Diabetes and Chronic Liver Disease: Etiology and Pitfalls in Monitoring

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The liver is one of the major targets for insulin and its counterregulatory hormones, such as glucagon. Chronic liver disease (CLD) is often associated with glucose intolerance and diabetes. CLD is very prevalent in the general U.S. population and includes 2% of adult Americans (5.3 million) infected with hepatitis B or C and an estimated 31% or more with non-alcoholic fatty liver disease (NAFLD). The population of Americans with CLD continues to expand because of the epidemics of obesity and diabetes. In some subpopulations such as the morbidly obese, the prevalence of NAFLD is as high as 88%. The association of NAFLD with concurrent diabetes increases general mortality.

Liver cirrhosis from alcohol abuse is another important cause of CLD. Genetic conditions such as hemochromatosis (HC), cystic fibrosis, and sclerosing cholangitis are less frequent causes of CLD. Their prevalence is population-based: for HC, the homozygous state prevalence is 0.6–1% in whites. Individuals with HC have an odds ratio for diabetes as high as 5.4 compared to control subjects.

Assessing glucose control using A1C or fructosamine (FA) testing in CLD has significant limitations. These limitations must be clearly understood to avoid misinterpretation of the results. Ordering these tests should sometimes be avoided altogether in patients with a high likelihood of falsely low results.

Relationship Between CLD and Diabetes

The presence of CLD is associated with significant impairment in glucose homeostasis. Glucose intolerance is seen in up to 80% of patients with CLD, and frank diabetes is present in 30–60%. Depending on its etiology, CLD has a significant impact on hepatic glucose metabolism. One of the common causes of CLD is chronic hepatitis C. Chronic hepatitis C is accompanied by insulin resistance, which causes impaired glucose tolerance. Multiple mechanisms have been implicated, including fat accumulation in hepatocytes, increased insulin resistance secondary to increased tumor necrosis factor (TNF)-α, and direct or autoimmune damage to β-cells by the virus.

In a study of 229 Japanese patients with hepatitis C (27.6% of whom had cirrhosis and 8.9% had chronic active hepatitis), 17.5% had diabetes compared to 5.3% in the control population. Their average BMI was normal at 22.4 kg/m², and only 10% of the patients had a family history of diabetes compared to 40% of control patients with diabetes.

Different hepatitis C virus (HCV) genotypes seem to have different potential for interfering with glucose metabolism. In vitro studies reveal that genotype 1 and 3 HCV interfere with insulin signaling. Clinically, in nonobese, nondiabetic adults infected with genotype 1 or 2 HCV, insulin resistance correlated significantly with the viral load and was independent of patients’ visceral adipose tissue area as measured by abdominal computed tomography scan.

In patients with genotype 1 HCV, sustained responders to interferon-ribavirin therapy showed a significant decrease in insulin resistance compared to the baseline insulin resistance index. Also, the incidence of overt diabetes was reported to be lower in cured patients than in nonresponders to antiviral therapy. However, other studies did not find similar beneficial effects of long-term viral clearance.

The presence of diabetes is accompanied by poor response to antiviral medications. In a recent study, only 23% of patients with both hepatitis C and diabetes achieved sustained viral response to pegylated interferon and ribavirin combination therapy compared to 46% of patients with hepatitis C but no diabetes. Patients with concur-

IN BRIEF

Patients with chronic liver disease have a high prevalence of glucose intolerance and diabetes because of the presence of insulin resistance and β-cell dysfunction. A1C levels in these individuals are frequently falsely low, limiting the utility of A1C measurement as a diagnostic test and monitoring tool.
rent diabetes also reported more side effects to therapy. In contrast, no clear relationship between insulin resistance or diabetes and infection was seen with hepatitis B virus infection.\textsuperscript{19,20} There is a strong association between NAFLD and type 2 diabetes, and the prevalence of both disorders is increasing related to an increase in the prevalence of obesity.\textsuperscript{2} Both visceral obesity and hepatic fat correlate with insulin resistance, which is an important precursor to the development of type 2 diabetes. NAFLD can be a precursor of cirrhosis, which may have a further impact on glucose metabolism.

