ORIGINAL ARTICLE

CONTENTS

Effect of Sitagliptin on Micro150-5p in patients with T2DM with left ventricular diastolic dysfunction

Aswer J Abdulkadhium, Bassim I Mohammad
DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS, COLLEGE OF MEDICINE, UNIVERSITY OF AL-QADISIYAH, AL-QADISIYAH, IRAQ

ABSTRACT

Aim: To clarify Sitagliptin effect on left ventricular diastolic dysfunction in T2DM, to investigate the potential effect of Sitagliptin on epigenetic modulation (Micro RNA150-5P) and inflammatory process.

Materials and Methods: This study was carried out at a single center and is cross-sectional, descriptive, and observational. A specialist cardiologist selected a cohort of sixty individuals who had both left ventricular diastolic failure and type 2 diabetes mellitus (T2DM). The study was carried out at AL-Diwaniyah teaching hospital and the department of pharmacology and therapeutics, school of medicine, university of Al-Qadisiyah, Iraq. Total RNA was isolated using Trizol reagent (Genaid, Korea) and the concentration of RNA was determined. The primer amplification was performed according to the instructions published by AddBio (Korea) for the AddScript RT-qPCR Syber master kit. Transthoracic echocardiography measuring were patients at rest utilizing a commercially accessible ultrasound machine (Vinno E20; Echo Ultrasound AS, china). Ultrasound imaging acquisitions were automatically saved from at least three following cardiac contractions for subsequent processing. Standard parameters (LVED, LVES, and LVEF) were acquired as previously explained.

Results: Our results indicate a significant down regulation of miR-150-5p in the Sitagliptin treated group ($P<0.0001$) in comparison with metformin treatment. This was analyzed by Graph pad prizim software (version 8.4.3).

Conclusions: The results of our study indicate that the expression of miR-150-5p is dramatically reduced in the cardiac tissue of individuals with diabetes. Furthermore, reducing the levels of miR-150-5p is linked to an enhancement in the functioning of the left ventricle, partially via reducing the occurrence of programmed cell death in heart muscle cells. Hence, suppressing the activity of miR-150-5p could be a new and effective approach for treating cardiac dysfunction associated with diabetes.

KEY WORDS: Type 2 diabetic mellitus, Left ventricular diastolic dysfunction, MicroRNA, miR-150-5p, Sitagliptin

Wiad Lek. 2025;78(5):1167-1175. doi: 10.36740/WLek/202972 DOI

INTRODUCTION

About 40% of people with diabetes have diastolic dysfunction, which is linked to insufficient glycemic control. MicroRNAs are a type of small molecules that are approximately twenty two nucleotides long, single-stranded, and have been conserved throughout evolution. MicroRNA modulates gene expression irrespective of alterations in the DNA genome sequence. Increased cardiac expression of miR-150 can potentially prevent ventricular fibrosis and hypertrophy via modulating transcription factor c-Myb and serum response factor. The reduction in the expression of miR-150 in the circulation is associated with left ventricular hypertrophy and ruptures. Non-insulin-dependent diabetes mellitus, often known as adult-onset diabetes, is a metabolic condition characterized by elevated blood glucose levels and reduced insulin sensitivity. This illness is linked to several cardiovascular risk factors, such as dyslipidemia, hypertension, and obesity. Formerly known as type 2 diabetes mellitus (T2DM) [1]. The Middle East has a significant occurrence of type T2DM in men, with Bahrain having a prevalence of about 33%, Saudi Arabia with 29 %, the United Arab Emirates was 25% [2] and Iraq with 13% [3]. Left ventricular diastolic dysfunction (LVDD) is a preclinical state characterized by the left ventricle's inability to adequately fill with blood during relaxation (diastole) at an appropriate pressure. In order to delay or prevent the development of heart failure in people with type 2 diabetes, it is essential to identify the risk factors for LVDD and an early stage of diabetic cardiomyopathy. This is important because this condition is highly prevalent and is associated with significant morbidity and mortality [4]22 women, mean age 63.7 ± 9.1 years.Metabolic syndrome (MetS) is a group of common cardiovascular risk factors, together with other systemic illnesses that have an inflammatory base, such as chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF), and anemia [5]. Diastolic dysfunction is observed in 40% of

