The Role of Gliclazide on microRNA-150 Expression in Patients with Type 2 Diabetes Mellitus and Left Ventricular Diastolic Dysfunction

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ABSTRACT

Back ground: Left ventricular diastolic dysfunction (LVDD) is a common complication observed in patients with type 2 diabetes mellitus(T2DM) and is associated with increased cardiovascular morbidity and mortality. MicroRNAs (miRNAs) have emerged as important regulators of gene expression and have been implicated in the pathogenesis of LVDD. This study aimed to investigate the role of gliclazide, an oral antidiabetic medication, on the expression of microRNA-150 (miR-150) in patients with T2DM and LVDD.

Objective: this study was to investigate the effects of the antidiabetic medication gliclazide on the expression of microRNA-150 (miR-150) in individuals with both left ventricular diastolic dystunction (LVDD) and type 2 diabetes mellitus (T2DM).

Method: A total of 62 patients with T2DM and LVDD were enrolled in this study and were randomly assigned to receive either gliclazide treatment or standard care for a period of 6 months . Blood samples were collected from all participants at baseline treatment period. The expression levels of miR-150 were measured using quantitative real-time polymerase chain reaction (qRT-PCR).

Result: the patients with T2DM and LVDD exhibited significantly increased expression of miR-150 compared to healthy controls. However, after 6 months of gliclazide treatment, there was a significant upregulation of miR-150 expression in the treatment group compared to the control group, These findings suggest that gliclazide treatment may have a beneficial effect on LVDD in patients with T2DM by modulating the expression of miR-150. MiR-150 has been implicated in the regulation of cardiac hypertrophy and fibrosis, which are key processes involved in the development of LVDD. Therefore, the upregulation of mir-150 by gliclazide may contribute to the amelioration of LVDD through the attenuation of cardiac remodeling.

Conclusion: The gliclazide treatment in patients with T2DM and LVDD was associated with a increase in miR-150 expression and improvements in diastolic function. These findings highlight the potential of miR-150 as a therapeutic target for the management of LVDD in patients with T2DM and suggest that gliclazide may have additional benefits beyond glycemic control in this patient population. Further research is warranted to elucidate the underlying mechanisms and clinical implications of miR-150 modulation in the context of LVDD and T2DM.

Keywords: Type 2 diabetes mellitus, left ventricular diastolic dysfunction, microRNA-150, gliclazide.

دور جليكلازيد على تعبير microRNA-150 في المرضى الذين يعانون من خلل وظيفي في البطين الأيسر وداء السكري من النوع الثاني

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الخلاصة

خلفية : يعد الخلل الوظيفي الانبساطي للبطين الأيسر (LVDD) من المضاعفات الشائعة التي لوحظت في المرضى الذين يعانون من داء السكري نوع٢ (T2DM) ويرتبط بزيادة معدلات المرض والوفيات القلبية الوعائية.
ظهرت (Micro RNAs(miRNAs)) كمنظمين مهمين للتعبير الجيني وقد تضمنت في التسبب في LVDD .

الاهداف : تهدف هذه الدراسة إلى دراسة دور الجليكلازيد ، وهو دواء مضاد لمرضى السكر عن طريق الفم ، في التعبير عن (Micro RNA-150(miRNA150) في المرضى اللذين يعانون من T2DM و LVDD .

الطريقة : تم تسجيل مجموعة ٦٢ مريضاً يعانون من T2DM و LVDD في هذه الدراسة وتم اختيارهم عشوائياً لتلقي العلاج بالجليكلازايد او الرعاية القياسية لمدة ٦ اشهر . تم جمع عينات الدم من جميع المشاركين في فترة العلاج الأساسية. تم قياس مستويات التعبير ل mir-150 باستخدام تفاعل البلمرة المتسلسل الكمي في الوقت الحقيقي (qRT-PCR).

