

A1c for You and Me

Can a simple, inexpensive blood test identify early atherosclerosis?

In medicine, we are good at identifying people who are at high risk of a disease or illness. This study explores the risk of progression of atherosclerosis in a low-risk population. How can we identify people who are at low risk now but are likely to progress to high risk later? How do we then decide who should have aggressive intervention to prevent the progression of atherosclerosis? This study explores using a simple, inexpensive blood test that can be combined with other risk evaluation tools to help us understand who is truly low risk and who is likely to move up the risk scale with atherosclerosis.



Abstract

- **Background:** The metabolic injury caused by protein glycation, monitored as the level of glycated hemoglobin (HbA1c), is not represented in most risk scores (i.e., Systematic Coronary Risk Estimation or atherosclerotic cardiovascular disease risk scale).
- **Objectives:** The purpose of this study was to assess the association between HbA1c and the extent of subclinical atherosclerosis (SA) and to better identify individuals at higher risk of extensive SA using HbA1c on top of key cardiovascular risk factors (CVRFs).
- **Methods:** A cohort of 3,973 middle-aged individuals from the PESA (Progression of Early Subclinical Atherosclerosis) study, with no history of cardiovascular disease and with HbA1c in the nondiabetic range, were assessed for the presence and extent of SA by 2-dimensional vascular ultrasound and noncontrast cardiac computed tomography.
- **Results:** After adjusting for established CVRFs, HbA1c showed an association with the multiterritorial extent of SA (odds ratio: 1.05, 1.27, 1.27, 1.36, 1.80, 1.87, and 2.47 for HbA1c 4.9% to 5.0%, 5.1% to 5.2%, 5.3% to 5.4%, 5.5% to 5.6%, 5.7% to 5.8%, 5.9% to 6.0%, and 6.1% to 6.4%, respectively; reference HbA1c $\leq 4.8\%$; $p < 0.001$). The association was significant in all pre-diabetes groups and even below the pre-diabetes cut-off (HbA1c 5.5% to 5.6% odds ratio: 1.36 [95% confidence interval: 1.03 to 1.80]; $p = 0.033$). High HbA1c was associated with an increased risk of SA in low-risk individuals ($p < 0.001$), but not in moderate-risk individuals ($p = 0.335$). Relative risk estimations using Systematic Coronary Risk Estimation or atherosclerotic cardiovascular disease predictors confirmed that inclusion of HbA1c modified the risk of multiterritorial SA in most risk categories.
- **Conclusions:** Routine use of HbA1c can identify asymptomatic individuals at higher risk of SA on top of traditional CVRFs. Lifestyle interventions and novel antidiabetic medications might be considered to reduce both HbA1c levels and SA in individuals without diabetes.

I am always looking for ways to prevent disease and to risk stratify people to know when interventions are indicated. This study explored the association between HbA1c and subclinical atherosclerosis in a large group of asymptomatic middle-aged individuals without diabetes and with no known cardiovascular disease (CVD) and a low-moderate cardiovascular (CV) risk on the European Society of Cardiology SCORE index. The predictors included in the Score index are age, sex, systolic blood pressure, total cholesterol, and smoking status. All participants were also assessed by 2-dimensional vascular ultrasound (2DVUS) and cardiac computed tomography (heart scan) to see if vascular disease was present. The risk factors and imaging findings were then compared to hemoglobin A1c (HbA1c) levels to see if there was a correlation. Glucose sticking to proteins and fats is called glycation and the end products of this process cause vascular damage. HbA1c is a measure of glucose sticking to hemoglobin so HbA1c could be a marker of glucose sticking throughout the vascular tree, thus a glycation marker. Therefore, a low-risk individual with a high HbA1c might still have vascular disease, but since they don't have any symptoms, it is termed subclinical atherosclerosis.

This study found that HbA1c was a linear variable. As the level increased (meaning higher average blood glucose over the past 3 months) so did the risk of having subclinical atherosclerosis. When people get to the prediabetes level of HbA1c (5.7%-6.4%) there is evidence of subclinical atherosclerosis. But even at a level of 5.6, there was a significantly increased

risk of subclinical atherosclerosis. So, at an HbA1c level of 5.6% or higher, we need to consider risk factor modification to avoid progression of subclinical atherosclerosis. When it comes to blood glucose (and insulin levels), lower is better.

Glycated Hemoglobin and Subclinical Atherosclerosis in People Without Diabetes. Xavier Rossello, Sergio Raposeiras-Roubin, Belén Oliva, et al. J Am Coll Cardiol. 2021 Jun, 77 (22) 2777–2791.