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Assessment of Left Ventricular Systolic Function in Type 2 Diabetic Patients with Nonalcoholic Fatty Liver Disease Using Three- dimensional Speckle-Tracking Echocardiography

Ramadan Ghaleb Mohamed[1], Saud M. Elsaughier[1], Ahmed Abdellatif Ali Suliman [2], Zain El Abdeen Ahmed Said [3], Hala Abdalla Mahmoud[2], Ahmed Gaber Kenawy Abdelhalim [2], Khaled Abo Bakr Khalaf [4], Wael Abd Elgwad Elsewify [2]

1 Cardiology Department, Faculty of Medicine, Aswan University, Aswan, Egypt
2 Internal medicine Department, Faculty of Medicine, Aswan university, Aswan, Egypt.
3 Internal medicine Department, Faculty of Medicine, Assuit university Assuit, Egypt.
4 Tropical medicine Department, Faculty of Medicine, Assuit university Assuit, Egypt.

Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is the commonest liver affection that linked with type II DM ***and*** much researches take into account NAFLD as one of risk factors of cardiovascular affection in type II DM patients. So in our study we aimed to detect the early affection of LV functions in patients with type II DM and NAFLD, by using speckle tracking imaging.

Methods: This study was a patient-control study conducted on 200 type 2 diabetic patients divided into two groups; 100 patients with moderate to severe NAFLD (cases) and 100 patients without NAFLD (control), all patients underwent Abdominal ultrasound to diagnose fatty liver and evaluation of LV functions by using 3D speckle tracking imaging.

Results: 2DEF, 3DEF, GLS, GRS, GCS, and GAS of the cases were significantly lower than the control group (P value <0.05). There is a significant negative correlation between BMI, HbA1c, cholesterol, triglycerides, AST, ALT, and HOMA- IR and between all 3D strain domains (GLS, GRS, GCS, and GAS) of type 2 DM.

Conclusion: LV systolic function was affected sub-clinically in Egyptian Type 2 diabetic patients with nonalcoholic fatty liver disease (NAFLD) using 3D-STE. 3D- STE can be used effectively as an essential and also noninvasive technique in order to evaluate LV function in NAFLD with T2DM.

Key Words: GLS, NAFLD, T2DM.

Introduction

Non-alcoholic fatty liver disease (NAFLD), which makes up 80% of metabolic syndrome, is characterized by macro-vesicular alterations without steatosis (an inflammation) in non-alcoholic persons **(1),** and is typically linked to obesity, diabetes, and hyper-lipidemia **(2).**

Since obesity is becoming more common among young adults, many countries have highlighted it as a public health concern **(3).** Mortality among obese populations as a result of metabolic syndrome and related risk factors, which include insulin resistance, hypertension, and hyperlipidemia **(4).**

Clinical evidence gathered over the past 200 years has demonstrated the alarming rise in the occurrence of heart failure and its worse poorer prognosis among individuals with diabetes when compared to those without the disease (**5).**

Heart and liver failure combined with hepatic congestion and hypoxic hepatitis, as well as severe liver illnesses and cirrhosis, to form a cardio-hepatic complex **(6).** The reliable and popular echocardiographic indicator of systolic performance is the ejection fraction (EF). In cardiology, LVEF holds a unique position for therapeutic studies that form the basis of current therapy recommendations' evidence **(7).**

Recently, speckle tracking echocardiography (STE) is employed to quantify all cardiac function dynamics. By using STE, we may simply adjust the myocardial function through speckle motions while eliminating Doppler angle errors **(8).**

Because 3D echocardiography produces high-quality images, it is a valuable non- invasive technique for bedside use in routine cardiac examinations, contributing to the correct detection of left ventricular disorders (**9).**

Therefore, the purpose of the current study was to assess cardiac functions utilizing speckle tracking imaging in order to identify early subclinical left ventricular impairment in patients with diabetes.

Methods:

This study was a case-control study conducted at Aswan University Hospital in the period from November 2021 to October 2023. The study recruited 200 patients with type 2 DM (100 patients without fatty liver as a control group and 100 patients with NAFLD). Patients with hypertension, history of coronary or rheumatic heart disease, history of hepatitis, alcoholics, history of chemotherapy and history of cardiac or liver operations were excluded from the study. Written consent was obtained from each patient.