النتائج : أظهرت النتائج ان المرضى اللذين يعانون من T2DM و LvDD اظهروا زيادة كبيرة في التعبير عن miR-150 مقارنة بالضوابط الصحية. ومع ذلك ، بعد ٦ اشهر من العلاج بالجليكلازايد ، كان هناك تحسن كبير في تعبير miR-150 في مجموعة العلاج مقارنة بالمجموعة الضابطة ، وتشير هذه النتائج الى ان العلاج بالجليكلازايد قد يكون له تأثير مفيد على LVDD في المرضى اللذين يعانون من T2DM عن طويق تعديل التعبير mir-150 وقد تورط mir-150 في تنظيم تضخم القلب والتليف ، وهي العمليات الرئيسية المشاركة في تطوير LVDD . لذلك ، فإن تنظيم mir-150 بواسطة الجليكلازايد قد يساهم في تحسين LVDD من خلال تخفيف إعادة التأثير القلب .

الخاتمة : ارتبط علاج الجليكلازايد في المرضى اللذين يعانون من T2DM و LVDD مع زيادة في التعبير mir-150 والتحسينات في وظيفة القلب الانبساطي . تسلط هذه النتائج على إمكاناتmir-150 كهدف علاجي لإدارة LVDD في المرضى اللذين يعانون من T2DM وتشير الى ان الجليكلازايد قد يكون له فوائد إضافية تتجاوز السيطرة على نشبة السكر في الدم في هذه المجموعة من المرضى . هناك مايبرر اجراء المزيد من البحث لتوضيح الاليات الأساسية والاثار السريرية لتعديل mir-150 في سياق LVDD و T2DM .

الكلمات المفتاحية : داء السكري من النوع الثاني، خلل وظيفي انبساطي البطين الأيسر، microRNA-150، غليكلازيد.

INTRODUCTION

The most prevalent metabolic problems in type2 diabetes (T2DM) include incretin system deficiencies, insulin resistance (IR), and inadequate insulin production. T2DM is a complex disease. It's critical to comprehend that T2DM is complex and that the environment and genes interact to produce its effects.[1] T2DM is the result of several interactions between environmental, genetic, and epigenetic variables[2]

Additionally, there is a substantial heritable genetic correlation between T2DM and a family history. The chance of developing the disease doubles in the presence of a mother who exhibits the disease phenotype and rises to 40% if one of the close relatives has diabetes.[3] Through DNA methylation and histone modification, epigenetics modifies and alters genes by changing gene expression patterns.[4] Combining genome sequencing, epigenetic analysis, and other methods could improve our knowledge of genetic risk models and the pathophysiology of type 2 diabetes.[4]

On the other hand, those with a family history of diabetes may be less likely to develop diabetes if they maintain a normal BMI and increase their physical activity.[5]

When problems in glucose metabolism exist, but the requirements for diabetes are not fulfilled, the condition has been referred to as pre-diabetes. For instance, a glucose level measured two hours after an oral glucose tolerance test might be >7.8 mmol/l (140 mg/di) but < 11.1 mmol/l (200 mg/di) or fasting blood glucose >5.6 mmol/l (100 mg/dl) but <7.0 mmol/| (126 mg/di). There is an elevated risk of macrovascular disease in addition to the increased chance of developing diabetes, which increases in tandem with the rate at which fasting and 2-hour plasma glucose levels rise (Figure 1)[6].

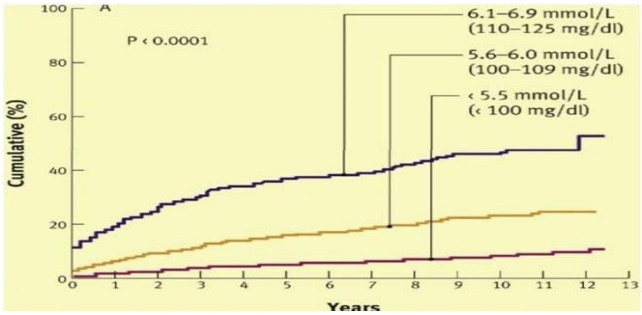

Figure 1:Cumulative incidence of diabetes according to initial fasting plasma glucose, reproduced with permission of the American Diabetes Association from Dinnen SF et al. Diabet Car 1998; 21:1408-13.[6]

Even in the absence of atherosclerotic disease progression, diabetes can alter the structure and function of the heart. Preceding systolic dysfunction and potentially leading to symptomatic heart failure left ventricular diastolic dysfunction (LVDD) is believed to be one of the earliest pre-clinical signs of diabetic cardiomyopathy.[7]. Left ventricular diastolic dysfunction (LVDD) is caused by increased left ventricular (LV) chamber stiffness and impaired LV relaxation, which strongly correlate with myocardial fibrosis (MF)[8].

