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Cover Page Footnote

Acknowledgement: we thank all the residents and nursing staff who supported us to recruit and withdraw samples from all participants.

ORIGINAL ARTICLE

The Association of Diurnal Blood Glucose Variability With Subclinical Cardiac Disease in Patients With Type 2 Diabetes Mellitus

Walid Shehab-Eldin [a,*], Ahmed El-ashmawy [b], Mahmoud K. Ahmed [c], Nesreen Elhelbawy [d], Alaaeldin Dawood [a], Mostafa Elnajjar [a]

[a] Department of Internal Medicine, Faculty of Medicine, Menoufia University, Egypt
[b] Shebien Elkom Fever Hospital, Menoufia, Egypt
[c] Department of Cardiology, Faculty of Medicine, Menoufia University, Egypt
[d] Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Menoufia University, Egypt

Abstract

Background: **The relationship between glycemic control and the risk of cardiac disease in patients with Type 2 Diabetes Mellitus (T2DM) is controversial. 1,5-Anhydroglucitol (1,5-AG) is a biomarker of Glucose Variability (GV) and has been associated with clinical cardiovascular disease. However, its association with Subclinical Cardiac Disease (SCD) is unknown.**

Aim of the work: **Study the association between GV and SCD.**

Subjects and methods: **A cross-sectional study was conducted on 46 asymptomatic patients with T2DM as T2DM individuals group. Another 46 non-diabetic age and sex matched subjects were included as the healthy group. 1,5-AG was measured for all subjects. M-mode echocardiography in parasternal long axis view was used to measure Left Ventricular (LV) end diastolic dimension, LV end systolic dimension, ejection fraction, interventricular septum, LV posterior wall thickness, LV fractional shortening, left atrial dimension and aortic root dimension. Global Longitudinal Strain (GLS) was assessed by speckled tracking echocardiography.**

Results: **There were no significant differences between both groups as regarding age, sex, BMI, AST, ALT, and serum creatinine. 1,5-AG was lower in T2DM individuals group. As regarding the echo parameters no significant difference found between both groups regarding left ventricular, left atrial and aortic root dimensions. T2DM individuals group showed a statistically significant higher mitral valve area, apical 2 chambers, apical 4 chambers, apical longitudinal axis and GLS. No correlation found between HbA1c and any echo parameters while 1,5-AG showed a significantly negative correlation with apical 2 chambers, apical 4 chambers, apical longitudinal axis and GLS. ROC curve analysis detected 1,5-AG less than 7.51 ng/ml as the best cut off value with sensitivity of 85.7%, specificity 75% to diagnose patients with T2DM and SCD.**

Conclusion: **1,5-AG might be used as an additional surrogate marker to identify patients with T2DM and SCD.**

Keywords: Glucose variability, Subclinical cardiac disease

1. Introduction

Cardiovascular disease (CVD) is the major cause of death in patients with type 2 Diabetes Mellitus (T2DM) [1]. It also has a considerable impact on direct medical costs of T2DM management [2]. Heart failure (HF) is the most common presentation of CVD in patients with T2DM [3]. 30-40% of patients with HF have T2DM [4] and patients with T2DM have more

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* Corresponding author. Diabetes and Endocrinology Unit, Faculty of Medicine, Menoufia University, Egypt, 3, Elzakzoky st, Menouf, Menoufia, Egypt.
E-mail address: waleedshehab2000@gmail.com (W. Shehab-Eldin).

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than double the risk to develop HF [5]. The prognosis of survival of those patients is almost half the survival of non-diabetic population [6]. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification described patients with T2DM as stage A HF even without any symptoms or structural changes [7].

Before patients develop the full-blown picture of HF, they pass into an asymptomatic (subclinical) stage. Patients usually go undiagnosed during this stage due to lack of screening programs [8]. Subclinical cardiac dysfunction can be detected by decreased left ventricular ejection fraction (LVEF), increased left atrial volume (LAV), and higher left ventricular (LV) mass as measured by ordinary echocardiography [9]. However, echocardiography has two compromises. The first is the difficulty to detect early stages of the disease [10]. The second is the great inter-person and intra-person variability [11].

In recent years, cardiac strain has emerged as a more sensitive measure of myocardial function. Global longitudinal strain (GLS) assesses the total deformation or shortening during the cardiac cycle of longitudinal myocardial fibers [12]. GLS may both diagnose and exclude acute coronary syndrome better than LVEF [13]. In a meta-analysis on 5721 patients from 15 clinical trials, GLS has better intra- and inter-observer reproducibility compared to LVEF [14]. That is why GLS is preferred in clinical practice especially for mild systolic dysfunction [15]. Speckle tracking echocardiography is the most recent method to detect subclinical cardiac function [16].