patients with diabetes and is linked to insufficient glycemic control. Investigators typically consider LVDD as the primary sign of cardiac remodeling in persons with diabetes mellitus (DM). LVDD primarily involves impaired relaxation and increased stiffness of the left ventricle. These abnormalities are likely caused by alterations in the quantity or quality of calcium regulatory proteins and the extracellular matrix [6]. T2DM negatively affects important functions, including viability, protective mechanisms against oxidative stress, and secretory capacity. This suggests that T2DM disrupts glucose regulation and insulin sensitivity by reducing the expression of non-coding RNAs (ncRNAs) and promoting apoptosis [7]. MicroRNAs are a type of small molecules that are approximately 22 nucleotides long. They are single-stranded and have been conserved throughout evolution. MicroRNA modulates gene expression irrespective of alterations in the DNA genome sequence. Cardiac miRNAs are recently discovered regulators of gene expression in the heart that have a substantial impact on modulating both transcriptional and post-transcriptional processes in diabetic cardiomyopathy and heart failure. The ability of miR-150 to regulate monocyte accumulation was shown to play a cardioprotective Function in a murine model of acute myocardial infarction [8]. Further studies have shown that the heightened production of miR-150 in the heart can hinder the enlargement of cardiac muscle cells and the formation of scar tissue by regulating the function of serum response factor and transcription factor c-Myb. The reduction in the concentration of miR-150 in the bloodstream is linked to the enlargement and bursting of the left ventricle, miR-150 plays a role in left ventricular remodeling (LVR) by suppressing the expression of its target genes, including C-reactive protein and adrenergic receptor beta 1 [9]. The abundant presence of dipeptidyl peptidase-4 in the blood vessels, heart muscle, and immune cells claims that this protein may have an impact on cardiovascular function [10]. Sitagliptin is a drug that specifically blocks the activity of an enzyme called dipeptidyl peptidase-4 (DPP-4). This enzyme breaks down two hormones called glucagon-like peptide-1 and glucose-dependent Insulinotropic polypeptide. By inhibiting DPP-4, Sitagliptin increases the amount of these hormones in the body. This leads to an increase in insulin secretion from the pancreas in response to glucose, and a decrease in the production of glucose by the liver. Sitagliptin enhances inflammation, collagen metabolism, lipid content, myocardial apoptosis (RIP3 expression), and cardiac function in diabetic rats. This facilitates the identification of supplementary benefits of Sitagliptin that extend beyond its capacity to reduce blood glucose levels [11]. DPP-4 is also found as CD26 on the surfaces of many cells, such as leukocytes, where it acts as an inflammatory mediator. If DPP-4 and CD26 are really proinflammatory, their inhibitors, like as Sitagliptin, have the potential to be anti-inflammatory and potentially antiatherogenic. This is because atherosclerosis is a persistent inflammation of the artery wall [12].

AIM

To clarify Sitagliptin effect on left ventricular diastolic dysfunction in T2DM, to investigate the potential effect of Sitagliptin on epigenetic modulation (Micro RNA150-5P) and inflammatory process.

MATERIALS AND METHODS

This study is an observational cross-sectional descriptive study conducted at a single center. It focuses on patients with type 2 diabetes mellitus that are of Iraqi nationality. The physician, who specializes in cardiology, diagnosed and selected all potential patients. The study was carried out at Al-Diwaniyah teaching hospital and the Department of Pharmacology and Therapeutics, Medicine College, Al-Qadisiyah University, Iraq.

SUBJECTS

Sixty adults were enrolled in this study (25 male and 36 female) aged 20-75 years old. Patients with HbA1c, renal or hepatic impairment, ejection fraction less than 50%, pregnancy, heart failure <50% ejection fraction, obesity (BMI ≥ 30) and psychiatric patient were considered as exclusion criteria. Information was taken from the patients: Name, age, gender, Weight, height, BMI, and comorbidities smoker.

DRUG USED IN THE STUDY

All patients included in the study were taking oral tablet 1000mg Metformin twice daily (30 patient) and oral tablet sitagliptin 50 mg plus 1000mg Metformin twice daily (30 patients).

ETHICAL APPROVAL

The study was confirmed by the Ethics Committee of the College of Medicine, University of Al-Qadisiyah, Iraq, (letter 30/3042) on July 27th, 2024. All patients were given a thorough explanation of the treatments and their agreement was obtained before any work was done. All patients will be informed verbally about the procedure, and the purpose of the study, before enrolling in the study, all participants will provide their written informed consent.