The fundamental process of left ventricular diastolic relaxation impairment and subsequent myocardial stiffness are linked to the development of left ventricular hypertrophy and related myocardial interstitial fibrosis.[9]

If treatment is not received, diastolic dysfunction can eventually lead to diastolic heart failure, which is why it's critical to identify it at an early stage[10].

Short RNA transcripts with 18–24 nucleotides, known as microRNAs, control the translational gene expression level.[11]

MicroRNAs (miRNAs) can serve as prognostic and diagnostic biomarkers because it has been demonstrated that they are altered in cardiovascular diseases (CVD) and T2DM.[12].

Circulating miR-150-5p has been shown to have a negative correlation with left heart failure patients' illness severity and prognosis[13]. This observation could be explained by the fact that miR-150-5p actively suppresses specific pro-apoptotic genes[14] or inhibits p53 activity, a critical factor in the induction of apoptosis[15]. Consequently, apoptosis is activated in cardiomyocytes by miR-150-5p deficiency, essential for advancing heart failure.[16]. This research paper looks at the possible function of Gliclazide, an oral hypoglycemic agent, on the manifestation miR-150 in patients with T2DM and LVDD. The study design involved a randomized controlled trial with an intervention assessment of miR-150 expression levels.

Sulphonylureas is the drug used in type-2 diabetes, among which Gliclazide is taken as a standard model drug. Gliclazide is a second-generation drug widely (employed because of its selective inhibitory activity towards K + ATP channels, antioxidant activity, low incidence of creating severe hypoglycemia, and other haemobiological qualities[17]

Gliclazide, an oral antihyperglycemic medication, treats non-insulin-dependent diabetic mellitus (NIDDM)[18].

The mechanism of action of Gliclazide is bound to the β cell sulfonylurea receptor (SUR1). This binding subsequently blocks the ATP-sensitive potassium channels. The binding results in the channels' closure and decreases potassium efflux, leading to depolarization of the β cells. This opens voltage-dependent calcium channels in the β cell, resulting in calmodulin activation, which leads to exocytosis of insulin-containing secretory granules.[19]

Due to the special aminoazabicyclo-octane ring in its structure, Gliclazide has been demonstrated to have antioxidant qualities in addition to its hypoglycemic action. Gliclazide has antioxidant properties separate from its antihyperglycemic action. Gliclazide is an effective free radical scavenger in vitro, according to Scott et al. ...[17]

because of its anti-inflammatory properties, which prevent diabetes complications by lowering the plasma concentration of IL-6, which is mainly produced by macrophages.[20].

METHODS

This cross-sectional study was conducted in Al-Diwaniyah Teaching Hospital, Diwaniyah, Iraq, for the period (July 2023 through June 2024). Of the patients diagnosed with T2DM and LVDD, aged between 45 and 65 years, 36 of the participants were female and 26 of them male, who are receiving standard care for diabetes management. The patients were randomly allocated into two groups: the Gliclazide group and the Metformin group. The Gliclazide group received Gliclazide (90mg) as an add-on therapy to their existing antidiabetic regimen. In contrast, the Metformin group continued their standard treatment, Gliclazide + Metformin (90/1000), for at least six months.

Patient Inclusion Criteria

- T2DM
- HbA1C (6.5-9)
- Age 45-65 years
- Onset of Diseases >3 years
- Onset of current therapy at least six months

Patient Exclusion criteria:

- HbA1C > (9)
- Renal impairment (eGFR < 30 ml/min/1.73m2 of body surface area) or dialysis
- Hepatic impairment
- Pregnancy
- Overt heart failure
- EF, which is less than 50
- Psychiatric patient

Baseline demographic characteristics, clinical data, and assessment of body mass index BMI(The weight of the patients included in the study is measured by electronic scale in kg. The height is measured by height scale in m²). The blood samples with 1 ml were collected from the patients aspirated from the antecubital vein, placed in 1 ml EDTA tube, and stored at -20 C until the DNA extraction. Assessment of Left Ventricular Diastolic Function: Diagnosis and grading of LVDD was performed by transthoracic echocardiography utilizing ultrasound machine (Vinno E20, Echo

