Letter

Diabetes Metab J 2023;47:879-881
https://doi.org/10.4093/dmj.2023.0328
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Glimepiride Compared to Liraglutide Increases Plasma Levels of miR-206, miR-182-5p, and miR-766-3p in Type 2 Diabetes Mellitus: A Randomized Controlled Trial (*Diabetes Metab J* 2023;47:668-81)

Da Young Lee

Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea

Type 2 diabetes mellitus (T2DM) is a consequence of various pathogenic processes, including insulin resistance and relative impairment in insulin secretion. It is also a major risk factor for cardiovascular disease (CVD), which remains a leading cause of death among patients with diabetes [1]. However, classic biomarkers, such as lipid levels, glycosylated hemoglobin, and C-reactive protein levels, have limitations in predicting the risk of CVD [2]. Several novel biomarkers from different pathophysiological pathways have been identified to predict CVD, and the incorporation of these biomarkers into risk assessment may enhance risk stratification in secondary prevention [2].

MicroRNA (miRNA) is a short, single-stranded, non-coding RNA molecule consisting of about 22 nucleotides that play critical roles in regulating gene expression and are prevalent in human plasma and other bodily fluids [3]. It is involved in both RNA silencing and post-transcriptional regulation of gene expression. MiRNA functions by base-pairing with complementary sequences in mRNA molecules, which then silences messenger RNA (mRNA) molecules by cleaving the mRNA strand into two pieces, destabilizing mRNA by shortening its poly(A) tail, or translating the mRNA into proteins [3]. The human genome encodes nearly 2,300 miRNAs.

In humans, nearly 2,300 miRNA are encoded and appear to target about 60% of genes. Many miRNAs are evolutionarily conserved, which implies that they have important biological functions. miRNAs can also act as potential biomarkers for various diseases [4].

A growing body of evidence has suggested that circulating miRNAs could be potential biomarkers for T2DM [5]. For instance, circulating miRNA-21 has been identified as an early predictor of reactive oxygen species-mediated damage in subjects with high risk of developing diabetes and in drug-naïve T2DM [5]. Moreover, miRNAs play an important role in metabolic homeostasis through regulation of multiple genes [6]. They have thus attracted substantial scientific interest as diagnostic and prognostic biomarkers in T2DM [6]. Various miRNAs, as well as their target genes, are implicated in the complex pathophysiology of T2DM [6]. According to some results, miR-30a-5p, miR-30d-5p and miR-30c-5p are the most widely regulated miRNAs across all specified ontologies; hence they are the most promising biomarkers of T2DM [6].

In the context of CVD, platelet activation is one of the underlying mechanisms of atherosclerosis, which is a common T2DM complication, often leading to ischemic events in the later stages of the disease [6]. Platelets contain large amounts of miRNAs that are found in circulating body fluids, including the blood [6]. These miRNAs have attracted substantial scientific interest as diagnostic and prognostic biomarkers in T2DM

Corresponding author: Da Young Lee https://orcid.org/0000-0003-1907-2859
Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
E-mail: ddkristin412@gmail.com

[6]. A common gene (protein kinase cAMP-dependent type I regulatory subunit alpha [PRKAR1A]) linked to glucose metabolism, blood coagulation, and insulin signaling is targeted by miRNAs in T2DM [6].

In another study, exosomal miRNAs were demonstrated to play a significant role in the development and progression of diabetic heart disease (DHD) [7]. These circulating miRNAs have the potential to act as biomarkers under DHD conditions. Additionally, they can also affect the progression of disease under diabetic conditions [7]. A systematic review and meta-analysis of miRNA expression profiling in heart failure (HF) identified 57 consistently dysregulated miRNAs related to HF, including miR-21, miR-30c, miR-210-3p, let-7i-5p, miR-129, let-7e-5p, and miR-622 [8]. Dysregulated miRNAs have been linked to various cardiovascular pathologies and have provided new perspectives on disease mechanisms and potential diagnostic and therapeutic targets [4,8]. Further validation in larger-scale studies is needed to verify these conclusions [9].

