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

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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
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 thiazolidenediones 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.

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) ≥ 126 mg/dl, PPPG ≥ 200 mg/dl or HbA1c ≥ 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 X² 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 ≤ 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/M². 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
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).

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

|                  | T2DM individuals | Healthy | t-test | P value |
|------------------|------------------|---------|--------|---------|
|                  | N = 46           | N = 46  |        |         |
| **Mean ± SD**    |                  |         |        |         |
| **Age (years)**  | 50.56 ± 11.77    | 46.54 ± 14.19 | 1.48 | 0.14 |
| **Sex (Male/Female)** | 18/28 | 23/23 | X² = 1.1 | 0.29 |
| **BMI (Kg/M²)**  | 28.70 ± 3.83     | 27.22 ± 5.06 | 1.59 | 0.12 |
| **Serum creatinine (mg/dl)** | 0.11 ± 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, X² = Chi squared test.

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

|                  | T2DM individuals | Healthy | t-test | P value |
|------------------|------------------|---------|--------|---------|
|                  | N = 46           | N = 46  |        |         |
| **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 |
| **LVDD (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 |
| **E (m/sec)**    | 0.11 ± 0.19      | 0.17 ± 0.26 | 3.14* | 0.002 |
| **E/E’**         | 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 |
6. Discussion

The present work showed a significant difference between diabetic and non-diabetic subjects as regarding regional strain pattern and E/E 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 cost 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

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       |
| LVSS (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       |
| E (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.
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 37,229 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 3,927 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 9,145 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
population. Curr Heart Fail Rep 2017;14(4):301–10. https://doi.org/10.1007/s11897-017-0342-z.
[9] Cermakova P, Muller M, Armstrong AC, Religa D, Bryan RN, Lima JAC, et al. Subclinical cardiac dysfunction and brain health in midlife: CARDIA (Coronary Artery Risk Development in Young Adults) brain magnetic resonance imaging substudy. J Am Heart Assoc 2017;6(12). https://doi.org/10.1161/JAHA.117.006750.
[10] Babu NMS, Srinath SC, Lahiri A, Chase D, John B, Roshan J. Three-dimensional echocardiography with left ventricular strain analyses helps earlier prediction of right ventricular pacing-induced cardiomyopathy. J Saudi Heart Assoc 2018;30(2):102–7. https://doi.org/10.1016/j.jsha.2017.03.005.
[11] De GL, Oscarsson A, Engvall J. Variability in echocardiographic measurements of left ventricular function in septic shock patients. Cardiovasc Ultrasound 2015;13:19. https://doi.org/10.1186/s12947-015-0018-9.
[12] Karlsen S, Dahlslett T, Grenne B, Sjøli B, Smiseth O, Edvarden T, et al. Global longitudinal strain is a more reproducible measure of left ventricular function than ejection fraction regardless of echocardiographic training. Cardiovasc Ultrasound 2019;17(1):8. https://doi.org/10.1186/s12947-019-0005-7.
[13] Dahlslett T, Karlsen S, Grenne B, Eek C, Sjøli B, Skulstad H, et al. Early assessment of strain echocardiography can accurately exclude significant coronary artery stenosis in suspected non-ST-segment elevation acute coronary syndrome. J Am Soc Echocardiogr 2014;27(5):512–9. https://doi.org/10.1016/j.echo.2014.01.019.
[14] Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 2014;100(21):1673–80. https://doi.org/10.1136/heartjnl-2014-305538.
[15] Erbsoll M, Andersen MJ, Valeur N, Mogensen UM, Waziri H, Moller JE, et al. The prognostic value of left atrial peak reservoir strain in acute myocardial infarction is dependent on left ventricular longitudinal function and left atrial size. Circ Cardiovasc Imaging 2013;6(1):26–33. https://doi.org/10.1161/CIRCIMAGING.112.978296.
[16] Abduch MC, Alencar AM, Mathias Jr W, Vieira ML. Cardiac mechanics evaluated by speckle tracking echocardiography. Arq Bras Cardiol 2014;102(4):403–12. https://doi.org/10.1016/j.abcard.2014.08.004.
[17] Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodríguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol 2015;3(2):105–13. https://doi.org/10.1016/S2213-8587(14)70219-0.
[18] Seferovic PM, Petrie MC, Filippatos GS, Anker SD, Rosano G, Bauersachs J, et al. Type 2 diabetes mellitus and heart failure: a position statement from the European society of cardiology. Eur J Heart Fail 2018;20(5):853–72. https://doi.org/10.1002/ejhf.1170.
[19] Edvardsen T, et al. Global longitudinal strain is a more reproducible measure of left ventricular function than ejec- tion fraction-the Hoorn Study. Neth J Med 2008;66(3):110–7.
[20] Adamo E, Cagnacci S, Guedes J, et al. Impact of diabetes mellitus, hypertension, and obesity on practice guidelines. J Am Coll Cardiol 2011;62(16):e293–303. https://doi.org/10.1016/j.jacc.2011.07.030.
[21] Wang P, Huang R, Lu S, Xia W, Sun H, Sun J, et al. Hba1c below 7% as the goal of glucose control fails to maximize the cardiovascular benefits: a meta-analysis. Cardiovasc Diab etol 2015;14:124. https://doi.org/10.1186/s12933-015-0285-5.
[22] Nichols GA, Koro CE, Gallion CM, Ephross SA, Brown JB. The incidence of congestive heart failure associated with anti-diabetic therapies. Diabetes Metab Res Rev 2005;21(1):51–7. https://doi.org/10.1002/dmr.480.
[23] Suh S, Kim JH. Glycemic Variability: How Do We Measure It and Why Is It Important? Diabetes Metab J 2015;39(4):273–82. https://doi.org/10.4093/dmj.2015.39.4.273.
[24] Dungan KM. 1,5-anhydroglucitol (GlycoMark) as a marker of short-term glycemic control and glycemic excursions. Expert Rev Mol Diagn 2008;8(1):9–19. https://doi.org/10.1586/14775159.8.1.9.