In a large study of > 800,000 patients in the Veterans Affairs health system, a twofold higher prevalence of NAFLD and hepato-cellular carcinoma in men with preexistent diabetes was reported compared to control patients without diabetes.\textsuperscript{21} The presumed sequence of events leading to the development of NAFLD and subsequent cirrhosis in these individuals are increased circulating free fatty acids induced by insulin resistance, saturation of the hepatocytes with VLDL cholesterol, and subsequent increased mitochondrial oxidative stress inducing inflammation, necrosis of hepatocytes, and increased collagen production in the liver.\textsuperscript{10}

### Parameters for Monitoring Glycemic Control

Several indicators of long-term glucose control are available. These indicators are glycated proteins (hemoglobin, albumin, and total proteins), and all are a reflection of glucose levels as well as of the turnover rate of their substrate (Table 1). The only test that is well standardized and in wide use is the A1C test.

#### A1C testing
Glycated hemoglobin, measured by high-performance liquid chromatography, is the gold standard for monitoring blood glucose control in diabetes and can now also be used to diagnose diabetes when its results are \(\geq 6.5\%).\textsuperscript{22} A1C represents the percentage of hemoglobin that suffers irreversible non-enzymatic glycosylation at one or two of the amino-terminal valine of the \(\beta\)-chain; the result is known as a Schiff base.

The product of this fast, unstable process can slowly form an irreversible ketoamine through Amadori rearrangement.\textsuperscript{23} This stable ketoamine form remains for the lifespan of the red blood cell (RBC) (~ 120 days), and its value has been shown to be well corre-

| **Table 1. Methods of Monitoring Diabetes Control in Patients With CLD: Clinical Relevance and Limitations** |
|-------------------------------|---------------------------------|----------------------------------|
| **Test**                      | **General Relevance**           | **Limitations in CLD and Observations** |
| A1C                           | Estimate of average blood glucose during the past 3 months | Likely to be falsely low. Avoid during or after antiviral hepatitis C therapy (hemolysis). Consider checking hemoglobin/hematocrit, liver function tests, and reticulocytes in every patient with CLD and diabetes. If there is severe anemia or high RBC turnover, expect A1C to be inaccurate, and consider alternative parameters for monitoring. |
| Fructosamine (FA)             | Estimate of average blood glucose during the past 2 weeks | Likely inaccurate in patients with dysproteinemia, very low serum albumin levels, or proteinuria. |
| Glycated albumin (GA)         | Not used in general practice; overall similar significance to FA | Similar to FA |
| Composite parameters (e.g., CLD-A1C) | An attempt to combine and then compensate for disadvantages and advantages of different markers | Not validated in clinical practice; not studied in patients with proteinuria |
| Frequent self-management of blood glucose | Relevant if blood glucose is checked several times a day at different times of the day; downloadable glucose meter memory readily reports blood glucose average. | Advise patients to check before and 2 hours after meals at different times of day. Appears to be best parameter to monitor in CLD. Easy to implement in motivated patients. Independent of therapy. |
| Continuous glucose monitoring | Currently recommended in insulin-treated patients, especially those with recurrent hypoglycemia episodes | Not offered routinely; not always covered by medical insurance. Considered off-label for patients not treated with insulin. |
related to the mean plasma glucose levels for this period. This has been validated by the Diabetes Control and Complications Trial and was reevaluated in the international A1C-Derived Average Glucose (ADAG) study.

A1C also correlates with the risk for developing chronic complications of diabetes. The degree of glycosylation is dependent on the degree of hyperglycemia, but also on the lifespan of the RBCs. Abnormal hemoglobins, many of them clinically silent, interfere with and can either falsely elevate or falsely lower A1C measurements depending on the testing method used.

The American Diabetes Association (ADA) current diabetes care standards assume that a normal A1C is ≤ 5.6%. Individuals are considered to be at risk for diabetes when their A1C is between 5.7 and 6.4% and are diagnosed with diabetes when their A1C is ≥ 6.5%. ADA also recommends A1C testing routinely in all patients with diabetes at initial assessment and then as part of continuing care, with a target of A1C of < 7% for microvascular disease prevention.

Of note, the ADAG trial, as well as similar earlier trials, excluded patients with a potentially altered relationship between A1C and average glucose values. In the ADAG study, the presence of anemia (hematocrit < 39% in men and < 36% in women), reticulocytosis, history of blood loss or transfusions, chronic renal or liver disease, and high-dose vitamin C or erythropoietin treatment were criteria for exclusion.

Fructosamine and glycated albumin
Fructosamine (FA) is a term used to describe proteins that have been glycated, forming stable ketoamines, by a similar nonenzymatic reaction with glucose as described for hemoglobin. Measuring FA by a spectrophotometric assay may be less expensive than measuring A1C, but the assay may be affected by hypertriglyceridemia, hyperbilirubinemia, hemolysis, and low serum protein and albumin levels. Some authors advocate correcting FA results for serum albumin or protein levels, but there is no consensus on applying this correction. The normal range of FA is method- and laboratory-dependent (by spectrophotometric assay, it ranges around 160–280 μmol/l).

