Low Glycated Hemoglobin and Liver Disease in the U.S. Population

Andrea L. Christman, BA1,2 Mariana Lazo, MD, PhD1 2 Jeanne M. Clark, MD, MPH1,2,3 Elizabeth Selvin, PhD, MPH1,2

OBJECTIVE—To characterize the association of low HbA1c values (<4.0%) with liver enzymes and steatosis.

RESEARCH DESIGN AND METHODS—Cross-sectional study of 12,533 participants without diabetes aged <20 years in the Third National Health and Nutrition Examination Survey (1988–1994). Logistic regression models were adjusted for demographic, lifestyle, and health status variables.

RESULTS—HbA1c values ranged from 3.2 to 15.7%, and 84 participants had HbA1c <4.0% in the population (mean age 44, 52% female, 15% black or Hispanic). We observed J-shaped associations between HbA1c, and liver enzymes and hepatic steatosis. In adjusted models, HbA1c <4.0% was strongly associated with elevated alanine aminotransferase (OR 3.62 [95% CI 1.09–12.02]) and aspartate aminotransferase (6.80 [2.90–15.43]).

CONCLUSIONS—Low HbA1c values were associated with liver enzymes and steatosis in the U.S. population. Liver disease may partially explain the association of HbA1c with mortality and other long-term outcomes.

Recent studies show that low HbA1c in nondiabetic individuals is associated with increased mortality (1–3). The biologic processes underlying this association remain unclear, although liver disease has been hypothesized (2,4). Our objective was to examine the association between low HbA1c (<4.0%); elevated liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT); and hepatic steatosis in U.S. adults.

RESEARCH DESIGN AND METHODS—The Third National Health and Nutrition Examination Survey (NHANES III 1988–1994) was a cross-sectional survey of the U.S. population (5) and is described in detail elsewhere (6,7). We restricted our analyses to 12,533 participants without self-reported diabetes who had complete information on variables of interest.

HbA1c was measured via high-performance liquid chromatography (interassay coefficient of variation <2.0%), and values <4.0% or >11.0% were repeated for verification (7). If hemoglobin variants were present, affinity chromatography was used (7). We considered ALT, AST, and GGT elevated if they were above the laboratory-defined upper limit of normal: ALT, >40 units/L for men, >31 units/L for women; AST, >37 units/L for men, >31 units/L for women; and GGT, >51 units/L for men, >33 units/L for women (7). Hepatic steatosis detected by ultrasound was available for all participants aged 20 to 74 years and was defined as present or absent (8).

We used logistic regression to examine the association between HbA1c categories and elevated liver enzymes and hepatic steatosis. We repeated our analyses among participants who never consumed alcohol (n = 3,771). To assess the continuous associations, we fit restricted cubic splines (9). We conducted a sensitivity analysis excluding participants with anemia (hemoglobin <13.5 g/dL in men and <12.0 g/dL in women), presumed iron overload (serum ferritin saturation >44% and serum ferritin <10 ng/mL), or hepatitis B or C (n = 12,568, after exclusions). To compare low HbA1c to low fasting glucose, we modeled the 1st percentile versus the rest of the values for HbA1c (cutpoint, 4.0%) and fasting blood glucose (cutpoint, 73.4 mg/dL) in the morning fasting subsample (n = 8,747). All analyses accounted for the complex survey design (5).

RESULTS—Characteristics of the population are shown in Supplementary Table 1. HbA1c ranged from 3.2 to 15.7%. The prevalence of elevated ALT, AST, or GGT was 5.9, 5.3, and 13.8%, respectively. The prevalence of hepatic steatosis was 18.8%.

We observed J-shaped associations between HbA1c and elevated liver enzymes and hepatic steatosis (Fig. 1). The adjusted odds ratios (ORs) and 95% CIs are shown in Supplementary Table 2. In adjusted models with HbA1c 5.0–5.5% as reference group, HbA1c <4.0% was associated with elevated ALT (OR 3.62 [95% CI 1.09–12.02]) and AST (6.80 [2.90–15.43]). HbA1c <4.0% was also associated with elevated GGT and with hepatic steatosis, but these were not statistically significant. In addition, we found trends for higher total bilirubin, higher AST-to-ALT ratio, lower serum albumin, and lower platelets in individuals with HbA1c <4.0% (Supplementary Table 1).

When we restricted our analysis to participants with no history of alcohol consumption, HbA1c <4.0% was significantly associated with elevated ALT, AST, and GGT but not hepatic steatosis. After excluding participants with anemia, iron overload, hepatitis B or C, and HbA1c <4.0%, the ORs remained elevated but were no longer statistically significant.

HbA1c below the 1st percentile was associated with elevated ALT (OR 3.18 [95% CI 1.00–10.27]) and AST (5.80 [2.55–13.19]) but not with elevated GGT or hepatic steatosis (Supplementary Table 3). Fasting glucose below the 1st percentile...
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CONCLUSIONS—We observed J-shaped associations of HbA1c with liver enzymes and hepatic steatosis in this sample of U.S. adults (8). Specifically, HbA1c values <4.0% were significantly associated with elevated ALT and AST, while associations with hepatic steatosis and elevated GGT were less pronounced. After exclusion of participants with anemia, iron overload, and hepatitis B or C, these associations were no longer significant.

New recommendations for the use of HbA1c for diagnosis of diabetes (10) will likely result in more HbA1c testing. In light of evidence that very low HbA1c values are associated with total mortality (1–3), it is important to understand the clinical significance of low HbA1c values. Our study extends prior work in NHANES III, which reported elevated ALT and AST and a high prevalence of hepatitis C (11.1%) in individuals with low HbA1c (2). Hypothesized mechanisms by which low HbA1c values may be associated with both abnormal liver function and increased mortality include alcohol consumption, abnormal erythrocyte turnover and function (e.g., anemia and iron overload) (11,12), the viral hepatitides (2), and abnormally low glycemia (2). We found little evidence that this association was mediated by alcohol consumption. After excluding participants with anemia, iron overload, and hepatitis B or C, the association of HbA1c values <4.0% and elevated AST was no longer significant, suggesting these factors may partially mediate the association. We did not observe an association between low fasting glucose and liver disease, suggesting that the association with low HbA1c may be independent of glycemic pathways. Low HbA1c may be a general marker of poor health, analogous to low cholesterol levels (13).

Certain limitations of this study should be considered when interpreting our results. We had one measurement of the liver enzymes, and previous studies demonstrate variability in markers (14) and ultrasound is moderately reliable for detecting hepatic steatosis compared with liver biopsy (15). Although the NHANES III study protocol included repeat HbA1c testing for extreme HbA1c values and we performed sensitivity analyses, we could not exclude based on decreased erythrocyte life span per se (hemolysis), which may alter HbA1c (11). Strengths of this study include the large study population, rigorous data collection procedures, and nationally representative design. We examined the association of HbA1c with liver disease across the entire spectrum of HbA1c values in nondiabetic individuals, and we included a comprehensive liver disease assessment.

In conclusion, we observed J-shaped associations between HbA1c and elevated liver enzymes and hepatic steatosis by ultrasound in a representative sample of the U.S. population. Additional work is needed to determine how liver disease may be related to the observed associations of low HbA1c with total mortality.
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