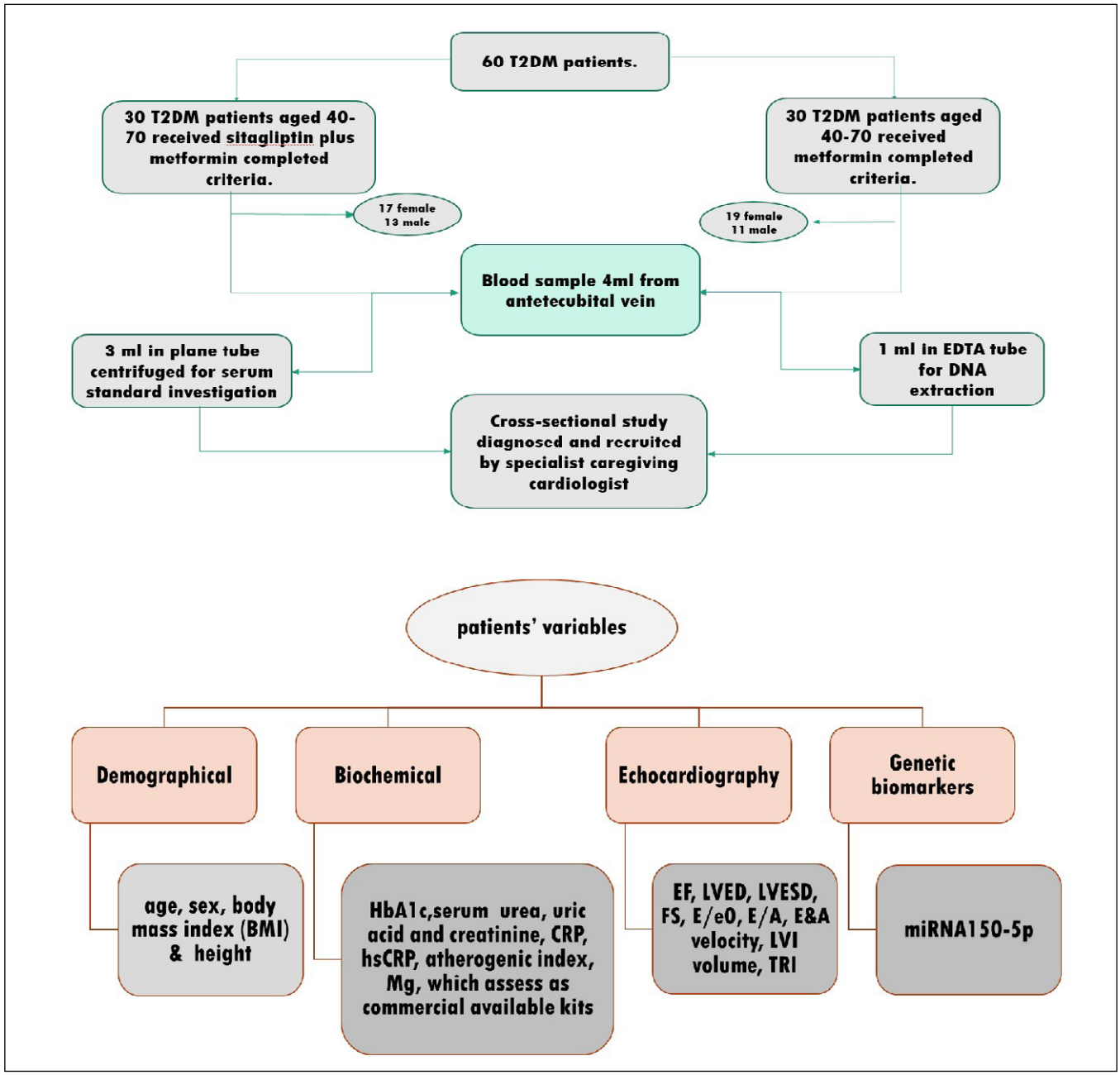

Fig. 1. All patients' variables workup at baseline were collected and assessed for echocardiography and biomarkers

BLOOD SAMPLE

The blood samples with 4 ml were collected from the patients that were aspirated from antecubital vein. Each sample was divide into two divisions, the first one was 1 ml blood was placed in 1 ml EDTA tube and refrigerated at a temperature of -20C until the time of RNA extraction. The second division was 3 ml blood in plane tube was centrifuged to extract serum for measuring (atherogenic index, blood urea, serum creatinine, uric acid, RBS, Magnesium). All patients' variables workup at baseline were collected and assessed for echocardiography, demographical and genetic biomarkers (Fig. 1).

DIASTOLIC FUNCTIONAL ELEMENTS

We measured the left atrial volume using the apical four-chamber view and the area-length approach, adjusted according to the individual's body surface area. The parameters measured for mitral inflow velocities using pulsed Doppler include the E velocity (m/s), Apex and length of A velocity, and E-wave deceleration time. The parameters measured mitral annular diastolic velocity (e0 and E/e0 ratio) using Doppler tissue imaging in pulsed waves. The E/e0 ratio split by SV was utilized as a proxy for LV diastolic stiffness and Tricuspid regurgitation velocity [13]. Fig. 2. demonstrate three parameter to measure mitral inflow and assessing left ventricular filling pressures and