Ultrasound AS, China)and the following cut off values indicating aberrant diastolic function were used to define LVDD in accordance with the most recent guidelines[21]. Patients who satisfied all of these criteria were diagnosed with abnormal diastolic function. Septal e' {septal mitral annulus velocity(early diastole) } is less than 7 cm/s and/or lateral e' {lateral mitral annulus velocity(early diastole)} is less than 10 cm/s. The velocity of tricuspid regurgitation (TR) is more than 2.8 m/ left atrial volume index is greater than 34 millilitres per square meter. Micro RNA 150 levels were measured at baseline at the beginning of RNA extraction. RNA concentration was measured by Quantus™ Fluorometer (Promega, USA) then The ADDBio (Korea) kit was used to reverse transcribe the entire RNA to cDNA. By adding H2O (6µl) to Reverse transcriptase (RT), The total volume is 40µl after adding 2X the script, 20µl of cDNA, 4µl of dNTPs, 2µl of random oligoshexamer, and 8µl of RNA. In the presence of transcript levels comparable to those of GAPDH mRNA, Galectin-3 gene expression was measured using the comparative Ct technique (ΔΔCt) and normalized to the level of the control group. As advised by (Schmittgen and Livak, 2008), this was accomplished. Enhancing the impact of the Galectin-3 gene was carried out using the following primers (Papaspyridonos et al., 2008).

Gene of Interest (miR-150-5p) Sequence (5'->3') miR-150-5p-Forward Template strand (5'……3')TCAATGCCCTGTCTCCCAAC and miR-150-5p-Reverse the template strand TTCCCAAGTCCCTATCCCCC. Housekeeping gene (HKG) or internal reference gene; human Glyceraldehyde 3-phosphate dehydrogenase Sequence (5'->3') GAPDH-F template strand CAGAACATCATCCCTGCCTCTA and GAPDH-R Template strand (5'……3') CCAGTGAGCTTCCCGTTCA.

Quantitative Reverse transcriptase PCR (RT-qPCR) Preparation Amplification via RT-qPCR: Initially, AddScript RT-qPCR Syber master (AddBio, Korea) was used to accomplish the amplification. The reaction contained:

- A total of 20 µl is obtained by adding H2O (4 µl) to AddScript RT-qPCR (10 µl), forward primer (0.05 pmol/20 µl) (2 µl), and reverse primer (0.05 pmol/20 µl) (2 µl), along with cDNA (2 µl).
- Data normalisation for RT-qPCR:
- The transcript levels were normalized to those of GAPDHmRNA using the delta-delta Ct technique, as described by Schmidtgen and Livak (2008). The following formula was used:- 2-ΔΔCT = [(AT-CT internal control-(AT-CT gene of interest-) sample A-(AT-CT internal control-) sample B)].
- Note: Sample A means one particular group.
- Sample B means another particular group

Statisticalanalysis

Graph pad prism software (version 8.4.3) was applied to data analysis. Each data set was displayed as mean #standard deviation (SD), and a difference with P values less than 0.05 was regarded as statistically significant.

RESULT

After the intervention period, there is a statistical difference between the two groups. MicroRNA 150 levels significantly increased in the Gliclazide group compared to the Metformin group ($p < 0.0001$). Significantly different ($P < 0.05$). Mean:- for metformin 1.299 and 13.55 for Gliclazide with Std. Deviation for Metformin is 0.7457 and 4.224 for Gliclazide.

The assay amplification efficiency in tested groups for (miR-150-5p).