Several mechanisms had been proposed to explain the pathogenesis of HF in patients with T2DM [17–19].

Although many studies showed improvement of HF with improved glycemic control, other studies failed to reach to the same conclusion [20]. Even it may be exaggerated. For example, the incidence of HF increased by 17% with tight glycemic control in a meta-analysis on 3517 patients collected from 15 clinical trials [21]. Moreover, treatment of T2DM with thiazolidendiones or insulin may increase the incidence and risk of mortality due to HF [22]. All these studies used glycated haemoglobin (HbA1c) as a marker for glycemic control. They neglected a recent measure of glycemic control which is diurnal glucose variability (GV) that might be involved as a surrogate marker of glycemic control.

Glucose variability refers to oscillations of blood glucose that occur throughout the day including hypoglycemic periods and postprandial excursions [23]. GV could be evaluated by continuous glucose monitoring which is not feasible from the practical point of view. 1,5-Anhydroglucitol (1,5- AG) is a natural monosaccharide found in our food. It competes with glucose for tubular reabsorption so its level decreases during times of hyperglycemia and return to normal levels after approximately 2 weeks in the absence of hyperglycemia [24]. It might be a better predictor of short term glucose excursion and GV than HbA1c in patients with T2DM [25].

GV may be a new predictor for the development of adverse cardiac events [26]. Considering it as a therapeutic target in addition to HbA1c might increase the sensitivity and specificity for the diagnosis of glycemic control.

Abbreviations

1,5-AG	1,5 − anhydroglucitol
ACCF/AHA	The American College of Cardiology Foundation/American Heart Association
AUC	Area under the Curve
CVD	Cardiovascular disease
FPG	Fasting Plasma Glucose
GLS	Global longitudinal strain
GV	Glucose variability
HbA1c	Glycated Haemoglobin
HF	Heart Failure
LA	Left Atrium
LV	Left Ventricular
T2DM	Type 2 Diabetes Mellitus

2. Aim of the work

To study the association between GV measured by 1,5-AG and subclinical cardiac disease measured by speckle tracking echocardiography.

3. Subjects and methods

The present work is a cross sectional study. Based on post review of literature that assumed on effect size 0.7 and SD of 1.2, sample size has been calculated at 95% CT and power 80% and it was 46 participants/group. It involved 46 patients (18 males/28 females) with T2DM as the T2DM individuals group and 46 healthy subjects (23 males/23 females) as the healthy group after taking written consent from all participants. Patients were recruited from the outpatient diabetic clinic in Menoufiya university hospital and fever hospital during the period from January 2019 to December 2019. Local ethical committee permission was obtained with the number 6/2017INTM before the start of the study.

Patients were included in the study if their Fasting Plasma Glucose (FPG) $\geq$ 126 mg/dl, PPPG $\geq$ 200 mg/dl or HbA1c $\geq$ 6.5% according to the ADA guidelines 2018 [27] or if they are receiving treatment for T2DM. All patients above 18 years who fulfilled these criteria and accept signing the consent were included in the study. 36 patients were receiving oral anti-diabetic drugs, 14 patients receiving insulin ± oral anti-diabetic drugs. Pregnant and breast feeding ladies as well as subjects who refused to sign the consent were excluded from the study. Patients with past history of cardiac, renal, hepatic or advanced chest disease were also excluded.

All patients were subjected to thorough history taking, complete physical examination including vital signs, general cardiac and abdominal examination in addition to anthropometric measurements. Blood samples were obtained from all patients on their routine clinical visits after overnight fasting for at least 8 hours. Samples were immediately centrifuged and serum stored at −80° C until assayed. FPG and PPPG were measured by the glucose oxidase method. AST, ALT, HbA1c, urea, and creatinine were measured by a routine clinical chemistry laboratory analyzer.

1,5-AG was measured by enzyme linked immunosorbent assay (ELISA) KIT (SunRed, Shanghai, China). This assay has 0.106 ng/ml sensitivity at assay range from 0.2 to 30 ng/ml. Results were obtained using the microplate reader (ELx 808 TM Absorbance microplate reader, BioTek) at wavelength 450 nm as recommended by the vendor.

Routine chest X ray and pelvi-abdominal ultrasound and 12- lead surface ECG were done for all participants and patients with IHD were also excluded from the study.