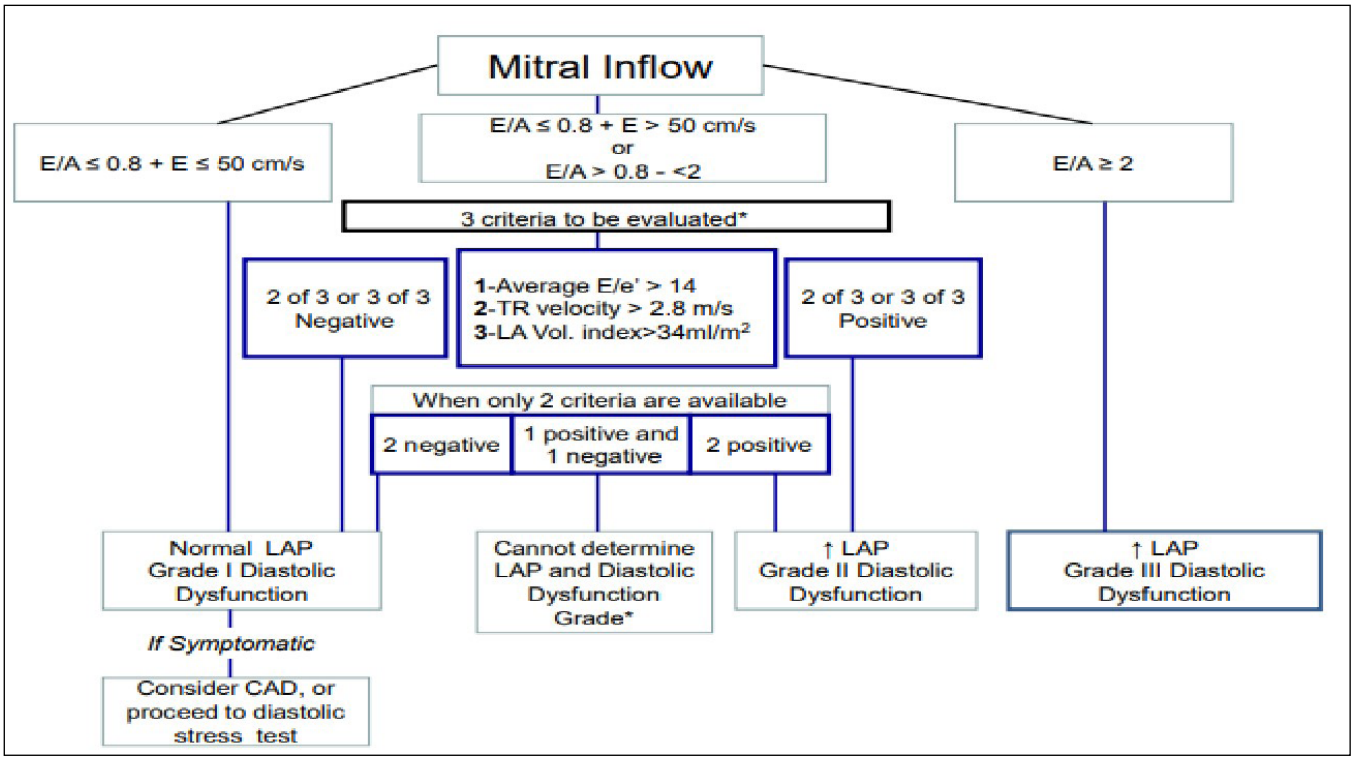

Fig. 2. Algorithm for assessing left ventricular filling pressures and grading left ventricular diastolic performance in patients with reduced left ventricular ejection fractions and patients with myocardial disease and normal left ventricular ejection fractions, taking into account clinical and other two-dimensional data

grading left ventricular diastolic performance in patients with reduced and normal left ventricular ejection fractions and patients with myocardial disease.

RNA EXTRACTION BY BLOOD SAMPLES WERE COLLECTED FROM ANTECUBITAL VEIN

QUANTITATIVE REVERSE TRANSCRIPTION REAL-TIME PCR (RT-QPCR)

Genomic RNA was extracted from blood samples using an RNA extraction kit from Genaid, Korea. The concentration of RNA was measured using a Quantus™ Fluorometer from Promega, USA. Subsequently, cDNA synthesis was performed using a cDNA synthesis kit from ADDBio, Korea.

GENE EXPRESSION OF MIR-150-5P

This study utilized the comparative Ct technique (ΔΔCt) to compare transcript levels of the target gene to the reference gene GAPDH mRNA. The normalization was done relative to the control group. This was achieved following the recommendation outlined in reference [13]. In order to accomplish this goal, the miR-150-5p gene was amplified utilizing the primers supplied by [14].

Gene of Interest (**miR-150-5p**) is: miR-150-5p-Forward: TCAATGCCCTGTCTCCCAAC

MiR-150-5p-Reverse: TTCCCAAGTCCCTATCCCCC

Housekeeping gene (**HKG**) or internal reference gene; human Glyceraldehyde 3-phosphate dehydrogenase is: GAPDH-F: CAGAACATCATCCCTGCCTCTA

GAPDH-R: CCAGTGAGCTTCCCGTTCA

QUANTITATIVE REVERSE TRANSCRIPTASE PCR (RT-QPCR) PREPARATION

RT-qPCR amplification: Initially, the amplification was accomplished using the AddScript RT-qPCR Syber master (AddBio, Korea). The heat conditions were conducted using BioRAD (USA).

RT-qPCR data normalization: was performed using the delta-delta Ct method, as described by [15]. This method involved normalizing transcript levels to those of GAPDH mRNA using the following formula:

2-ΔΔCT = [(CT gene of interest- CT internal control) sample A- (CT gene of interest- CT internal control) sample B)]

Note: Sample A refers to a specific group. Sample B refers to a distinct and specific group.

