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

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OBJECTIVE—To characterize the association of low HbA_{1c} 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—HbA_{1c} values ranged from 3.2 to 15.7%, and 84 participants had HbA_{1c} <4.0% in the population (mean age 44, 52% female, 15% black or Hispanic). We observed J-shaped associations between HbA_{1c} and liver enzymes and hepatic steatosis. In adjusted models, HbA_{1c} <4.0% was strongly associated with elevated alanine aminotransferase (OR 3.62 [95% CI 1.09–12.02]) and aspartate aminotransferase (6.80 [2.99–15.43]).

CONCLUSIONS—Low HbA_{1c} values were associated with liver enzymes and steatosis in the U.S. population. Liver disease may partially explain the association of HbA_{1c} with mortality and other long-term outcomes.

Diabetes Care 34:2548–2550, 2011

Recent studies show that low HbA_{1c} 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 HbA_{1c} (<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.

HbA_{1c} 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 HbA_{1c} 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 transferrin saturation >44% and serum ferritin <10 ng/mL), or hepatitis B or C (n = 11,593, after exclusions). To compare low HbA_{1c} to low fasting glucose, we modeled the 1st percentile versus the rest of the values for HbA_{1c} (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. HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 5.0–5.5% as reference group, HbA_{1c} <4.0% was associated with elevated ALT (OR 3.62 [95% CI 1.09–12.02]) and AST (6.80 [2.99–15.43]). HbA_{1c} <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 HbA_{1c} <4.0% (Supplementary Table 1).

When we restricted our analysis to participants with no history of alcohol consumption, HbA_{1c} <4.0% was significantly associated with elevated ALT, AST, and GGT but not hepatic steatosis. After excluding participants with anemia, iron overload, and hepatitis B or C, the ORs remained elevated but were no longer statistically significant.

HbA_{1c} 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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Received 20 May 2011 and accepted 29 August 2011.
DOI: 10.2337/dc11-0944
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-0944/-/DC1.