Conventional echocardiography

Echocardiographic examination was done by using the commercially available Vivid 9, General Electric Healthcare, Vingmed, Norway equipped with a 1.7–4 MHz phased-array transducer. Echocardiographic imaging was obtained in the parasternal short and long axis, and apical 3, 2 and 4-chambers views using standard transducer positions. LV end-systolic and diastolic volumes and diameters, LV posterior and septal thickness, ejection fraction and left atrial and aortic diameter were measured in accordance with the recommendations of the American Society of echocardiography [28]. Continuous and pulsed wave Doppler was used for assessment valvular function.

Doppler tissue imaging derived early mitral annular velocity wave (E′ wave) was measured from septal annular site in apical four chamber view and the ratio of early mitral flow E wave to the early annular mitral wave (E/E′ ratio) was measured.

Left ventricular global strain by 2-D speckle tracking echocardiography.

Three points in the LV were anchored, apex and annular hinge points in apical 4, 3 & 2 chamber views. Frame rate was selected between 40–90 or at least 40% of HR. Then after activation of automated function imaging, digital data were transferred for off-line analysis, using Vivid Nine system Echo Pac, GE Vingmed, Horton, Norway. The system processed the data and after finishing tracing and auto processing of the three views, the global strain and Bull's eye report were obtained. Peak LV Strain is the peak negative value that was obtained at or before aortic valve closure.

4. Statistical Analysis

Data were calculated using SPSS Version 21 and given as the mean ± SD. The normality of data was first tested with one-sample Kolmogorov-Smirnov test. Group differences were analyzed by Student's t test, Mann-Whitney test, and X^2 for normally distributed, non-normally distributed, and non-continuous variables respectively. Relationships between 1,5-AG and HbA1c% with other factors were assessed by Pearson correlation analysis. ROC analysis was performed to study sensitivity, specificity and area under the curve (AUC) of 1,5-AG to diagnose subclinical cardiac disease.

For all above mentioned statistical tests done, the threshold of significance is fixed at 5% level (p-value). The results was considered:

- Non-significant when the probability of error is more than 5% ($p > 0.05$).
- Significant when the probability of error is less than 5% ($p \leq 0.05$).

The smaller the p-value obtained, the more significant are the results.

5. Results

The present work included 46 (18 males/28 females) patients with T2DM with a duration of DM 15.23 ± 8.7 years as the T2DM individuals group. Their age is 50.56 ± 11.77 years and BMI is 28.7 ± 3.83 kg/M^2. In addition 46 apparently healthy subjects were included as the healthy group. There were no significant differences between both groups as regarding age, sex, BMI, AST, ALT, and serum creatinine. As expected, the T2DM individuals group showed higher FPG, PPPG and HbA1c than the healthy group. 1,5-AG as an indicator of glucose

Table 1. Demographic and laboratory data of the studied groups.

	T2DM individuals N = 46	Healthy N = 46	t -test	P value
	Mean ± SD	Mean ± SD		
Age (years)	50.56 ± 11.77	46.54 ± 14.19	1.48	0.14
Sex (Male/Female)	18/28	23/23	$X^2 = 1.1$	0.29
BMI (Kg/M^2)	28.70 ± 3.83	27.22 ± 5.06	1.59	0.12
Serum creatinine (mg/dl)	0.86 ± 0.10	0.84 ± 0.08	1.0	0.32
ALT (mg/dl)	27.48 ± 7.10	25.59 ± 4.56	1.52	0.13
AST (mg/dl)	30.41 ± 7.25	29.87 ± 7.70	0.35	0.73
Fasting Plasma Glucose (mg/dl)	115.28 ± 22.37	76.33 ± 11.54	10.50	<0.001
Post prandial Plasma Glucose (mg/dl)	151.87 ± 36.05	108.80 ± 15.49	7.44	<0.001
HbA1c (%)	7.38 ± 1.09	5.33 ± 0.81	10.25	<0.001
1,5 AG (ng/ml)	6.23 ± 1.30	8.72 ± 2.23	6.55	<0.001

SD = standard deviation, X^2 = Chi squared test.

variability was lower in the T2DM individuals group ($P < 0.001$) (Table 1).

As regarding the echo parameters there were no significant difference between both groups regarding LVEDD, LVESD, EF, IVSD, PWTd, FS, LA dimension and Aortic root dimension. Peak velocity of early diastolic mitral flow wave (E wave), the ratio of early (E wave) to late mitral flow (A wave) velocities (E/A ratio) and mitral annular early diastolic wave peak velocity (E′ wave) were lower in the T2DM individuals group while E/E′ ratio and late mitral flow diastolic peak velocity were higher in T2DM individuals group.

