To the Editor:

We appreciate the interest of Schiavon and colleague in our study investigating the impact of direct acting antiviral drugs on glycemic control in patients with diabetes mellitus and chronic hepatitis C virus (HCV) and we welcome the discussion about the limitations of hemoglobin A1c (HbA1c) testing in patients with cirrhosis. Accurate assessment of glycemic control in chronic liver disease is imperative given that glucose intolerance has been reported to be as high as 80%\(^1\) and that pre-liver transplantation alterations in glucose metabolism can persist long-term following transplantation.\(^2\)

We agree that HbA1c is an imperfect marker of glycemic control in any patient where shorter red blood cell (RBC) lifespan is observed.\(^3\) Cirrhosis patients are well described to have such conditions, namely related to portal hypertension with hypersplenism and blood loss due to acute gastroesophageal varical hemorrhage or chronic occult blood loss due to portal hypertensive gastropathy.\(^4\) In addition, nutritional compromise and hemolytic anemia are also common in cirrhosis, effectively leading to shorter RBC lifespans.\(^5\)

As Schiavon, \textit{et al.} mention, the largest inaccuracy in HbA1c testing is seen in the most advanced liver disease and significant underestimation of glycemic control has been well documented in liver transplant candidates with decompensated cirrhosis.\(^5\) We would point out that all 16 study patients with cirrhosis had well compensated cirrhosis without clinically significant portal hypertension and a mean Model for End Stage Liver Disease (MELD) score of just 8.6. Given the absence of portal hypertension associated hepatic decompensation, we feel that the suggested diagnostic inaccuracy due to the aforementioned issues seems impertinent.

Additionally, hemoglobin values for the entire cohort were normal at the start and end of treatment with DAAs. When limiting analysis to include only the 16 patients with cirrhosis, hemoglobin levels decreased from 14.6 g/dL to 14.4 g/dL. While ribavirin has been shown to induce hemolytic anemia,\(^6\) hemoglobin values actually increased while on treatment from 14.0 g/dL to 14.2 g/dL in the nine subjects (five with cirrhosis) who received ribavirin, effectively controlling for potential significant hemolytic anemia.

Although Schiavon, \textit{et al.} suggest the oral glucose tolerance test as the preferred assessment of glycemic control in patients with cirrhosis, the feasibility of administering this test to patients with cirrhosis is questionable. Patients with cirrhosis have significantly more gastrointestinal symptoms than patients without cirrhosis,\(^7\) many of which are byproducts of ascites, malnutrition or portal collopathy. As such, expecting these patients to tolerate an oral glucose tolerance test may be unreasonable as failure to complete the oral glucose tolerance test in the non-cirrhotic population has been reported to be as high as 15%.\(^8\)

In conclusion, while HbA1c has inherent limitations in patients with decompensated cirrhosis, we feel that in our highly selective cohort of both patients without cirrhosis and those with well compensated disease without portal hypertension, the HbA1c values are accurate and should be interpreted as such in the setting of the limitations outlined by the original manuscript. Future study of the impact of HCV therapy on insulin resistance should continue...
to account for the limitations of HbA1c testing until a more reliable metric for diabetes diagnosis and management arrives.

REFERENCES


Correspondence and reprint request:
Jonathan G. Stine, M.D., MSc, FACP
Division of Gastroenterology and Hepatology
University of Virginia.
JPA and Lee Street, MSB 2145, P.O. Box 800708.
Charlottesville, VA 22908-0708. United States.
Tel.: 434-924-2959. Fax: 434-244-7529