In patients with stable glycemic control, there seems to be a linear relationship between FA and A1C. Currently, measuring FA is recommended in patients with abnormal hemoglobins and in those requiring monitoring for more recent changes in diabetes control, such as pregnant women with diabetes. The correlation of FA with average glucose has not been validated as well as the correlation of A1C with average glucose.

Glycated albumin (GA) has been advocated as a more accurate parameter compared to FA in some subgroups, such as patients undergoing hemodialysis. It can be expressed in absolute value (g/dl) or as percentage of total albumin. Because > 50% of the measured FA is represented by GA, the significance and limitations of this method are similar. Albumin has a half-life of 14–20 days—much shorter than that of the RBC. Therefore, these tests indicate average blood glucose levels over a 2- to 3-week period.

Assessing A1C in CLD
Among patients with CLD, anemia, portal hypertension, hypersplenism, and variceal bleeding can be common complications. These factors can contribute to longer or shorter RBC survival and can lead to alteration of the A1C. Factors such as nutritional anemia can lead to increased RBC survival and falsely elevated A1C levels, whereas bleeding and hemolysis can lower RBC survival time and falsely lower A1C values. In our clinical experience, we frequently find that individuals with cirrhosis have A1C levels that are much lower than their fingerstick blood glucose measurements would suggest.

Very few studies are dedicated to systematically evaluating the accuracy of A1C in CLD patients. In a screening of 20,000 measurements of A1C, patients with a very low A1C (below the normal range) were analyzed further. Of nine abnormally low results, six were the result of cirrhosis, two resulted from hematological neoplasms with anemia, and one was due to hemoglobin F.

In a small case series (15 patients with compensated cirrhosis and 20 patients with chronic hepatitis), 40% of cirrhotic patients with diabetes had A1C levels below reference range for patients without diabetes, whereas FA was elevated in one-third of the patients and normal for the others.

Anemia is frequently present in CLD. Occasionally, autoimmune hepatitis can be associated with hemolytic anemia, but hypersplenism is more frequent as a cause of reduced RBC survival. Iron deficiency, vitamin B12 and folate deficiency anemia (often seen in alcoholism or malnutrition), and anemia of chronic disease are other common causes of anemia.

Theoretically, RBC lifespan is longer in nutrient-deficiency anemia, which would lead to an elevation in A1C. However, studies in patients without diabetes who have iron deficiency have reported a significant decrease in baseline A1C of 1.2–1.3% once iron deficiency is corrected.

In a recently published study based on data from the National Health and Nutrition Examination Survey, iron deficiency was associated with a shift in A1C distribution from < 5.5
to ≥ 5.5% in > 6,600 adult women without diabetes.

In late pregnancy, women without diabetes who had a drop in ferritin, transferase, and mean corpuscular hemoglobin tended to have an increase of AIC unrelated to glucose levels or GA concentration. Similar findings were recently reported in pregnant women with diabetes.

Reports in children with type 1 diabetes have also found a decrease in AIC with iron repletion independent of blood glucose control. In contrast, some studies in children without diabetes have failed to replicate a difference between iron-deficient and iron-replete subjects.

The clinical significance of these findings remains to be studied. Most likely, stringent physiological mechanisms are in place to limit the lifespan of older RBC’s; therefore, the increase in AIC resulting from iron or vitamin deficiency should be minimal. Some studies suggest that the decrease in AIC is limited to the “active phase” of recovery from iron or vitamin deficiency when RBC turnover is increased.

Measuring FA or GA in CLD
FA and GA are parameters of diabetes control that are less standardized and less frequently used. They can potentially be inaccurate in CLD as well. It is known that the half-life of albumin is significantly increased in liver disease from a normal half-life of 10.5 days to 11.3 days in chronic hepatitis and up to 15.9 days in cirrhosis, mainly through decreased degradation induced by the hypoalbuminemia itself.

Albumin levels can correlate with liver injury but not with the activity of the underlying disease by histology. Other factors, such as protein-losing gastroenteropathy related to portal hypertension or the presence of nephropathy, can contribute to hypoalbuminemia and affect albumin turnover. The extent of glycation seems to be dependent on the plasma albumin concentrations; therefore, opposing trends can skew FA/GA in different directions, making interpretation of the results quite difficult.