On the other hand, the T2DM individuals group showed a statistically significant lower apical 2 chambers, apical 4 chambers, apical longitudinal axis and global strain pattern (Table 2) (Fig. 1).

No correlation found between HbA1c and any echo parameters. On the other hand 1,5-AG showed a significantly negative correlation with apical 2 chambers, apical 4 chambers, apical longitudinal axis and global strain pattern (Fig. 2) (Table 3).

Setting the mean value of the global strain pattern of the healthy group 19.99% as the normal value, ROC curve analysis was plotted to show the best cut off value to diagnose subclinical cardiac disease. 1,5-AG less than 7.51 ng/ml was the best cut off value with sensitivity of 85.7%, specificity 75% and AUC 0.81 with accuracy of 84.8% at 95% CI 0.63-0.99 (Fig. 3).

Table 2. Comparison between the studied groups regarding Echo parameters.

	T2DM individuals N = 46	Healthy N = 46	t-test	P value
	Mean ± SD	Mean ± SD		
IVSD (cm)	1.0 ± 0.13	0.95 ± 0.17	1.76	0.08
IVSS (cm)	1.5 ± 0.77	1.38 ± 0.19	0.12	0.91
LVIDd (cm)	4.15 ± 0.88	4.49 ± 0.61	1.61	0.11
LVIDs (cm)	3.4 ± 1.09	3.19 ± 0.32	0.86	0.39
LVPWD (cm)	1.2 ± 0.51	1.19 ± 0.57	1.31	0.19
LVPWS (cm)	1.53 ± 0.37	1.44 ± 0.29	1.32	0.19
EDV (ml)	106.11 ± 26.74	114.84 ± 20.93	1.75	0.09
ESV (ml)	42.5 ± 25.47	37.17 ± 8.23	0.59	0.56
EF (%)	65.5 ± 4.52	67.11 ± 4.02	1.80	0.08
SV (ml)	66.98 ± 16.68	73.89 ± 21.52	1.72	0.09
FS (%)	36.67 ± 7.36	38.23 ± 5.43	1.16	0.25
Aortic diameter (cm)	3.05 ± 0.33	2.95 ± 0.39	1.39	0.17
Lt. atrium diameter (cm)	3.56 ± 0.71	3.43 ± 0.42	1.08	0.28
MVE (m/sec)	0.66 ± 0.14	0.81 ± 0.30	3.04*	0.003
MVA (m/sec)	0.86 ± 0.20	0.71 ± 0.20	3.52*	0.001
MV (E/A)	0.80 ± 0.29	1.18 ± 0.44	4.73**	<0.001
È (m/sec)	0.11 ± 0.19	0.17 ± 0.26	3.14*	0.002
E/È	9.71 ± 2.79	8.44 ± 3.94	2.20*	0.03
Apical 2 chamber (%)	−15.85 ± 6.66	−18.58 ± 10.98	2.82*	0.006
Apical 4 chamber (%)	−16.11 ± 6.16	−18.94 ± 5.13	2.39*	0.02
Apical long axis (%)	−15.7 ± 3.2	−21.14 ± 2.69	8.81**	<0.001
Global strain pattern	−15.86 ± 3.45	−19.99 ± 2.03	6.96**	<0.001

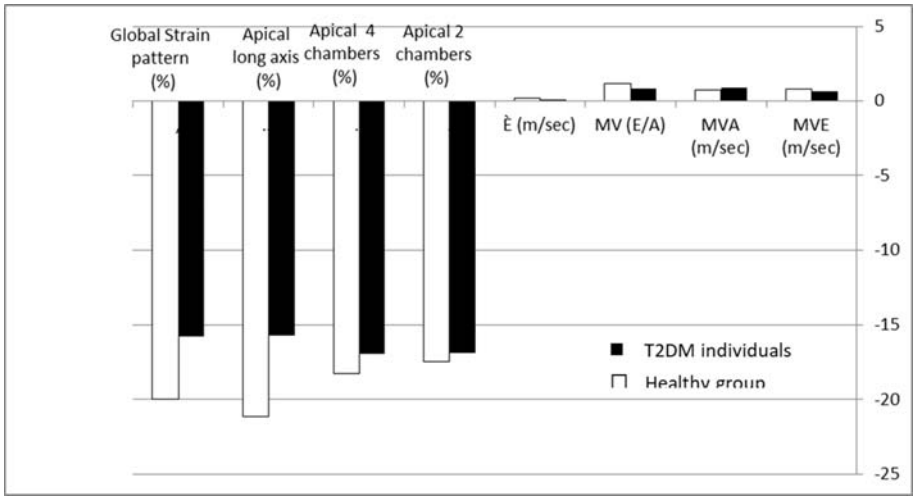

Fig. 1. Comparison of echo parameters between the T2DM individuals and the healthy groups.

