKI:SUN:YWYY.0.2020-01-021

40. Huaying G, Xiuying L, Lingli J, Qingqing W, Liping K. A study on self-monitoring compliance and factors influencing self-monitoring in elderly patients with type 2 diabetes mellitus. *Chin J Health Stat* (Chinese) (2022) 39(05):717–20.

41. Gill M, Chhabra H, Shah M, Zhu C, Lando H, Caldarella F. Association between provider specialty and healthcare costs and glycemic control for patients with diabetes. *J Med Econ* (2018) 21(7):704–8. doi: 10.1080/13696998.2018.1467324

42. Porta M, Curletto G, Cipullo D, Rigault DLLR, Trento M, Passera P, et al. Estimating the delay between onset and diagnosis of type 2 diabetes from the time

course of retinopathy prevalence. *Diabetes Care* (2014) 37(6):1668–74. doi: 10.2337/dc13-2101

43. Jones AG, Lonergan M, Henley WE, Pearson ER, Hattersley AT, Shields BM. Should studies of diabetes treatment stratification correct for baseline HbA₁c? *PloS One* (2016) 11(4):e0152428. doi: 10.1371/journal.pone.0152428

44. Giugliano D, Maiorino M, Bellastella G, Chiodini P, Esposito K. Relationship of baseline HbA₁c, HbA₁c change and HbA₁c target of < 7% with insulin analogues in type 2 diabetes: a meta-analysis of randomised controlled trials. *Int J Clin Pract* (2011) 65(5):602–12. doi: 10.1111/j.1742-1241.2010.02619.x

45. Frias JP, Bonora E, Cox DA, Bethel MA, Kwan A, Raha S, et al. Glycaemic efficacy of an expanded dose range of dulaglutide according to baseline glycated haemoglobin (HbA₁c) subgroup: *Post hoc* analysis of AWARD-11. *Diabetes Obes Metab* (2021) 23(12):2819–24. doi: 10.1111/dom.14533

46. Lee S, Liu T, Zhou J, Zhang Q, Wong WT, Tse G. Predictions of diabetes complications and mortality using HbA₁c variability: a 10-year observational cohort study. *Acta Diabetol* (2021) 58(2):171–80. doi: 10.1007/s00592-020-01605-6

47. Wang MC, Li CI, Liu CS, Lin CH, Yang SY, Li TC, et al. Effect of blood lipid variability on mortality in patients with type 2 diabetes: a large single-center cohort study. *Cardiovasc Diabetol* (2021) 20(1):228. doi: 10.1186/s12933-021-01421-4

48. Li S, Hou L, Zhu S, Yi Q, Liu W, Zhao Y, et al. Lipid variability and risk of cardiovascular diseases and all-cause mortality: A systematic review and meta-analysis of cohort studies. *Nutrients* (2022) 14(12):2450. doi: 10.3390/nu14122450

49. Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, Tesfaldet B, et al. Long-term complications in youth-onset type 2 diabetes. *N Engl J Med* (2021) 385(5):416–26. doi: 10.1056/NEJMoa2100165

50. Lee S, Zhou J, Wong WT, Liu T, Wu W, Wong I, et al. Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. *BMC Endocr Disord* (2021) 21(1):94. doi: 10.1186/s12902-021-00751-4

51. Cai Z, Chen Z, Fang W, Li W, Huang Z, Wang X, et al. Triglyceride to high-density lipoprotein cholesterol ratio variability and incident diabetes: A 7-year prospective study in a Chinese population. *J Diabetes Investig* (2021) 12(10):1864–71. doi: 10.1111/jdi.13536

52. Wen G, Jie L, Yamei W, Xiaoqian C, Haiyan S, Bing X. Different effects of lipid components on insulin secretion in patients with type 2 diabetes and subjects with normal glucose metabolism. *Chin Jouurnal Endocrinol Metab* (2015) 7:599–600. doi: 10.3760/cma.j.issn.1000-6699.2015.07.009

53. Sunil B, Ashraf AP. Dyslipidemia in pediatric type 2 diabetes mellitus. *Curr Diabetes Rep* (2020) 20(10):53. doi: 10.1007/s11892-020-01336-6

54. Martins RA, Jones JG, Cumming SP, Coelho ESM, Teixeira AM, Veríssimo MT. Glycated hemoglobin and associated risk factors in older adults. *Cardiovasc Diabetol* (2012) 11:13. doi: 10.1186/1475-2840-11-13

55. Wu L, Parhofer KG. Diabetic dyslipidemia. *Metabolism* (2014) 63(12):1469–79. doi: 10.1016/j.metabol.2014.08.010

56. Hsiung C, Chang Y, Lin C, Chang C, Chou W, Chu H, et al. The causal relationship of circulating triglyceride and glycated hemoglobin: A mendelian randomization study. *J Clin Endocrinol Metab* (2020) 105(3):908–19. doi: 10.1210/clinem/dgz243

57. Ting H, Yan X, Qing-Xing S. Analysis of the relationship between glycosylated hemoglobin and fasting blood glucose, blood lipids in patients with type 2Diabetes mellitus. *J Med Inf* (2022) 35(18):147–9.

58. Bulut T, Demirel F, Metin A. The prevalence of dyslipidemia and associated factors in children and adolescents with type 1 diabetes. *J Pediatr Endocrinol Metab* (2017) 30(2):181–7. doi: 10.1515/jpem-2016-0111

59. Peng TC, Wang CC, Kao TW, Chan JY, Yang YH, Chang YW, et al. Relationship between hyperuricemia and lipid profiles in US adults. *BioMed Res Int* (2015) 2015:127596. doi: 10.1155/2015/127596

60. Lu W, Xu Y, Shao X, Gao F, Li Y, Hu J, et al. Uric acid produces an inflammatory response through activation of NF-κB in the hypothalamus: implications for the pathogenesis of metabolic disorders. *Sci Rep* (2015) 5:12144. doi: 10.1038/srep12144

61. Su H, Liu T, Li Y, Fan Y, Wang B, Liu M, et al. Serum uric acid and its change with the risk of type 2 diabetes: A prospective study in China. *Prim Care Diabetes* (2021) 15(6):1002–6. doi: 10.1016/j.pcd.2021.06.010

62. Kim HK, Lee M, Lee YH, Lee BW, Cha BS, Kang ES. Uric acid variability as a predictive marker of newly developed cardiovascular events in type 2 diabetes. *Front Cardiovasc Med* (2021) 8775753. doi: 10.3389/fcvm.2021.775753

63. Pilemann-Lyberg S, Hansen TW, Tofte N, Winther SA, Theilade S, Ahluwalia TS, et al. Uric acid is an independent risk factor for decline in kidney function, cardiovascular events, and mortality in patients with type 1 diabetes. *Diabetes Care* (2019) 42(6):1088–94. doi: 10.2337/dc18-2173