[25] Sun J, Dou JT, Wang XL, Yang GQ, Lu ZH, Zheng H, et al. Correlation between 1,5-anhydroglucitol and glycemic excursions in type 2 diabetic patients. Chin Med J (Engl) 2011; 124(22):3641–5.

[26] Gerbaud E, Darier R, Montaudon M, Beauvieux MC, Cof Sun J, Dou JT, Wang XL, Yang GQ, Lu ZH, Zheng H, et al. Correlation between 1,5-anhydroglucitol and glycemic excursions in type 2 diabetic patients. Chin Med J (Engl) 2011; 124(22):3641–5.

[27] Classi

[28] Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging 2018;11(2 Pt 1):260–74. https://doi.org/10.1016/j.jcmg.2017.11.017.

[29] Yokota S, Tanaka H, Mochizuki Y, Soga F, Yamashita K, Tanaka Y, et al. Association of glycemic variability with left ventricular diastolic function in type 2 diabetes mellitus. Cardiovasc Diabetol 2019;18(1):166. https://doi.org/10.1186/s12933-019-0971-5.

[30] Chaudhary AK, Aneja GK, Shukla S, Razi SM. Study on correlation between 1,5-anhydroglucitol and glycemic excursions. Expert Rev Mol Diagn 2008;8(1):9–19. https://doi.org/10.1586/14775159.8.1.9.

[31] Chillaron JJ, Roux JA, Benaiges D, Pedro-Botet J. Subclinical cardiovascular disease in type 2 diabetes mellitus: To screen or not to screen. World J Clin Cases 2014;2(9):415–21. https://doi.org/10.12998/wjcc.v2.12.415.

[32] Navarro-Vidal B, Banegas JR, Leon-Munoz LM, Rodriguez-Artalejo F, Graciani A. Achievement of cardiometabolic goals among diabetic patients in Spain. A nationwide population-based study. PLoS One 2013;8(4):e61549. https://doi.org/10.1371/journal.pone.0061549.

[33] Ernande L, Bergerot C, Girend N, Thibault H, Davidsen ES, Gautier Pignon-Blanc P, et al. Longitudinal myocardial strain alteration is associated with left ventricular remodeling in asymptomatic patients with type 2 diabetes mellitus. J Am Soc Echocardiogr 2014;27(5):479–88. https://doi.org/10.1016/j.echo.2014.01.001.

[34] Paolillo S, Salvioni E, Filardi PP, Bonomi A, Sinagra G, Gentile P, et al. Long-term prognostic role of diabetes mellitus and glycemic control in heart failure patients with reduced ejection fraction. Int J Cardiol 2020. https://doi.org/10.1016/j.ijcard.2020.04.079.

[35] Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001;103(22):2668–73. https://doi.org/10.1161/01.cir.103.22.2668.

[36] Takahashi S, Shimada K, Miyazaki K, Miyazaki T, Sai E, Ogita M, et al. Low and exacerbated levels of 1,5-anhydroglucitol are associated with cardiovascular events in patients after first-time elective percutaneous coronary intervention. Cardiovasc Diabetol 2016;15(1):145. https://doi.org/10.1186/s12933-016-0459-5.

[37] Standl E, Schnell O, Ceriello A. Postprandial hyperglycemia and glycemic variability: should we care? Diabetes Care 2011;34(Suppl 2):S120–1. https://doi.org/10.2337/db10-1230.

[38] Selvin E, Rawlings A, Lutsey P, Maruthur N, Pankow JS, Steffes M, et al. Association of 1,5-Anhydroglucitol with cardiovascular disease and mortality. Diabetes 2016;65(1): 201–8. https://doi.org/10.2337/db15-0607.

[39] Liang M, McEvoy JW, Chen Y, Sharrett AR, Selvin E. Association of a Biomarker of Glucose Peaks, 1,5-Anhydroglucitol, With Subclinical Cardiovascular Disease. Diabetes Care 2016;39(10):1752–9. https://doi.org/10.2337/dc16-0840.

[40] Tang X, Zhong J, Zhang H, Luo Y, Liu X, Peng L, et al. Visit-to-visit fasting plasma glucose variability is an important risk factor for long-term changes in left cardiac structure and function in patients with type 2 diabetes. Cardiovasc Diabetol 2019;18(1):50. https://doi.org/10.1186/s12933-019-0854-9.

[41] Statella LN, Cassapanca P, Baranauskas J, Serafini M, Vaglio E, Palma P, et al. The effect of glycaemic control and glycaemic variability on mortality in patients hospitalized with congestive heart failure. Diabetes Metab Res Rev 2011;27(1):85–93. https://doi.org/10.1002/dmrr.1155.

[42] Quaglia L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NADPH-oxidase activation. Diabetes 2003;52(11):2795–804. https://doi.org/10.2337/diabetes.52.11.2795.