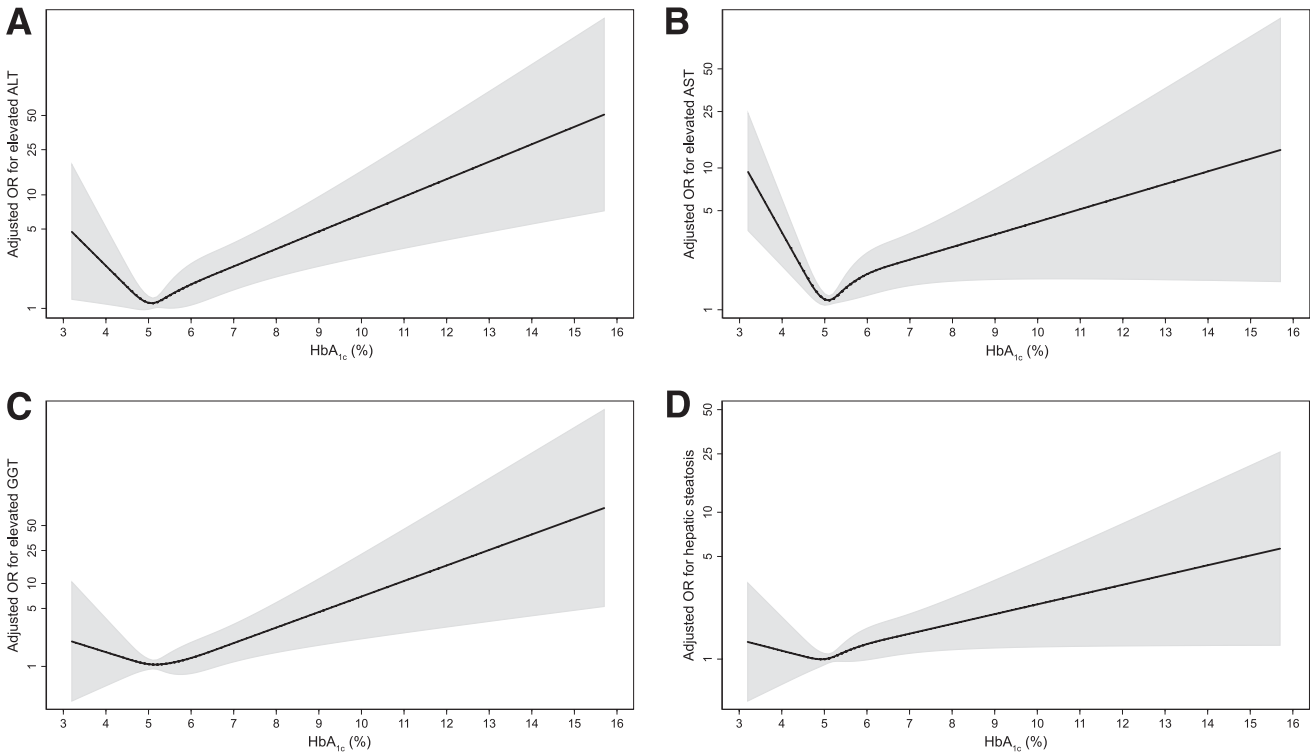

Figure 1—*Adjusted ORs of elevated ALT* (A)*, elevated AST* (B)*, elevated GGT* (C)*, and hepatic steatosis on ultrasound* (D) *by HbA_{1c} value. The figures show adjusted ORs from cubic spline modes. The shaded area is the 95% CI. The ORs were adjusted for age (years), race/ethnicity (non-Hispanic white; non-Hispanic black; Mexican American), sex (male; female), education (<12 years; 12 years; >12 years), income (below poverty level; above or at poverty level), smoking status (never; former; current ≤1 pack per day; current >1 pack per day), BMI (kg/m^2), history of hypertension, total cholesterol (mmol/L), HDL cholesterol (mmol/L), C-reactive protein (mg/dL), alcohol consumption (never; former low/moderate [<5 drinks/day for men or women]; former high [≥5 drinks/day for men or women]; current low [≤1 drink/day for women or ≤2 drinks/day for men]; current moderate/high [>1 to <5 drinks per day for women or >2 to <5 drinks per day for men]; current high [≥5 drinks/day for men or women]), history of cardiovascular disease, history of nonskin cancer, and health status (excellent; very good; good; fair; poor).*

was not significantly associated with elevated ALT, AST, GGT, or hepatic steatosis.

CONCLUSIONS—We observed J-shaped associations of HbA_{1c} with liver enzymes and hepatic steatosis in this sample of U.S. adults (8). Specifically, HbA_{1c} 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 HbA_{1c} for diagnosis of diabetes (10) will likely result in more HbA_{1c} testing. In light of evidence that very low HbA_{1c} values are associated with total mortality (1–3), it is important to understand the clinical significance of low HbA_{1c} 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 HbA_{1c} (2). Hypothesized mechanisms by which low HbA_{1c} 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 HbA_{1c} values <4.0% and elevated ALT and AST were 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 HbA_{1c} may be independent of glycemic pathways. Low HbA_{1c} 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 HbA_{1c} testing for extreme HbA_{1c} values and we performed sensitivity analyses, we were not able to assess the potential influence of decreased erythrocyte life span per se (hemolysis), which may alter HbA_{1c} (11). Strengths of this study include the large study population, rigorous data collection procedures, and nationally representative design. We examined the association of HbA_{1c} with liver disease across the entire spectrum of HbA_{1c} values in nondiabetic individuals, and we included a comprehensive liver disease assessment.

In conclusion, we observed J-shaped associations between HbA_{1c} 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 HbA_{1c} with total mortality.

Acknowledgments—A.L.C. was supported by National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Training Grant T32-DK-062707. M.L. was supported by NIH/NIDDK Grant R01-DK-083393 and by the American Diabetes Association. J.M.C. was supported by NIH/NIDDK Grant R01-DK-083393. E.S. was supported by NIH/NIDDK grants K01-DK-076595 and R01-DK-089174.

No potential conflicts of interest relevant to this article were reported.

A.L.C. analyzed data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. M.L. and J.M.C. researched data, contributed to discussion, and reviewed and edited the manuscript. E.S. contributed to discussion and reviewed and edited the manuscript.

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