STATISTICAL ANALYSIS

Statistical analyses were performed by SPSS version (29) for biochemical assessment were calculated. P value <0.05 was considered statistically significant. The data were shown as ± SE of mean. t-test for Equality of Means are

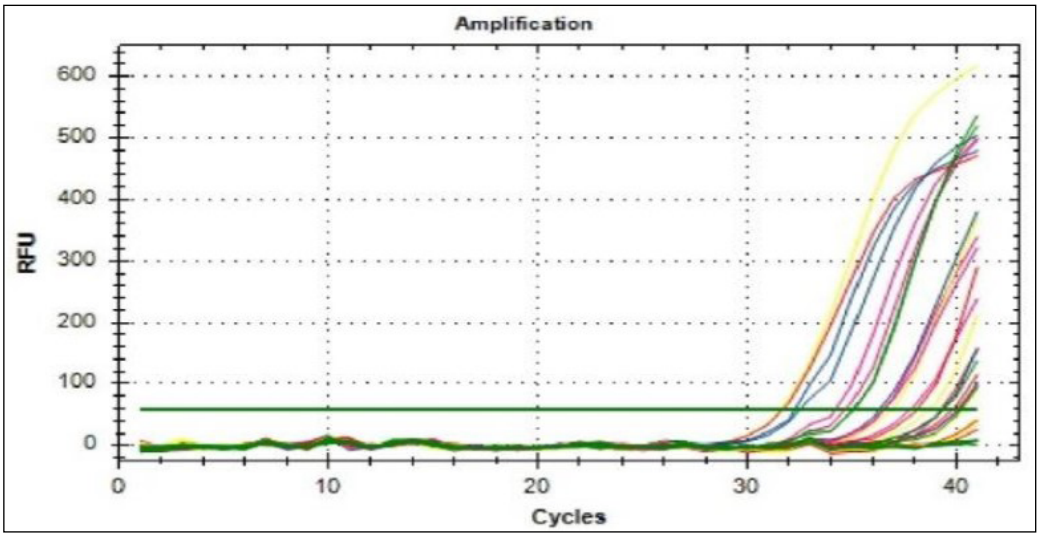

Fig. 3. The amplification curve of the tested samples was analyzed to determine the expression of the gene of interest (miR-150-5p) in the Metformin group

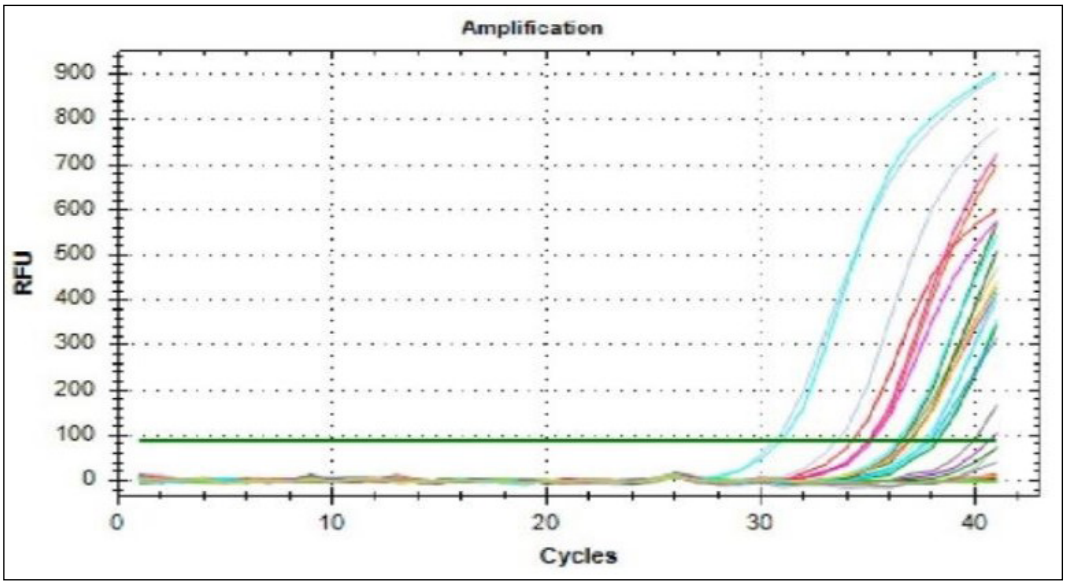

Fig. 4. The graph showing the increase in magnitude of the tested samples showing the expression of the gene of interest (miR-150-5p) in the Sitagliptin group