All patients of our study were subjected to the following investigation:

- Full history taking and physical examination
- Laboratory investigation (lipid profile, HbA1C, HOMA-IR and liver enzymes such as ALT and AST).
- Abdominal ultrasound for fatty liver diagnosis using a GE Vivid E9 device **(Fig1)**.
- 3D speckle tracking echocardiography **(Fig 2 and 3)**. **Procedure:**

Patients were placed in the left lateral position. Three-lead electrocardiography was used. The echocardiography examination was carried out by a GE-Vivid E9 machine equipped with an M5S-D probe (1.5–4.5 MHz). Standard 2-D images of three consecutive cardiac cycles were recorded. 3D echocardiographic LV full-volume images acquisition occurred during four consecutive cardiac cycles and the transducer at a frame rate of 25–50 frames/second. Patients were asked to hold breath and multi- beats were recorded.

Statistical analysis

Data was analyzed using IBM-SPSS (statistical package for social science) version 26.0 (SPSS Inc., Chicago, IL, USA). Quantitative data was presented as mean ± standard deviation (SD) and median (range). Shapiro- Wilks test was used for quantative data normality testing, assuming normality at $P > 0.05$. This was analyzed using independent sample t-test or Mann Whitney U test as appropriate. The accepted level of significance was considered if $p < 0.05$.

Ethical approval:

IRB approval was obtained from the Medical Ethic Committee, Faculty of Medicine Aswan University. The study was carried out in accordance with the Helsinki Declaration guidelines and in line with STROBE checklist for research ethics. The title and objectives of the study were explained to all patients prior to the start of study. A written informed consent was obtained from the patient before the participation in the study. All collected data was confidential and was used for the purpose of scientific research only. Every research participant had the complete right and freedom to withdraw at any time from the study without any consequences on the medical service provided.

Results:

This case-control study was conducted at Aswan University Hospital from November 2021 to October 2023. It included 200 T2DM patients that further divided into two groups: Group A, included 100 patients without fatty liver as control and Group B, included 100 patients with NAFLD.

NAFLD cases were insignificantly (p = 0.885) younger (53.3 ± 6.4 years) than control patients (54 ± 7.4 years). Contrarily, BMI of the NAFLD cases was significantly (p < 0.001) higher than control **(Table 1)**. Also, HbA1c, cholesterol, triglycerides, AST, ALT, and HOMA-IR of NAFLD cases were significantly (p < 0.001) higher than control **(Table2)**. Likewise, NAFLD cases had significantly (p < 0.001) lower 2DEF, 3DEF, GLS, GRS, GCS, and GAS than control **(Table 3)**.

Moreover, there was a significant negative correlation between BMI, HbA1c, cholesterol, triglycerides, AST, ALT, and HOMA-IR and between all the 3D strain domains (GLS, GRS, GCS, and GAS) of T2DM **(Table 4)**. BMI, HbA1c, AST, and HOMA-IR were identified as independent predictors for GLS among T2DM cases. Also, BMI, cholesterol, HbA1c, and HOMA-IR were independent predictors for GRS among T2DM. Additionally, HbA1c, triglycerides, and HOMA-IR were independent predictors for GCS among T2DM. As well, BMI, HbA1c, and HOMA-IR were independent predictors for GAS among T2DM **(Table 5)**.

Table 1: Baseline Characteristics of the Studied Sample

	Control (n = 100)	NAFLD (n = 100)	P-value
Age/years (Mean ± SD)	54.04 ± 7.4	53.30 ± 6.3	= 0.451*
Sex			
Male	52 ((52%)	59 ((59%)	= 0.319**
Female	48 ((48%)	41 ((41%)	
BMI (Mean ± SD)	22.02 ± 3.2	29.78 ± 6.3	**< 0.001***
HbA1C (Mean ± SD)	6.78 ± 0.6	9.55 ± 1.5	**< 0.001***
HOMA-IR	0.90 ± 0.3	2.24 ± 1.0	**< 0.001***

***Independent Sample t-test was used to compare the differences in Mean between groups**
****Chi-square test was used to compare the differences in Frequency between groups**

Table 2: comparison between both groups as regard laboratory investigations.

	Control (n = 100)	NAFLD (n = 100)	P-value
Cholesterol Level (mg/dl)	168.51 ± 16.7	264.72 ± 40.1	**< 0.001***
Triglyceride Level (mg/dl)	192.51 ± 18.9	302.49 ± 53.5	**< 0.001***
Liver Enzymes			
AST Level (IU/L)	21.03 ± 7.5	42.37 ± 7.1	**< 0.001***
ALT Level (IU/L)	29.10 ± 7.1	53.06 ± 7.8	**< 0.001***

Table 3: Echocardiography Examination of the Studied Sample.

