Overview

The mechanism by which hyperglycemia causes vascular complications in diabetes is poorly understood. We have advanced the concept that glycation-inactivation of the complement regulatory protein CD59 promotes complement-mediated tissue damage, a novel mechanism contributing to the pathogenesis of diabetes complications.

Human CD59, a key inhibitor of MAC formation contains a glycation-prone motif formed by residues K41 and H44 that is unique to humans (PGAS 2000). The K41-H44 motif makes human CD59 sensitive to inactivation by glycation, as demonstrated by site-directed mutagenesis.

We developed a specific ELISA for CD59 and used it to measure plasma GCD59 in samples from human studies evaluating acute and chronic glucose handling, and glucose responses to insulin therapy (AJH, 2013; JCEM 2014).

We hypothesized that blood levels of glycated CD59 (GCD59) represent a novel biomarker in diabetes and tested this hypothesis in 4 human studies.

Study 1

GCD59 was measured in 400 consecutive individuals with or without T2D.

Individuals with T2D had significantly higher GCD59

Non-diabetic: HbA1c 5.6 ± 0.03

Diabetic: HbA1c 8.7 ± 0.1

GCD59 was independently associated with Hba1c

Adjusted p STS Model p-value

Diabetes -36.5 -0.34 0.0001

No Diabetes 1.19 0.31 0.29 0.0001

Combined 19.8 0.21 0.65 0.0001

Study 2

GCD59 was measured in 109 individuals with no history of T2D who underwent an OGTT.

GCD59 was an independent predictor of 2-hour plasma glucose in OGTT

Univariate analysis

Variable β STS p-value

Gender (female) -36.5 -0.34 0.0001

Fasting Glucose (mg/dL) 1.19 0.31 <0.01

GCD59 (SPU) 10.5 0.23 0.027

Age (years) 0.66 0.16 0.04

Hba1c (%) 11.4 0.13 <0.01

BMI (kg/m²) -0.50 -0.07 0.43

Race (white) 4.52 0.04 0.56

GCD59 was also positively associated with 26-hour plasma glucose in univariate but not in multivariate analysis that included known univariate predictors of OGTT results

Study 3

A cohort of 21 individuals with poorly controlled diabetes were subjected to intensified insulin treatment for 8 weeks; blood glucose was measured 4 times/day (28 weekly) and other parameters weekly.

GCD59 paralleled the decline in weekly average glucose

Study 4

BACKGROUNDD: Gestational Diabetes Mellitus (GDM) is a major risk factor for adverse pregnancy outcomes. Screening for GDM with glucose load tests (1 or 2 steps) is now standard of care for all pregnant women. There is agreement that a simpler, shorter, patient-friendly, sensitive and specific test would be a much better screen for GDM.

Frozen archival plasma samples from the POPs study were assayed for GCD59.

FPO Study Participants tested (Mean ±SEM)

GCD59

Normal 1.19 0.31 0.29 <0.001

n = 54

n = 47 n = 54

We observed robust relationships between single blood levels of GCD59 and both acute (OGTT) and chronic measures of glucose handling (Hba1c) in non-pregnant individuals.

Single GCD59 measurements predicted GDM with high sensitivity and specificity and also paralleled glucose trends during active insulin therapy. We conclude that GCD59 may represent a promising new biomarker for the diagnosis and monitoring of pre-diabetes, diabetes and GDM.

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