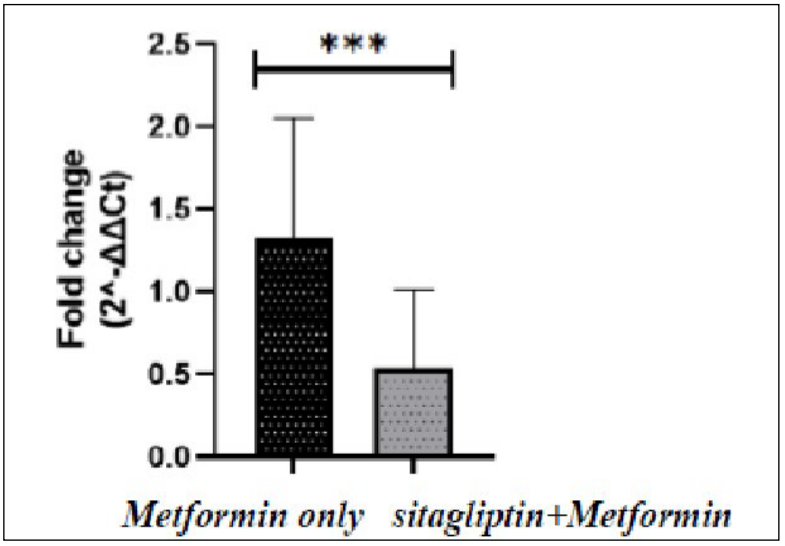

Fig. 5. Graphical represented the differences between concentration of miR-150-5p gene in the group treated with Sitagliptin plus metformin and concentration of miR-150-5p gene in the metformin group

Table 1. Values of Echocardiographic parameter of recruited diabetics patients (n = 60)

Characteristic	LVEDV(ml)	LVESV(ml)	EF (%)	FS (%)
Metformin				
Mean	124.1360	47.63	61.9550	33.5960
Std. Error Mean	6.36829	3.326	0.88655	0.62250
		Sitagliptin+ Metformin		
Mean	122.9200	50.04	64.3004	35.4771
Std. Error Mean	6.47052	3.837	0.93989	0.68989
P value	0.465	0.255	0.010	0.009

Table 2. Value of LVDD grades for recruited diabetic patients (n=60)

Drug	Grade 2	Grade 1	Normal	Mean Rank	p-value
Metformin	27	3	_	21.71	0.001
Sitagliptin/metformin	9	19	2	40.60	

Table 3. Comparison of Micro RNA 150-5P mean and Std. Error of Mean in diabetic's patient

Characteristic	Mean	Std. Error of Mean	P value
	Micro RNA 150-5P		
Metformin	1.320	0.1333	<0.0001
Sitagliptin + Metformin	0.5367	0.08638	

used. For genotyping frequencies, statistical analysis was performed with Graph Pad Prism software (version 8.4.3).

RESULTS

ECHOCARDIOGRAPHIC PARAMETER

The mean ± SE of LVEDV(ml) ,LVESV(ML), EF(%),%FS of patients Metformin group were 124.1360 ± 6.36829, 48.0007± 3.23524, 61.9550± 0.88655, 33.5960 ± 0.62250 respectively, and the mean ± SE of LVEDV(ml), LVESV(ML), EF(%), %FS of patients Metformin plus sitagliptin were 131.2379 ±7.65425, 50.04 ±3.837, 64.3004 ±0.93989, 35.4771±0.68989 respectively in. Table 1.

GRADES OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION

In this study which included 60 Iraqi type 2 diabetics patients about 36 patients (60%) were grade 2 and 22 patients (36.6%) were grade 1 with 2 patient (5%) have normal.

EFFICIENCY OF THE ASSAY'S AMPLIFICATION IN TESTED GROUPS FOR (MIR-150-5P)

The amplification curves demonstrate successful amplification, with matching crossing thresholds (CT), as the number of cycles increases with the round forming unit (RFU) (Fig. 3).

The amplification curves demonstrate successful amplification, with associated crossing threshold (CT) values, as the number of cycles increases with the round forming unit (RFU) (Fig. 4).

The results indicate a substantial reduction in the expression of miR-150-5p in the group treated with Sitagliptin (P<0.0001), as compared to the group treated with metformin (Fig. 5, Table 3).

DISCUSSION

ECHOCARDIOGRAPHIC PARAMETER AND EFFECT OF SITAGLIPTIN/METFORMIN

This study performed a subgroup analysis that specifically investigated the effects of sitagliptin on echocardiographic measures of diastolic function. Participant in our study has a diagnosis of type 2 diabetes and exhibits left ventricular diastolic dysfunction, which is indicated by an ejection fraction greater than 50%. This study investigates the impact of metformin alone compared to a combination of sitagliptin and metformin. The results indicate that sitagliptin has a notable and beneficial impact on echocardiographic parameters, specifically on EF (ejection fraction) and FS (fractional shortening). According to these data, it appears that giving sitagliptin may have a protective effect on the relaxation of the heart muscles