6. Discussion

The present work showed a significant difference between diabetic and non-diabetic subjects as regarding regional strain pattern and E/È ratio. LV strain pattern is a sensitive parameter that detects early left ventricular systolic dysfunction [29]. Asymptomatic diastolic dysfunction is an early manifestation of cardiac dysfunction and precedes the development of systolic dysfunction [30] [31]. Our finding confirms the presence of asymptomatic subclinical cardiac disease in patients with T2DM. However the recent ADA guidelines do not recommend screening of asymptomatic high risk patients with T2DM for CVD. They explained that by the mandatory aggressive treatment to attain strict metabolic goal in such patients whether symptomatic or asymptomatic and screening programs are not coast effective [32]. This ideal way of thinking is not true [33]. In fact the majority of patients with T2DM are not achieving good cardio-metabolic goals [34]. In a prospective study on 154 asymptomatic patients with T2DM and preserved LVEF ≥50%, LV remodeling had progressed only in patients with low GLS less than 18% after 3 years of follow up [35]. In addition, GLS was independently associated with changes in both LV end-systolic and end-diastolic volumes over 3-years period. Identifying those high risk patients with early diastolic dysfunction narrows the scope and directives

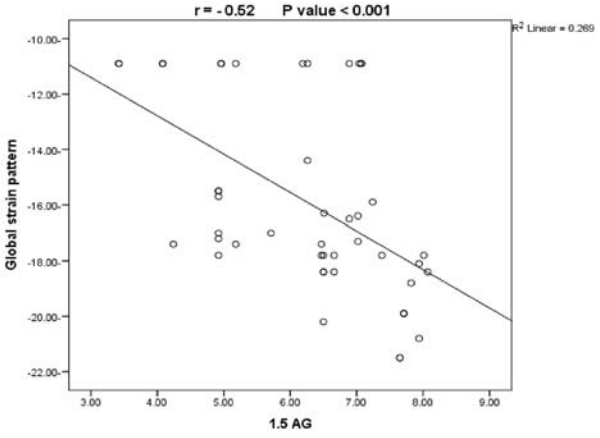

Fig. 2. correlation between 1,5-AG and global strain pattern in T2DM individuals group.

Table 3. Correlation between both 1.5 AG and HbA1c and Echo parameters.

	1.5 AG		HbA1c	
	r	P value	r	P value
IVSD (cm)	−0.19	0.20	0.11	0.47
IVSS (cm)	−0.25	0.09	0.15	0.31
LVIDd (cm)	0.08	0.61	−0.06	0.69
LVIDs (cm)	−0.009	0.95	−0.09	0.56
LVPWD (cm)	0.05	0.77	0.007	0.96
LVPWS (cm)	−0.12	0.43	0.20	0.19
EDV (ml)	0.01	0.94	0.003	0.98
ESV (ml)	0.17	0.25	0.08	0.60
EF (%)	−0.22	0.16	0.18	0.25
SV (ml)	−0.20	0.19	−0.04	0.81
FS (%)	0.11	0.47	0.19	0.21
Aortic diameter (cm)	0.02	0.91	−0.25	0.10
Lt. atrium diameter (cm)	0.12	0.42	0.26	0.09
MVE (m/sec)	−0.12	0.43	−0.01	0.95
MVA (m/sec)	−0.009	0.95	0.05	0.74
MV (E/A)	−0.09	0.54	0.08	0.62
È (m/sec)	−0.19	0.20	−0.27	0.07
Apical 2 chamber (%)	−0.48*	0.001	0.18	0.12
Apical 4 chamber (%)	−0.45*	0.002	0.21	0.08
Apical long axis (%)	−0.54*	<0.001	0.27	0.07
Global strain pattern	−0.46*	0.001	0.28	0.06

r = correlation coefficient.