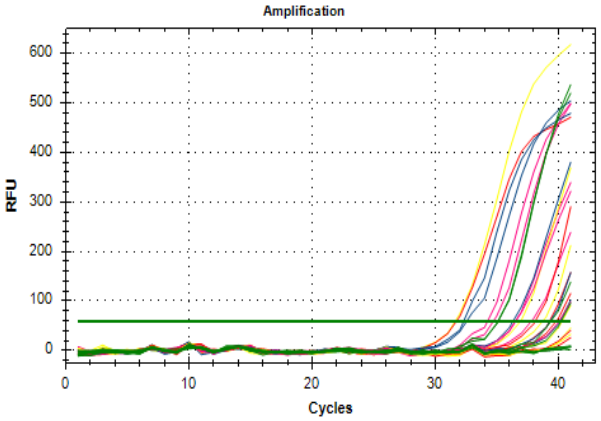

Figure 2: amplification curve of the tested samples for expression of the gene of interest(miR-150-5p) in Metformin. The successful amplification curves with the corresponding crossing threshold (CT) are the number of cycles with the round forming unit (RFU).

Gliclazide group

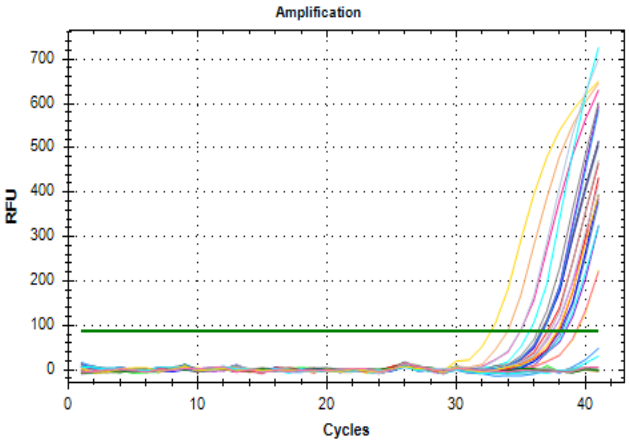

Figure: amplification curve of the tested samples for expression of the gene of interest in the Gliclazide group (miR-150-5p). The successful amplification curves with the corresponding crossing threshold (CT) are the number of cycles with the round forming unit (RFU).

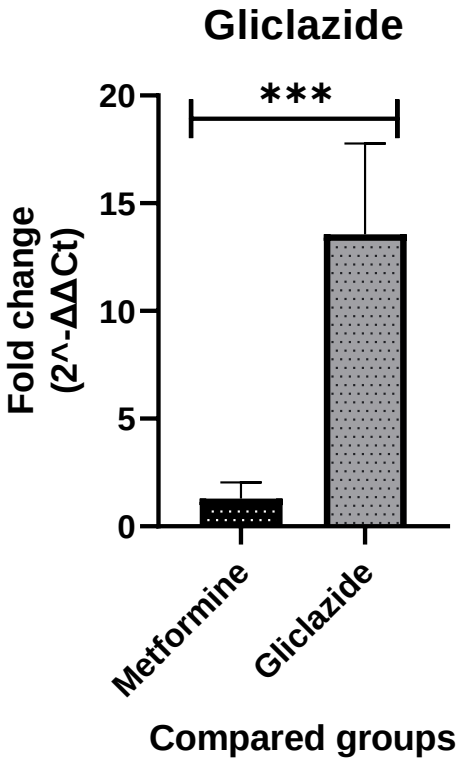

Figure 4: Gene expression of miR-150-5p in the gliclazide treatment group. This shows significant upregulation of miR-150-5p in the Gliclazide-treated group (P<0.0001) compared to metformin treatment. This was analyzed using GraphPad Prism software (version 8.4.3).

DISCUSSION

The key findings of this study are that treatment with the antidiabetic drug gliclazide significantly increased the expression of miR-150 in individuals suffering from left ventricular diastolic dysfunction and type 2 diabetes mellitus (T2DM)(LVDD).

The observed increase in miR-150 expression with Gliclazide is an essential and novel finding, as previous studies have reported dysregulation of miR-150 in the setting of diabetic cardiomyopathy. These studies have demonstrated miRNAs' critical role in regulating numerous pathways and the possibility of using miRNAs as a therapeutic agent to treat various illnesses, including diabetes, cancer, and cardiomyopathies.[21]. previous studies show miR-150-5p was significantly downregulated in AHF patients compared with healthy subjects[22]. An additional investigation by Goren et al.[23] assessed the levels of 186 microRNAs in the serum of 30 patients with stable chronic systolic heart failure and 30 controls. It showed that only 4 (miR-423-5p, miR-320a, miR-22, and miR-92b) were more highly expressed in the HF patient group, with a 90% specificity and sensitivity. Furthermore, there was a correlation with significant prognostic factors such as elevated serum BNP levels, a wide QRS, and dilatation of the left ventricle and left atrium. Previous studies show miR-150 inhibits OS cell proliferation and sensitizes osteosarcoma (OS) cells to Doxorubicin(DOX)

