ketoacidosis will have positive urine ketone readings, but hyperglycemia is not usually present. Positive urine ketone readings are found in up to 30% of first morning urine specimens from pregnant women (with or without diabetes), during starvation, and after hypoglycemia (295).

*Blood ketone determinations.* Blood ketone determinations that rely on the nitroprusside reaction should generally not be used for diagnosis of DKA as results do not quantify βOHB, the predominant ketone in DKA. If βOHB measurements are not readily available, increased blood ketones by the nitroprusside reaction, when combined with hyperglycemia and tests confirming metabolic acidosis, would confirm the presence of DKA. Blood ketone determinations that use the nitroprusside reaction should not be used to monitor the course of therapy in any setting, since AcAc and acetone may increase as βOHB falls during successful therapy (295, 298). Blood ketone determinations that measure βOHB specifically are useful for both diagnosis (299, 301) and ongoing monitoring of DKA (298, 299). Resolution of acidosis or reduction in blood βOHB is traditionally the marker for successful treatment of DKA, rather than serial measurement of ketones by the nitroprusside reaction. One small study in children with DKA found that use of a POC assay for βOHB decreased time to conversion from intravenous to subcutaneous insulin. However, the comparator was conversion when urine ketones were negative, which is not a typical marker for resolution (308). Although some guidelines specifically recommend use of point-of-care (POC) blood βOHB to follow the course of treatment for DKA, others do not. A systematic review of the components of DKA management protocols in adults did not find strong evidence for any specific measurements in assessing the treatment course of DKA (309).

*Reference intervals.* βOHB reference intervals differ among assay methods, but concentrations in healthy individuals fasted overnight are generally <0.5 mmol/L. Individuals with well-documented diabetic ketoacidosis (serum bicarbonate <15 mmol/L, arterial pH <7.3, plasma glucose >14.9 mmol/L [250 mg/dL]) generally have βOHB concentrations >2 mmol/L (299).

#### EMERGING CONSIDERATIONS AND KNOWLEDGE GAPS/ RESEARCH NEEDS

Since hospitalization rates for DKA are increasing (310), further studies are needed to determine more optimal home testing strategies to detect impending ketonemia. Studies are needed to establish cutoffs for βOHB for diagnosing DKA and to evaluate whether following βOHB concentrations during treatment of DKA offers any clinical advantage over more traditional management approaches (e.g., measurements of serum bicarbonate, anion gap, or pH) (299).

## Hemoglobin $A_{1c}$

#### DESCRIPTION/INTRODUCTION/TERMINOLOGY

Glycation refers to the nonenzymatic attachment of glucose to available amino groups on proteins. The extent of glycation reflects the exposure of the protein to mean glycemia integrated over time as a function of the lifespan and turnover of the protein. Hemoglobin in the RBC has an average circulating lifespan of approximately 120 days and glycated hemoglobin therefore usually indicates the average glucose concentration over the preceding 60 to 90 days. The terms glycated hemoglobin, glycohemoglobin, glycosylated, and glucosylated hemoglobin, Hb $A_1$, Hb $A_{1c}$, and $A_{1c}$ have all been used; however, these terms are not interchangeable. The current acceptable term for glycation of hemoglobin in general is glycated hemoglobin (GHb). Hb $A_{1c}$ is the specific glycated species that is modified by glucose on the N-terminal valine of the hemoglobin beta chain. Assay methods that measure total glycated hemoglobins (e.g., boronate affinity methods) should be calibrated to report results equivalent to Hb $A_{1c}$ to harmonize results. Hb $A_1$ is composed of Hb $A_{1a}$, Hb $A_{1b}$, and Hb $A_{1c}$ and should not be measured or reported. The term "A1C test" is commonly used and recommended by the ADA in place of Hb $A_{1c}$ to facilitate communication with people with diabetes. As described herein, most of the clinical outcome data that are available for the effects of metabolic control on complications [at least for the DCCT (50) and UKPDS (49, 52)] used assay methods that quantified Hb $A_{1c}$. In order to harmonize results, most clinical studies of glucose control recommend the use of Hb $A_{1c}$ assays that are traceable to the DCCT assay, as was done in the UKPDS. In this paper, we use the abbreviation GHb to include all forms of glycated hemoglobin and Hb $A_{1c}$ to describe the consensus accepted measurement to which all assays are translated and reported for use in clinical practice.

In addition to GHb assays, approved and commercially available assays that measure total glycated protein (termed fructosamine) or glycated albumin in the serum or plasma are available. Concentrations of these glycated proteins also reflect mean glycemia, but over a much shorter time (15 to 30 days, reflecting the turnover of albumin) than GHb (60 to 90 days) (295, 311–316). However, the clinical utility of glycated proteins other than hemoglobin has not been clearly established. Few published studies have convincingly demonstrated a relationship between glycated protein levels and the chronic complications of diabetes (317).