	Control (n = 100)	NAFLD (n = 100)	P-value
EF%			
2-D	67.25 ± 4.8	59.70 ± 7.9	< **0.001***
3-D	65.58 ± 4.5	56.86 ± 7.7	< **0.001***
STE			
GLS%	19.66 ± 0.9	14.63 ± 2.5	< **0.001***
GRS%	50.05 ± 1.8	37.86 ± 3.1	< **0.001***
GCS%	19.28 ± 0.8	15.62 ± 2.7	< **0.001***
GAS%	33.85 ± 1.6	30.07 ± 3.4	< **0.001***

Table 4. Correlation between patients' characteristics and 3D strain.

	GLS		**GRS**		**GCS**		**GAS**	
	r	P value	r	P value	r	P value	r	P value
Age	0.012	0.867	0.059	0.405	0.074	0.298	-0.010	0.885
BMI	-0.554	**<0.001**	-0.613	**<0.001**	-0.433	**<0.001**	-0.400	**<0.001**
HbA1c	-0.952	**<0.001**	-0.717	**<0.001**	-0.448	**<0.001**	-0.457	**<0.001**
Cholesterol	-0.659	**<0.001**	-0.781	**<0.001**	-0.500	**<0.001**	-0.443	**<0.001**
Triglycerides	-0.576	**<0.001**	-0.721	**<0.001**	-0.386	**<0.001**	-0.414	**<0.001**
AST	-0.698	**<0.001**	-0.769	**<0.001**	-0.550	**<0.001**	-0.449	**<0.001**
ALT	-0.701	**<0.001**	-0.797	**<0.001**	-0.558	**<0.001**	-0.485	**<0.001**
HOMA-IR	-0.622	**<0.001**	-0.866	**<0.001**	-0.606	**<0.001**	-0.435	**<0.001**

Table 5: Predictive factors for 3D strain in T2DM patients (N=200).

	GLS		**GRS**		**GCS**		**GAS**	
	β	P value	β	P value	β	P value	β	P value
BMI	-0.166	0.003	-0.145	<0.001	-0.120	0.068	-0.151	0.044
HbA1c	-0.192	0.030	-0.225	0.001	-0.231	0.027	-0.312	0.009
Cholesterol	-0.213	0.063	-0.177	0.034	-0.246	0.069	0.076	0.618
Triglycerides	0.147	0.145	-0.017	0.822	0.353	0.003	0.032	0.812
AST	-0.227	0.035	-0.117	0.132	-0.111	0.377	0.019	0.895
ALT	-0.052	0.653	-0.124	0.144	-0.051	0.708	-0.145	0.354
HOMA-IR	-0.265	<0.001	-0.297	<0.001	-0.396	<0.001	-0.229	0.004

