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NOVEL TRANSLATIONAL METHODS

Diabetes Exacerbates Myocardial Ischemia Reperfusion Injury by Down-Regulation of MicroRNA and Up-Regulation of O-GlcNAcylation

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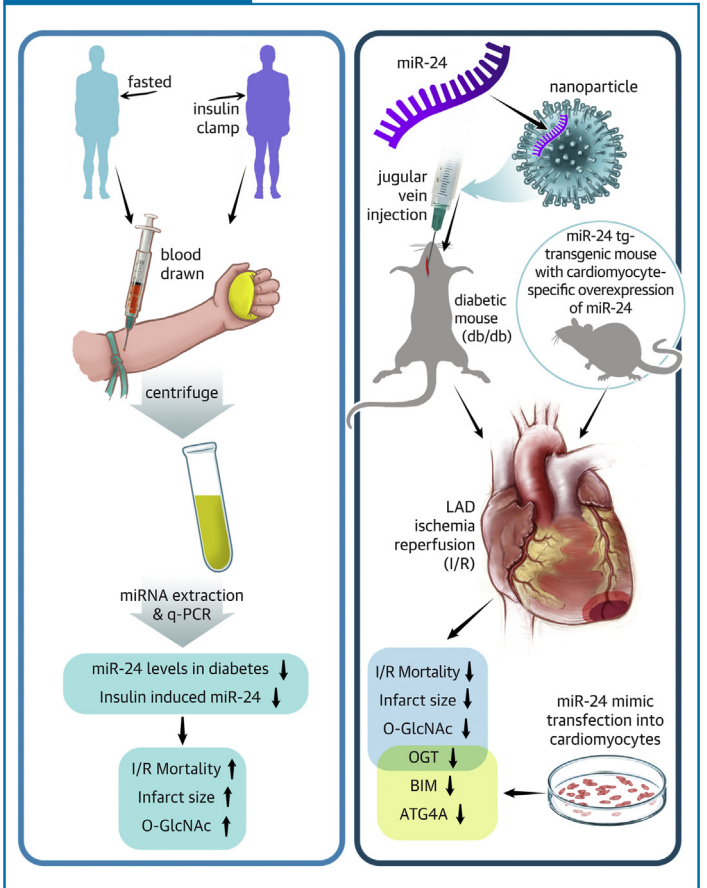
VISUAL ABSTRACT



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HIGHLIGHTS

- **Optimal treatment for patients with diabetes and myocardial infarction remains a challenge.**
- **Hyperglycemia- and hyperinsulinemia-induced miR-24 reduction and O-GlcNAcylation in the diabetic heart contributes to poor survival in diabetic myocardial ischemia reperfusion (I/R) and increased infarct size post-I/R.**
- **Overexpression of miR-24 in murine hearts significantly reduces myocardial infarct size.**
- **miR-24 targets multiple key proteins including O-GlcNac transferase, ATG4A (a key protein in autophagy), and BIM (a pro-apoptosis protein) to protect the myocardium from I/R injury.**
- **miR-24 is a promising therapeutic candidate for diabetic I/R injury.**

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ABBREVIATIONS AND ACRONYMS

ATG4A = autophagy-related gene 4a

BIM = Bcl-2-like protein 11

CVD = cardiovascular disease

DM = diabetes mellitus

I/R = ischemia reperfusion

MI = myocardial infarction

OGT = O-GlcNac transferase

SUMMARY

Management for patients with diabetes experiencing myocardial infarction remains a challenge. Here the authors show that hyperglycemia- and hyperinsulinemia-induced microRNA-24 (miR-24) reduction and O-GlcNAcylation in the diabetic heart contribute to poor survival and increased infarct size in diabetic myocardial ischemia reperfusion (I/R). In a mouse model of myocardial I/R, pharmacological or genetic overexpression of miR-24 in hearts significantly reduced myocardial infarct size. Experimental validation revealed that miR-24 targets multiple key proteins, including O-GlcNac transferase, ATG4A, and BIM, to coordinately protect the myocardium from I/R injury. These results establish miR-24 as a promising therapeutic candidate for diabetic I/R injury. (J Am Coll Cardiol Basic Trans Science 2018;■:■–■) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation.

Diabetes mellitus (DM) is of growing concern, with a prevalence approaching 400 million worldwide and 30 million in the United States (1). Type 2 diabetes mellitus (T2DM), accounting for approximately 95% of DM, is particularly increasing due to insulin resistance from obesity (1). Both type 1 diabetes mellitus (T1DM) and T2DM enhance the risk for cardiovascular disease (CVD) by 2- to 6-fold (2), with mortality arising predominantly from acute thrombotic cardiovascular events (3). Intensive glycemic control appears to reduce the risk of CVD in T1DM (4). In contrast, whether there is a beneficial role for intensive glycemic control on CVD in T2DM remains unclear (5–13).

Over the past several years it has become clear that alterations in the expression of microribonucleic acid (microRNA or miRNA) contribute to the pathogenesis of diabetes (14–18). MicroRNAs are small (~22 nt) regulatory ribonucleic acid (RNA) molecules that functionally modulate the activity of specific messenger RNA targets involved in a wide range of physiological and pathological processes (19). Profiling of microRNA expression in patients with diabetes has identified signatures associated with diagnosis, progression, prognosis, and response to treatment (14). We recently reported that miR-24 is significantly reduced in both T1DM (glycated hemoglobin [HbA1c] >6.5% with absent C-peptide levels) and T2DM (HbA1c >6.5% with normal or higher C-peptide levels) due to hyperglycemia, contributing to endothelial dysfunction (20). In the present study, we have uncovered a possible unifying mechanism that reconciles the disparate glucose control and cardiovascular disease results between T1DM and T2DM. Excessive insulin in T2DM patients, from the use of insulin therapy on a background of increased insulin, leads to dysregulation of a key protective miRNA: miR-24. These results may present a significant therapeutic dilemma in treating patients with both T2DM and MI (21–23). Our study suggests that therapeutic strategies leading to reduced insulin usage, and thus up-regulating miR-24, potentially protect against acute cardiovascular events in T2DM.

METHODS

HUMAN STUDIES. Clamp study. A total of 5 individuals with T1DM participated in the study and underwent hyperinsulinemic (2 mU/kg/min) hypoglycemic (glucose ~2.8 mmol/l) clamp studies, as previously described (24). Subjects had no medical problems other than T1DM and had a normal physical examination and electrocardiogram. Blood tests confirmed normal liver and renal function, but absent C-peptide levels. Briefly, an intravenous catheter was inserted into an antecubital vein; a primed

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All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Basic to Translational Science* author instructions page.

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