during the filling phase (cardiac diastolic function), leading to a better outlook regardless of how well blood sugar is controlled and blood pressure levels. On the other hand, another study found that adding DPP-4 inhibitors, such as Sitagliptin, to standard antidiuretic treatments effectively reduced the advancement of carotid IMT [14,15]. The long-term administration of sitagliptin significantly prevented the advancement of heart failure in a rat model of heart failure [16]an enzyme that inactivates peptides that possess cardioprotective actions, correlates with adverse outcomes in heart failure (HF. Nevertheless, the administration of sitagliptin did not provide significant enhancement in the systolic function of individuals suffering from ischemic HF and type 2 diabetes mellitus [17]. Furthermore, Oe et al. discovered that the administration of sitagliptin to patients diagnosed with T2DM and LV (left ventricular) diastolic dysfunction did not result in any enhancement of the echocardiographic characteristics associated with this disease. The impact of DPP-4 inhibitors on cardiac function's therapeutic efficacy remains a topic of discussion due to the inconsistent outcomes observed [18]and, if so, it is attributable to the attenuation of PPH or to a direct cardiac effect of DPP-4i. We compared the effects of the DPP-4i, sitagliptin, and the alpha-glucosidase inhibitor, voglibose, on LV diastolic function in patients with type 2 diabetes.\nMethods: We conducted a prospective, randomized, open-label, multicenter study of 100 diabetic patients with LV diastolic dysfunction. Patients received sitagliptin (50 mg/day. Nogueira et al. found that sitagliptin had positive benefits on LVDD in persons diagnosed with T2DM who were receiving insulin therapy. However, these effects were not as evident in T2DM patients who were just receiving insulin [19].

MICRORNAS 150-5P AND EFFECT OF SITAGLIPTIN/METFORMIN

MicroRNAs (miRNAs) have significant implications in diverse cardiovascular conditions, specifically in the advancement and progression of illnesses, and therapeutic approaches targeting miRNAs hold crucial clinical importance [20]. The current study aimed to examine the impact of MicroRNA150-5P on the left ventricular function in individuals with diabetes. Within The results of our study showed that elevated glucose levels led to a notable decrease in the levels of miR-150-5p in the group treated with Sitagliptin ($P<0.0001$). Additionally, there was an improvement in echocardiographic parameters related to left ventricular diastolic dysfunction when compared to the group treated with metformin alone (control group). These findings suggest that Sitagliptin may have a beneficial effect as an additional therapy to metformin. Our investigation's findings are consistent with previous research results in patients with left ventricular dysfunction (LVDD), indicating a considerable decrease in the levels of miR-150 expression in the left ventricle during the initial stages of LVDD. The greatest significant decline, totaling about two-thirds, occurred at the 2 and 4-week marks. Afterwards, the levels of expressiveness began to regain, but they still remained below the normal levels. Prior studies have demonstrated a reducation in the level of miR-150 in hypertrophic cardiac tissue [21]. Furthermore, inhibiting miR-150 facilitated the onset and progression of myocardial hypertrophy, cardiac fibrosis, and heart failure. Cardiomyocytes' size decreased when MiR-150 was overexpressed. The concetration of miR-150-5p was significantly reduceed in individuals with severe left heart failure or in those with chronic systolic left heart failure and atrial fibrillation. The decrease in miR-150-5p is indicative of the advancement of the disease and is linked to an unfavorable outcome in these individuals. Our research validates the results of previous studies that have shown a negative correlation between the levels of circulating miR-150-5p and the severity of the disease, as well as the prognosis of patients with left heart failure. This is in contrast to other published studies that have found positive correlations among different circulating miRNAs and outcome. Nevertheless, our research contradicts a previous study that discovered a biomarker with high sensitivity and specificity for heart failure. This study specifically examined only five miRNAs and did not incorporate miR-150-5p. Furthermore, these studies were deficient in having a control group, which sets them apart from our study design in a fundamental manner.

CONCLUSIONS

The miR-150 has reduced levels in the bloodstream of individuals suffering from Left ventricular diastolic dysfunction with T2DM. MicroRNA-150 is likely to be decreased in this context and is considered an autonomous indicator for LVDD. Measuring it may provide extra benefits in detecting patients at risk of LVDD early on, which is a strong indicator of an unfavorable prognosis. Sitagliptin improved association epigenetics deregulations MicroRNA150-5p in patients with type 2 diabetes mellitus.

RECOMMENDATIONS

In order to investigate this correlation, further research utilizing a larger sample size, longer duration of follow-up with clinical outcomes and multi centric view is required. Future research should focus on epigenetics relationships and additional biomarkers in Iraqi diabetic's patients is required.