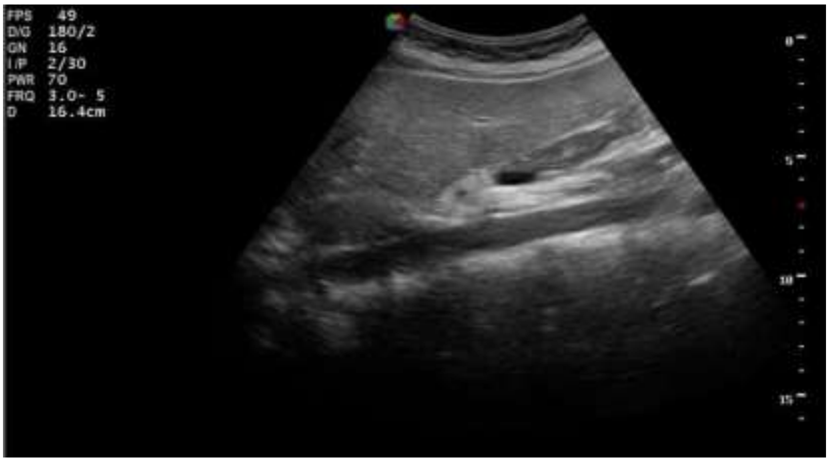

Fig. 1 Abdominal ultrasound for fatty liver

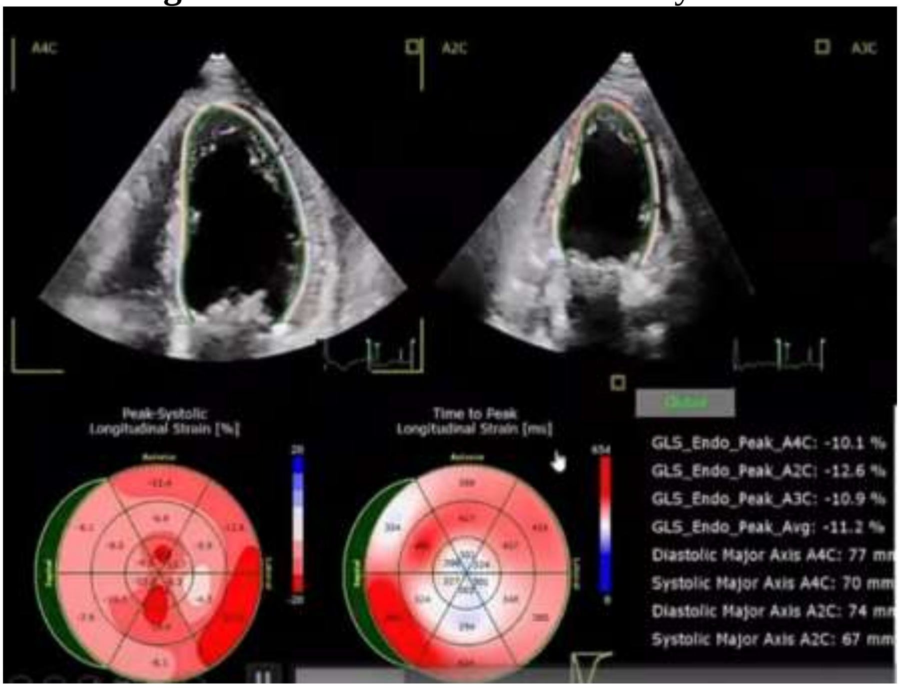

Fig. 2 3D speckle tracking echocardiography

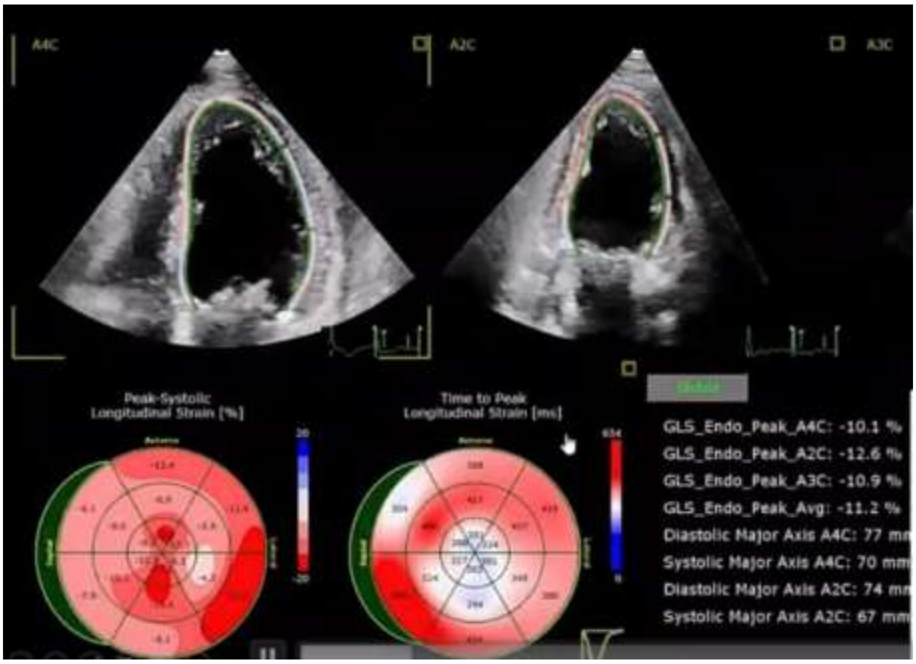

Fig. 3 3D speckle tracking echocardiography

Discussion

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic fat accumulation that is linked to insulin resistance, steatosis > 5%, lack of chronic illnesses, and abstinence from alcohol **(10)**. It is the most common liver affection associated with T2DM **(11)** that increases both morbidity and mortality **(12)**. Numerous studies include NAFLD as one of the cardiovascular affection risk factors in patients with T2DM. Bonapace offered valuable information by showing that the LV diastolic function was reduced in T2DM cases who also had NAFLD **(13)**. With its high frame rate and lack of angle dependence, 3D-STE monitoring and analysis of the left ventricle has greatly contributed to cardiac research **(14)**. This case-control study conducted to assess the LV systolic function using 3D-STE and to explore the effect of NAFLD on the cardiac function.