In an attempt to take advantage of albumin and hemoglobin turnover being altered in opposite directions by liver disease, a novel parameter was recently proposed. “CLD-AIC” is a conventional parameter defined as [(AIC + GA)/3]/2, where GA is expressed as the percentage of glycated albumin out of the total albumin. The authors studied 82 CLD patients (including 24 patients with diabetes) and found that CLD-AIC was well correlated to the AIC as calculated from monitoring blood glucose seven times a day. CLD-AIC was independent of liver function estimated by cholinesterase levels, platelet count, or albumin levels. Patients with renal disease were excluded from this study. Larger population data are needed to validate the use of new parameters such as CLD-AIC.

Impact of Medications on Monitoring
Special attention should be given to CLD patients on certain medications that can significantly alter the erythrocyte lifespan. Hemolysis is a known side effect of ribavirin therapy for hepatitis C. Severe anemia develops in ~ 10% of treated patients and is likely related to extensive ribavirin accumulation in erythrocytes followed by inhibition of intracellular energy metabolism and oxidative membrane damage. This leads to an accelerated extravascular hemolysis by the reticulo-endothelial system. Ribavirin can decrease the erythrocyte lifespan from 120 to 40 days.

In a study of 20 patients with chronic hepatitis without a history of glucose intolerance or diabetes, 20% had AIC results < 4.5%. In contrast, their FA levels were normal. In the subgroup treated with ribavirin, half of AIC results were below the nondiabetic reference. A case report has described an individual with CLD treated with ribavirin, who had a dramatic decrease in the AIC from 11 to 4.9 and then 4.4%. This decrease was related to ribavirin adverse effects rather than to improvements in blood glucose control.

Other Options for Monitoring Blood Glucose in CLD
Self-monitoring of blood glucose
Checking fingerstick blood glucose frequently and at different times of the day allows an accurate estimate of the real blood glucose control in all patients with diabetes. This strategy of monitoring might be of particular interest in CLD patients, given the drawbacks of the standard parameters discussed above. Downloading glucose readings from the glucose meter memory is particularly useful because computer programs can report an average blood glucose that can be compared to measured AIC (and the derivate estimated average glucose). Thus, any discrepancy between monitoring parameters can be readily evaluated.

Continuous glucose monitoring (CGM) with interstitial sensors is another option to be considered. At present, CGM is considered to be “a useful supplemental tool for adult patients on insulin that present with hypoglycemia unawareness and/or frequent hypoglycemic episodes.” CLD patients—especially those with cirrhosis—have poor hepatic glycogen reserve and therefore are at risk for severe hypoglycemic events. Moreover, insulin is a preferred therapy in cirrhotic patients with diabetes because most oral hypoglycemic agents have some potential for liver toxicity or altered metabolism in CLD. Thus, use of CGM should be considered in selected cases and espe-
frequently in insulin-treated patients with recurrent hypoglycemic episodes.

Conclusions
Measuring glycemic control can be challenging in patients with CLD. A summary of the different measures available and their strengths and limitations is shown in Table 1.

Measuring A1C is unreliable in patients with cirrhosis and in many patients with chronic hepatitis. Any increase in hemoglobin turnover secondary to gastrointestinal bleeding, hemolysis by hypersplenism, or medications can grossly underestimate glucose levels and thus give false reassurance to patients and physicians regarding the risk for developing diabetes complications. In view of current ADA recommendations, it may also delay diagnosis of diabetes if A1C is used for screening in this group of patients.

Because A1C is currently being used as both a diagnostic test and a parameter of good practice in monitoring glucose control in diabetic patients, it is easy to overlook the fact that its relationship with blood glucose has been established in patients without anemia, chronic kidney or liver disease, or therapies that can interfere with results. When measuring A1C in patients with CLD, physicians should be fully aware of its limitations. If A1C is measured in these patients, levels and dynamics of total hemoglobin, reticulocytes, medication use, and liver function tests should be reviewed for better interpretation of the results. FA or GA can be used as secondary parameters of monitoring blood glucose control, but they also have limitations that must be understood.

Reviewing actual blood glucose meter readings, provided that patients check their blood glucose frequently and at different times during the day, reflects the true degree of glucose control more accurately. CGM devices have the potential of measuring glycemic excursions in patients with CLD and should be considered in patients who use insulin, especially if they present with recurrent hypoglycemia.

In conclusion, an individualized approach tailored to the different stages of liver disease should be considered when monitoring diabetes in these challenging patients.

REFERENCES

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