REFERENCES

1. Olokoba AB, Obateru OA, Olokoba LB. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Med. J. 2012;27(4):269–273. doi: 10.5001/omj.2012.68. DOI
2. Meo SA et al. Prevalence of Type 2 Diabetes Mellitus among Men in the Middle East: A Retrospective Study. Am. J. Mens Health. 2019;13(3):155798831984857. doi: 10.1177/1557988319848577. DOI
3. Mansour AA et al. Prevalence and correlation of glycaemic control achievement in patients with type 2 diabetes in Iraq: A retrospective analysis of a tertiary care database over a 9-year period. Diabetes Metab. Syndr. Clin. Res. Rev. 2020;14(3):265–272. doi: 10.1016/j.dsx.2020.03.008. DOI
4. Nicolina A et al. Left Ventricular Diastolic Filling in Diabetes Mellitus With and Without Hypertension. Am. J. Hypertens. 1995;8(4):382–389. doi: 10.1016/0895-7061(95)00022-H. DOI
5. Paulus WJ, Tschöpe C. A Novel Paradigm for Heart Failure with Preserved Ejection Fraction: Comorbidities Drive Myocardial Dysfunction and Remodelling Through Coronary Microvascular Endothelial Inflammation. JACC. 2013;62(4):263–271. doi: 10.1016/j.jacc.2013.02.092. DOI
6. Weber KT. Extracellular Matrix Remodelling in Heart Failure. Circulation. 1997;96(11). doi:10.1161/01.CIR.96.11.4065. DOI
7. Kornicka K, Houston J, Marycz K. Dysfunction of Mesenchymal Stem Cells Isolated from Metabolic Syndrome and Type 2 Diabetic Patients as Result of Oxidative Stress and Autophagy may Limit Their Potential Therapeutic Use. Stem Cell Reviews and Reports. 2018;14(3):337–345. doi: 10.1007/s12015-018-9809-x. DOI
8. Liu Z, Ye P, Wang S et al. MicroRNA-150 Protects the Heart From Injury by Inhibiting Monocyte Accumulation in a Mouse Model of Acute Myocardial Infarction. Circulation. 2014. doi:10.1161/CIRCGENETICS.114.000598. DOI
9. Sakamoto M, Matsutani D, Kayama Y. Possibility of a New Therapeutic Strategy for Left Ventricular Dysfunction in Type 2 Diabetes. J. Clin. Med. Res. 2018;10(11):799–805. doi: 10.14740/jocmr3584w. DOI
10. Zhong J, Rao X, Rajagopalan S. An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: Potential implications in cardiovascular disease. Atherosclerosis. 2013;226(2):305–314. doi: 10.1016/j.atherosclerosis.2012.09.012. DOI
11. Gallwitz B. Sitagliptin: Profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes. Drugs Today Barc. Spain. 1998;43:13–25. doi: 10.1358/dot.2007.43.1.1043909. DOI
12. Makdissi A et al. Sitagliptin Exerts an Anti-inflammatory Action. J. Clin. Endocrinol. Metab. 2012;97(9):3333–3341. doi: 10.1210/jc.2012-1544. DOI
13. Schmittgen TD, Livak KJ. Analysing real-time PCR data by the comparative CT method," Nat. Protoc. 2008;3(6):1101–1108. doi: 10.1038/nprot.2008.73. DOI
14. Schmittgen TD, Livak Starr TNH, Allison J et al. Shifting mutational constraints in the SARS-CoV-2 receptor-binding domain during viral evolution. Science. 2022;377(6604). doi: 10.1126/science.abo7896. DOI
15. A Salles TA, dos Santos L, Barauna VG, Girardi ACC. Potential Role of Dipeptidyl Peptidase IV in the Pathophysiology of Heart Failure. Int J Mol Sci. 2015;16(2):4226–4249. doi: 10.3390/ijms16024226. DOI
16. Arturi, Succurro E, Miceli S et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. Endocrine. 2017;57(3):464-473. doi: 10.1007/s12020-016-1166-4. DOI
17. Hiroki Oe, Nakamura K, Kihara H et al. Comparison of effects of Sitagliptin and voglibose on left ventricular diastolic dysfunction in patients with type 2 diabetes: results of the 3D trial. Cardiovascular Diabetology. 2015;14(1):83. doi: 10.1186/s12933-015-0242-z. DOI
18. Nogueira KC, Furtado M, Fukui RT et al. Left ventricular diastolic function in patients with type 2 diabetes treated with a dipeptidyl peptidase-4 inhibitor- a pilot study. Diabetol. Metab. Syndr. 2014;6(1):103. doi: 10.1186/1758-5996-6-103. DOI
19. Yin K, Zhao L, Feng D et al. Resveratrol Attenuated Low Ambient Temperature-Induced Myocardial Hypertrophy via Inhibiting Cardiomyocyte Apoptosis. Cell. Physiol. Biochem. 2015;35(6):2451–2462. doi: 10.1159/000374045. DOI
20. Sayed D, Hong C, Chen I-Y et al. MicroRNAs Play an Essential Role in the Development of Cardiac Hypertrophy. Circ. Res. 2007;100(3):416-424. doi: 10.1161/01.RES.0000257913.42552.23. DOI
21. Peng Deng, Chen L, Liu Z et al. MicroRNA-150 Inhibits the Activation of Cardiac Fibroblasts by Regulating c-Myb. Cell. Physiol. Biochem. 2016;38(6):2103–2122. doi: 10.1159/000445568. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Aswer J Abdulkadhium
University of Al-Qadisiyah
P.O.Box 88 -Al-Qadisiyah -Al-Diwaniyah, Iraq
e-mail: asawer.jawad12@gmail.com

ORCID AND CONTRIBUTIONSHIP
Aswer J Abdulkadhium: 0009-0000-4246-0097 B C D E
Bassim I Mohammad: 0000-0001-6732-5940 A E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 15.07.2024
ACCEPTED: 15.03.2025