Regarding the sociodemographic and baseline clinical characteristics of the studied cohort, both groups were matched for age while NAFLD cases had significantly higher BMI than control. This was in agreement with Van Wagner et al‘s population-based CARDIA (Coronary Artery Risk Development in Young Adults) study that included 1827 patients grouped according to the presence of moderate-to- severe NAFLD **(15).** Also, Zamirian et al 2008 in a case- control study included 60 cases (30 patients with NAFLD and 30 patients without NAFLD) found similar results **(16)**. Likewise, the current results were in accordance with the findings of a study by Chang et al, 2019 that included 97 patients with T2DM, 30 without NAFLD and 67 with NAFLD **(17).**

Furthermore, this study revealed a substantial difference in mortality between the groups, which may be explained by obesity, which increases the risk of developing metabolic syndrome (MetS) and its comorbidities, which include T2DM, NAFLD, hypertension, hyperlipidemia, and cardiovascular disease (CVD). Thus, weight loss programs may lower mortality rate among obese cases **(18)**.

Regarding the laboratory findings, the current study found that the mean HbA1c, cholesterol, triglycerides, AST, ALT, and HOMA-IR were significantly higher in NAFLD cases than the control group. Similar results were reported by a study that included 150 patients with T2DM. Based on the clinical history of DM, there were two groups: group I included 87 patients with disease duration of 10-15 years, 63 people in group II with > 15 years disease duration and 50 healthy individuals were chosen as control. This study found that group II had lower levels of HDL and higher levels of glucose, triglycerides, glycosylated hemoglobin, LDL, and total cholesterol than the control group ($P < 0.05$) **(19)**. Additionally, VanWagner et al. found that compared to individuals without NAFLD, patients with NAFLD exhibited a higher prevalence of insulin resistance (mean HbA1c 6.4% versus 5.6%) **(15)**.

Likely, a case-control study done by Dong et al., that included 97 T2DM patients who had normal LV ejection fraction (LVEF >50%) were categorized into three groups according to the results of liver ultrasonography 30 of the T2DM patients were without NAFLD (group A), The other sixty-seven patients with NAFLD were classified into two groups (mild and moderate-to-severe): group B (32 mild NAFLD patient) and group C (35 moderate-to-severe NAFLD patients). Similarly, liver ultrasonography results from 97 T2DM patients with normal LV ejection fraction, in a case-control study by Dong et al., were used to divide patients into three groups (30 T2DM patients (group A) did not have NAFLD, the remaining 67 patients with NAFLD were further divided into two groups (30 cases with mild and 37 cases with moderate-to-severe) **(20)**. The authors found that NAFLD patients in group C had higher HbA1c, BMI, and ALT and AST levels compared to groups A and B, and ALT, AST levels for group B were higher than for group A ($p<0.05$) **(20)**.

In agreement with the current findings and according to Wang et al., T2DM without NAFLD cases and control had significantly lower blood ALT levels than did T2DM and NAFL cases ($P < 0.01$). In comparison to the control group, the fasting plasma glucose, HbA1c, and total cholesterol levels of the T2DM and NAFLD patients were considerably higher ($P < 0.001$, $P < 0.05$, and $P < 0.01$) **(14)**.

Respecting the echocardiographic characteristics, 2DEF, 3DEF, GLS, GRS, GCS, and GAS of the NAFLD cases were considerably lower than those of control. GLS, a measure of systolic function, was shown to be lower in NAFLD patients than non-NAFLD patients, suggesting that NAFLD cases had more subclinical systolic dysfunction. This finding was consistent with that of Singh et al. and Van Wagner et al. about the lower value of GLS in adults and adolescents with NAFLD **(21, 22)**.

Similarly, Dong et al., demonstrated that the 3D-STE-derived GCS, GRS, GLS, and GAS values were decreased in group C than in groups A and B ($p < 0.05$) **(20)**. Also, Zamirianet et al., showed that patients diagnosed with diastolic dysfunction in NAFLD cases and control were 16.7% and 10%, respectively. The E/e' ratio was significantly higher in the NAFLD group. ESD and EDD had a significant difference between the case and control, respectively. GLS was also significantly lower in NAFLD patients than in controls **(23)**. However, LVEF difference was insignificant between the groups ($P = 0.753$). Similar results were reported by Wang who found that GLS, GCS, and GRS values were significantly lower in T2DM cases than controls. Furthermore, patients with diabetes and NAFLD had severely lower GLS, GCS and GRS and GCS values than control. Unlikely, lower GLS, GAS, and GRS values than the patients with diabetes only.

