

# Alternative Markers of Hyperglycemia and Risk of Diabetes

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**OBJECTIVE**—Fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) are of interest for monitoring short-term glycemic control in patients with diabetes; however, their associations with diabetes risk are uncharacterized.

**RESEARCH DESIGN AND METHODS**—We used Cox proportional hazards models to examine the associations of fructosamine, glycated albumin, and 1,5-AG with incident diabetes in 1,299 participants, from the Atherosclerosis Risk in Communities (ARIC) Study (2005–2006), who had no history of diagnosed diabetes at baseline. Incident diabetes was self-reported during annual telephone calls.

**RESULTS**—There were 119 new cases of diabetes during a median follow-up of 3.3 years. When compared with the lowest quartile, the fourth quartiles of fructosamine and glycated albumin were significantly associated with diabetes risk (hazard ratio [HR] 3.99 [95% CI 1.93–8.28] and 5.22 [2.49–10.94], respectively). The fourth quartile of 1,5-AG was associated with a significantly lower diabetes risk (0.27 [0.14–0.55]). Associations were attenuated but still significant after adjustment for hemoglobin A<sub>1c</sub> (A1C) or fasting glucose.

**CONCLUSIONS**—Fructosamine, glycated albumin, and 1,5-AG were associated with the subsequent development of diabetes independently of baseline A1C and fasting glucose. Our results suggest these alternative biomarkers may be useful in identifying persons at risk for diabetes.

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**N**ontraditional serum markers of short-term glucose control may enhance our ability to monitor hyperglycemia in persons with diabetes. Fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG) have been of recent interest, particularly for use in populations in which interpretation of glycated hemoglobin (A1C) may be problematic (1–3), such as in the setting of anemia, hemolysis, or renal disease (4–6). Fructosamine is produced when blood glucose forms ketoamines by covalently binding to serum proteins (7). Similarly, glycated albumin is formed via glycation of serum albumin (1). 1,5-AG is a serum monosaccharide that is excreted in the urine at an accelerated rate in the

presence of glycosuria (2). Whereas fructosamine and glycated albumin increase in the presence of hyperglycemia, 1,5-AG decreases in the setting of elevated circulating glucose concentrations (1,7). The 1,5-AG is approved by the Food and Drug Administration for short-term monitoring of glycemic control in persons with diabetes and has been suggested for use in monitoring postprandial hyperglycemia (8,9).

Despite growing interest in fructosamine, glycated albumin, and 1,5-AG for monitoring short-term glycemic control (3,10,11), few studies have measured these novel serum measures in initially nondiabetic populations. It is unknown if they are associated with the future

diagnosis of diabetes. It is also unknown if these markers provide distinct information apart from A1C or fasting glucose concentrations. The purpose of this study was to examine the relationships of fructosamine, glycated albumin, and 1,5-AG with the risk of diagnosed diabetes and to determine if the associations were independent of baseline A1C or fasting glucose.

## RESEARCH DESIGN AND METHODS

### Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a community-based prospective cohort of 15,792 adults originally enrolled from 1987 to 1989 from four United States communities and followed-up for more than two decades (12,13). In 2005–2006, 2,045 ARIC participants were selected via a stratified sampling plan for participation in the Carotid Magnetic Resonance Imaging substudy (CARMRI) (14). Physical examinations, medical interviews, and laboratory tests were conducted as part of the CARMRI clinical visit. Our study population was limited to the 1,299 participants who did not have a diagnosis of diabetes at the 2005–2006 CARMRI visit (hereafter called baseline), who were fasting  $\geq 8$  hours, who had valid measurements of A1C, fasting glucose, fructosamine, glycated albumin, and 1,5-AG, who were not missing case status information, and who were not missing relevant covariate data at baseline. Baseline diabetes status was determined by self-reported physician diagnosis of diabetes or use of glucose-lowering medications.

Written informed consent was obtained from all participants, and the study protocol was approved by Institutional Review Boards at all clinical sites.

### Glycemic markers

The A1C and glucose were measured in 2005–2006 as part of the CARMRI protocol using a Roche Hitachi 911 Analyzer. The A1C was measured using a Tinaquant II immunoassay method (Roche Diagnostics, Basel, Switzerland) and calibrated to the Diabetes Control and Complications Trial assay. Glucose was

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