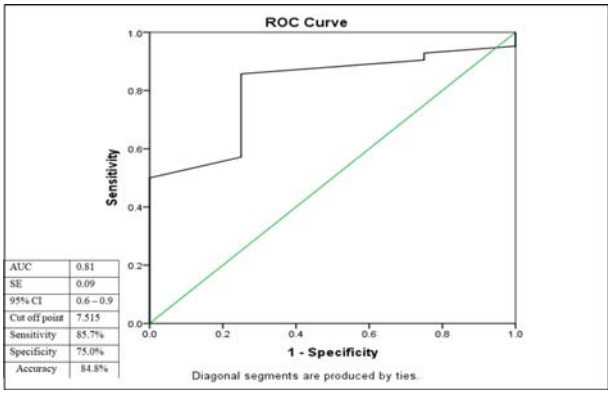

Fig. 3. ROC curve of 1.5AG (at a GLS = −19.99) for detection of subclinical cardiac disease in patients with T2DM.

aggressive early management to prevent the progression to HF.

Although the risk of HF in patients with T2DM is well established, the beneficial role of glycemic control as evaluated by HbA1c is questionable. In a meta-analysis study on 37229 patients with T2DM, no association was found between the degree of glycemic control and the risk of HF [20]. Similarly, Paolillos and colleagues found no relation between HbA1c% and long term prognosis of HF if HbA1c is below 8% in a recent study done on 3927 patients with T2DM and HF followed up for 3.66 years [36]. These findings are similar to our results as we did not find a correlation between HbA1c and all measures of cardiac function. On the other hand very poor glycemic control was found to be associated with increased incidence of HF in patients with T2DM [37]. Putting these contradictory data together may indicate the presence of another player than HbA1c that link the glycemic control with the development and progression of HF in patients with T2DM.

Our results showed a significant negative correlation between global strain pattern and 1,5-AG. So GV (represented by 1,5-AG) seems to be a new stronger link between glycemic control and subclinical cardiac disease. Previous reports confirmed the link between GV and myocardial damage and mortality [38] [39,40]. Few studies reported the association of 1,5-AG with subclinical cardiac disease. Menglu Liang and coworkers proved the association between 1,5-AG and myocardial damage as measured by high-sensitivity cardiac troponin T among 9145 asymptomatic patients with T2DM. However they did not study the link between 1,5-AG and cardiac function [41].

Recently, Tang et al confirmed the association between GV and left ventricular function on 445 patients with T2DM [42]. Their work however is less valuable if compared to our work as they depended on visit to visit variability in fasting plasma glucose. They also used routine echocardiography to evaluate the cardiac function which misses a lot of cases with early dysfunction. To the best of our knowledge, our work is the first to address the link between GV and subclinical cardiac function as measured by speckled tracing echocardiography. ROC curve analysis showed that 1,5-AG less than 7.51 ng/ml was the best cut off value to detect patients with global strain pattern below the mean of the healthy group (19.99%). The test has sensitivity of 85.7%, specificity 75% and AUC 0.81 with accuracy of 84.8% at 95% CI 0.63-0.99. Based on these results, 1,5-AG might be used as a simple biomarker which can early predict SCD specially when HbA1c is below 7%. Patients with 1,5-AG less than 7.51 are at increased risk of subclinical cardiac disease which is more risky to develop HF in the future. These results explain previous reports that showed the independent association between GV and increased mortality in patients with acute HF [43]. It should be noted that to fundamentally change clinical care with use of this new metrics based on our results is missing. It would be important to demonstrate that the metrics relate to and predict clinical outcomes. In this regard, studies including more patients and longer-term studies relating this outcome with diabetes complications are needed.

7. Limitations

Our work was not a mechanistic trial to explain how GV can induce HF. The correlation found between 1,5-AG and global strain pattern is weak, but significant. Previous studies explained this association through endothelial apoptosis by overproduction of reactive oxygen species [44]. The present work is a cross sectional trial. Prospective trials on a larger numbers of patients are needed to confirm our results.

8. Conclusion

Patients with T2DM have asymptomatic subclinical cardiac disease. Glucose variability in addition to hyperglycemia is associated with the risk of HF. 1,5-AG might be used as a novel reproducible biomarker that can predict subclinical cardiac disease in patients with T2DM.

Data availability

The data used to support the findings of this study are restricted by the ethical committee of Faculty of

Medicine, Menoufia University to protect patient privacy. Data are available from the corresponding author for researchers who meet the criteria for access to confidential data.

Authors' contribution

All the authors contributed adequately towards the completion of this study. All authors read and approved the manuscript.

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We don't have any fund and the authors withstand all the cost of the work.

Conflicts of interest

None declared.

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