The study examined the biological significance of miR-150 in OS carcinogenesis and found that miR-150 was overexpressed in the OS cell lines HOS. Using CCK-8, the effects miR-150 on OS cell growth were evaluated by measuring cell proliferation. The results showed that HOS and U2OS cell growth was dramatically suppressed by overexpressing miR-150...

Moreover, compared to the NC mimic + DOX group, the overexpression of miR-150 dramatically reduced the cell survival of HOS and U2OS in the DOX treatment group. These findings thus suggested that miR-150 reduced the proliferation of OS cells and increased their sensitivity to DOX.[24].

In our study, the ability of Gliclazide to upregulate miR-150 expression suggests a potential therapeutic mechanism by which this medication may exert protective effects on cardiac function in patients with T2DM.furthersupports the notion that modulation of miR-150 may be an essential pathway mediating the cardioprotective effects of Gliclazide. Therefore, the upregulation of miR-150 observed in the gliclazide group may have contributed to the observed improvements in diastolic function.

The precise mechanisms by which Gliclazide regulates miR-150 expression are not fully understood and warrant further investigation.

Possible mechanisms may involve the modulation of transcriptional factors or epigenetic modifications that control miR-150 gene expression. Additionally, Gliclazide may influence the biogenesis or stability miR-150 through interactions with various cellular pathways. However, the use of miRNAs is now limited by several issues, including their overlap in different cardiac diseases, challenges with isolation and sampling, a lack of standardized data, and high prices that currently make routine use impossible.

CONCLUSION AND RECOMMENDATION

This study demonstrates that Gliclazide, a widely used antidiabetic medication, can significantly upregulate the miR-150 expression in patients suffering from T2DM and LVDD.

More investigation is required to clarify the underlying mechanisms and investigate the therapeutic implications of these findings.