The LV myocardium has both longitudinal (70%) and circular fibers (30%) **(24)**. Longitudinal fibers act a fundamental role in LV systolic function **(25)**. In the current study, GLS reduction precedes the deterioration of LVEF; the main explanation for this was that the endocardium's longitudinal fibers were susceptible to harmful conditions including ischemia, hypoxia, and even pressure loading and numerous researches have demonstrated GAS as a novel metric **(26)**. It is associated with both longitudinal and circumferential motions and denotes an endocardial region deformation **(25)**. Wherefore, reduction in GAS is better indication for myocardial systolic dysfunction.

Regarding the correlation between 3D strain characteristics, there was significant negative correlation between BMI, HbA1c, cholesterol, triglycerides, AST, ALT, and HOMA-IR and between all 3D strain domains (GLS, GRS, GCS, and GAS) of T2DM. In contrast, VanWagner reported that there was no significant interaction between NAFLD and BMI in terms of e' velocity, E/e' ratio, or GLS **(27)**.

Previous research indicated that there may be a relationship between the myocardial function in NAFLD and the serum HbA1c level in addition to the presence and severity of NAFLD patients. Depending on serum HbA1c levels, patients may have different chances of developing cardiovascular dysfunction, according to previous research **(28)**. This data suggested that different degrees of heart disease may be linked to different serum HbA1c levels. Researchers propose using HbA1c as an index of glucose metabolism to evaluate the heart function in patients with non-alcoholic fatty liver disease (NAFLD). HbA1c is essential in predicting cardiac events **(29)**.

For the predictive factors for 3D strain in the studied cohort, it is found that BMI, HbA1c, AST, and HOMA-IR were identified as independent predictors for GLS. Also, BMI, cholesterol, HbA1c, and HOMA-IR were independent predictors for GRS. As well, HbA1c, triglycerides, and HOMA-IR were independent predictors for GCS among type 2 DM. While BMI, HbA1c, and HOMA-IR are independent predictors for GAS.

The current findings were in agreement with Dong et al., who detected that GLS, GRS, GCS, and GAS were independent predictors of NAFLD. Also, HbA1c was inversely associated with GLS, GRS, GCS, and GAS. E/E' also has negative correlation with GLS and GCS. Moreover, BMI was associated with GAS **(20)**. Likewise, Wang et al., 2018, HbA1c was independently associated with GLS, GCS, GAS and GRS. Also, GLS, GAS, and GRS were identified as independent predictors of NAFLD. In contrast, GCS did not prove to be associated with NAFLD. Plus, BMI was solely related to GLS **(14)**. Other research has suggested convincing evidence to indicate that NAFLD was independently associated with a decreasing value of GLS **(27)**. Consistently, Karabay et al., 2014 claimed that the reduction of GLS and GRS was more observed in NAFLD patients **(30)**. This study revealed a negative correlation between NAFLD and 3D strain parameters, thus LV systolic dysfunction could be deteriorated by the advance of NAFLD.

Conclusion:

In conclusion**,** it was found that LV systolic function was affected sub-clinically in Egyptian T2DM patients with NAFLD. Also, it is possible to assess LV function in NAFLD with T2DM using 3D-STE, which is a useful as a non-invasive method. Likely, all 3D strain domains (GLS, GRS, GCS, and GAS) showed strong negative connections with BMI, HbA1c, cholesterol, triglycerides, AST, ALT, and HOMA-IR among patients with T2DM.

Clinical Implications

This research boosted the evidence of the extent of NAFLD impact on the heart and added evidence for its importance as the risk factors affecting the systolic function of LV. Although subclinical LV anomalies can be detected by 3D-STE, diabetic patients still need to regularly exercise and monitor their weight. In addition, patient must know how to simultaneously evaluate lipid profile and blood glucose levels. As well, large-scale studies are required to delve more into the relationship between LV function and the severity of NAFLD and reduced glucose levels.

Study limitations

The current work encountered some shortcomings: it was a single-center study and liver biopsy was not performed to confirm the diagnosis of moderate to severe NAFLD; rather, it was based solely on ultrasonography.

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