Research related to circulating miRNAs and diabetes drugs is still limited. However, circulating miRNAs can provide promising opportunities for diagnosis and management of diabetes [6]. In a study entitled, "Glimepiride compared to liraglutide increases plasma levels of miR-206, miR-182-5p, and miR-766-3p in type 2 diabetes mellitus: a randomized controlled trial," Scherbak et al. [10] conducted post hoc analysis of a randomized controlled trial comparing metformin plus liraglutide 1.8 mg versus metformin plus glimepiride 4 mg during 18 weeks in patients with T2DM and subclinical HF. In this study, the authors focused on the potential influence of two different classes of glucose-lowering drugs, glimepiride and liraglutide, both widely used glucose-lowering agents, on the expression patterns of circulating miRNAs in individuals with T2DM [10].

This study yielded several noteworthy findings:

1. Glimepiride treatment led to significant changes in the expression levels of specific circulating miRNAs, including miR-206, miR-182-5p, and miR-766-3p.
2. Multivariate analysis indicated that the effects of glimepiride on miRNA expression patterns were more pronounced compared to liraglutide treatment.
3. Univariate analysis revealed that miR-182-5p played a significant role in the observed changes in diastolic functional reserve index.

The paper's findings suggest that miRNAs may serve as potential biomarkers for monitoring the effects of glucose-lowering drugs and their impact on cardiovascular health in T2DM patients. While glimepiride's effects on miRNAs were more pronounced, the specific mechanisms underlying these changes remain to be elucidated. This research may open avenues for further investigation into the potential impact of glucose-lowering drugs (e.g., sodium-glucose cotransporter 2) on circulating miRNA profiles and cardiovascular health in T2DM patients. In addition, this research indicate that miRNAs may have potential as biomarkers for the selection of personalized drugs and treatment strategies [5]. These studies are still in their early stages, and more research is needed on whether specific miRNAs can be used to predict or monitor the effects of diabetes drugs.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Ma CX, Ma XN, Guan CH, Li YD, Mauricio D, Fu SB. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. Cardiovasc Diabetol 2022;21:74.
2. Wong YK, Tse HF. Circulating biomarkers for cardiovascular disease risk prediction in patients with cardiovascular disease. Front Cardiovasc Med 2021;8:713191.
3. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell 2009;136:215-33.
4. Kaur A, Mackin ST, Schlosser K, Wong FL, Elharram M, Delles C, et al. Systematic review of microRNA biomarkers in acute coronary syndrome and stable coronary artery disease. Cardiovasc Res 2020;116:1113-24.
5. Kraczkowska W, Stachowiak L, Plawski A, Jagodzinski PP. Circulating miRNA as potential biomarkers for diabetes mellitus type 2: should we focus on searching for sex differences? J Appl Genet 2022;63:293-303.
6. Pordzik J, Jakubik D, Jarosz-Popek J, Wicik Z, Eyileten C, De Rosa S, et al. Significance of circulating microRNAs in diabetes mellitus type 2 and platelet reactivity: bioinformatic analysis and review. Cardiovasc Diabetol 2019;18:113.
7. Chandrasekera D, Katare R. Exosomal microRNAs in diabetic heart disease. Cardiovasc Diabetol 2022;21:122.
8. Shen NN, Wang JL, Fu YP. The microRNA expression profiling in heart failure: a systematic review and meta-analysis. Front Cardiovasc Med 2022;9:856358.

9. Abdallah HY, Hassan R, Fareed A, Abdelgawad M, Mostafa SA, Mohammed EA. Identification of a circulating microRNAs biomarker panel for non-invasive diagnosis of coronary artery disease: case-control study. BMC Cardiovasc Disord 2022;22:286.

10. Scherbak NN, Kruse R, Nystrom T, Jendle J. Glimepiride compared to liraglutide increases plasma levels of miR-206, miR-182-5p, and miR-766-3p in type 2 diabetes mellitus: a randomized controlled trial. Diabetes Metab J 2023;47:668-81.