REFERENCES

1. Gvazava IG, Karimova MV, Vasiliev AV, Vorotelyak EA. Type 2 Diabetes Mellitus: Pathogenic Features and Experimental Models in Rodents. ActaNaturae. 2022 Jul-Sep;14(3):57-68. doi: 10.32607/actanaturae.11751. PMID: 36348712; PMCID: PMC9611859.
2. Prasad RB, Groop L. Genetics of type 2 diabetes-pitfalls and possibilities. Genes (Basel). 2015 Mar 12;6(1):87-123. doi: 10.3390/genes6010087. PMID: 25774817; PMCID: PMC4377835.
3. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2014;7:587–591. doi: 10.2147/DMSO.S67400.
4. Introduction I. Monogenic Diabetes: What It Teaches Us on the Common Forms of Type 1 and Type 2 Diabetes. 2016;37(June):190–222.
5. Raji A, Seely EW, Arky RA, Simonson DC. Body fat distribution and insulin resistance in healthy Asian Indians and Caucasians. J ClinEndocrinolMetab. 2001;86(11):5366–5371. doi: 10.1210/jcem.86.11.7992.
6. Dinneen SF, Maldonado D, 3rd, Leibson CL, Klee GG, Li H, Melton LJ, 3rd, Rizza RA. Effects of changing diagnostic criteria on the risk of developing diabetes. Diabetes Care. 1998;21:1408–1413.
7. Disfunçãodiastólica do ventrículoesquerdo no diabetes: umaatualizaçãoLeft ventricle diastolic dysfunction in diabetes
8. Sarkar, Arghya&Tiwari, A. &Bhasin, P.S. &Mitra, M.. (2011). Pharmacological and pharmaceutical profile of Gliclazide: A review. Journal of Applied Pharmaceutical Science. 1. 11-19.
9. Liangjie Xu[1]*, Fen Zhang[1]*, Yi Liang[1], Tinpan Fan[1], Cuicui Zhou[1], Wei YuanDOI: 10.20452/pamw.16473 Published online: March 30, 2023
10. Association of Left Ventricular Diastolic Dysfunction With Cardiovascular Outcomes in Patients With Pre-dialysis Chronic Kidney Disease: Findings From KNOW-CKD StudySang HeonSuh1 Tae Ryom Oh1 Hong Sang Choi1 Front. Cardiovasc. Med., March 25 2022Sec. General Cardiovascular Medicine
11. Cm W, Pillai G, Divakar A, Bhaskaran R. Left Ventricular Diastolic Dysfunction in Type 2 Diabetes Mellitus: A Single-Centre Observational Study From a Tertiary Care Hospital in South India. Cureus. 2023 Feb 6;15(2):e34667. doi: 10.7759/cureus.34667. PMID: 36777969; PMCID: PMC9905643.
12. MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside By Margherita Ratti, Andrea Lampis, Michele Ghidini, MassimilianoSalati, Milko B. Mirchev, Nicola Valeri, JensC. Hahne • May 25, 2020
13. Saini VM, Liu KR, Surve AS, Gupta S, Gupta A. MicroRNAs as biomarkers for monitoring cardiovascular changes in Type II Diabetes Mellitus (T2DM) and exercise. J Diabetes MetabDisord. 2022 Jul 7;21(2):1819-1832. doi: 10.1007/s40200-022-01066-4. PMID: 35818628; PMCID: PMC9261151.
14. Scrutinio D, Conserva F, Passantino A, Iacoviello M, Lagioia R, Gesualdo L. Circulating microRNA-150-5p as a novel biomarker for advanced heart failure: A genome-wide prospective study. The Journal of Heart and Lung Transplantation: the official publication of the International Society for Heart Transplantation. 2017;36(6):616–24. Epub 2017/03/06. pmid:28259597
15. Tang Y, Wang Y, Park KM, Hu Q, Teoh JP, Broskova Z, et al. MicroRNA-150 protects the mouse heart from ischaemic injury by regulating cell death. Cardiovascular research. 2015;106(3):387–97. Epub 2015/04/01. pmid:25824147.

16. Liao JM, Cao B, Zhou X, Lu H. New insights into p53 functions through its target microRNAs. Journal of molecular cell biology. 2014;6(3):206–13. Epub 2014/04/18. pmid:24740682.
17. Micro-RNA 150-5p predicts overt heart failure in patients with univentricular heartsMasoodAbu-Halima, EckartMeese, Mohamad Ali Saleh, AndreasKeller, HashimAbdul-Khaliq, TanjaRaedle-Hurst Published: October 10, 2019
18. Vascular benefits of Gliclazide beyond glycemic control, Paul E Jennings November 2000Metabolism 49(10 Suppl 2):17-20 November 200049(10 Suppl 2):17-20.
19. National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 3475, Gliclazide. Retrieved May 8, 2024
20. Effects of Gliclazide on uric acid and C-reactive protein in alloxan-induced diabetic ratsJanuary 2013International Journal of TropicalMedicine 8(1):34-38January 20138(1):34-38, OjulariLekan Sheriff, S. A. Biliaminu, Elizabeth O Dangana
21. Lu TX, Rothenberg ME. MicroRNA. J Allergy Clin Immunol. 2018;141: 1202–1207. 10.1016/j.jaci.2017.08.034
22. Domenico Scrutinio, MD, a Francesca Conserva, PhD, a,b Andrea Passantino, MD, a Massimo Iacoviello, the Journal of Heart and Lung Transplantation, Circulating microRNA-150-5p as a novel biomarker for advanced heart failure: A genome-wide prospective study p.619.
23. Goren Y, Kushnir M, Zafrir B, Tabak S, Lewis BS, Amir O. Serum levels of microRNAs in patients with heart failure. European Journal of Heart Failure
24. Zhonghua Ling, Gentao Fan, Danhua Yao, Jianning Zhao, Yinhua Zhou, Jinzhu Feng, Guangxin Zhou, Yong Chen • November 22, 2019, MicroRNA-150 functions as a tumor suppressor and sensitizes osteosarcoma to doxorubicin-induced apoptosis by targeting RUNX2