

## Measures of Glycemic Control and The Case for More Frequent Testing of HbA1c

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Diabetes is a disease that is characterized by chronic hyperglycemia that causes glucose toxicity leading to long-term complications like retinopathy, neuropathy, and nephropathy. For diabetes disease management, people with diabetes and their healthcare providers currently use four or more measures of blood glucose. The four most commonly used measures are Self-Monitoring of Blood Glucose (SMBG), Fructosamine, Continuous Glucose Monitoring (CGM), and Hemoglobin A1c (Called HbA1c, A1c or glycated hemoglobin). In the future, Non-Invasive Glucose Monitoring may be possible and a number of companies are trying to develop this technology.

### Self-Monitoring of Blood Glucose (SMBG)

People with diabetes are able to test themselves using SMBG. To perform the test, a finger is pricked with a small needle and a drop of blood is placed onto a test strip in a small hand-held meter. In a few seconds, the meter displays the blood reading at that moment in time. Unfortunately, the USA and Europe use different units of glucose measurement. In the USA, the units are mg/dL and in Europe the units are “international units” (mmol/L). One can convert them by multiplying the mmol/L by 18 to get the mg/dL.

The history of SMBG has been published by Clarke and Foster [1]. In 1965 a research team at the Ames Research Division of Miles Laboratories under Ernie Adams went on to develop the first blood glucose test strip, the Dextrostix, a paper reagent strip which used the glucose oxidase/peroxidase reaction but with an outer semipermeable membrane which trapped red blood cells but allowed soluble glucose to pass through to react with the dry reagents [2]. A large drop of blood (approximately 50–100  $\mu$ L) was applied to the reagent pad, and after one minute the surface blood was gently washed away and the pad color visually assessed against a color chart to give a semiquantitative blood glucose value. In 1970, the Ames Research Division of Miles Laboratories

developed the first blood glucose meter. It combined dry chemistry test strips (Dextrostix) with reflectance photometry to measure blood glucose. These tests were only for the doctor’s office, not for home use. In 1980 Ames introduce the Dextrometer and a publication suggested home testing [3]. A technology breakthrough led to the development of electrochemical test systems which require much less blood and show good performance [4].

The major problem with SMBG is that it measures the current blood glucose value, but offer no indication of whether the blood glucose is increasing or decreasing. This had led to the development of Continuous Glucose Monitoring (CGM) described below.

### Fructosamine test

A fructosamine test has been available through laboratories since the early 1980s. This test measures the glycation of serum proteins and gives a measure of the average blood glucose over the previous 2 to 3 weeks. The test is useful for gestational diabetes and for those with hemoglobin abnormalities which interfere with the HbA1c test described below [5]. The main advantage of the test is that it can detect overall changes in blood glucose control within the previous few weeks, rather than months. So, when changes are being made in a diabetes treatment plan, this test may indicate in a more timely fashion than an A1c test how well the changes are working and whether other changes should be considered. Using a home test for fructosamine, this hypothesis was tested and published [6]. The study concluded that in the 3 months after a change in therapy for type 2 diabetes, weekly home testing of fructosamine, combined with therapeutic interventions led to a more rapid and significant improvement in glycemic control than did the usual regimen of glucose-only testing. This study did not test HbA1c for a comparison. Currently, the fructosamine test must be ordered and performed by your healthcare provider.

## Continuous Glucose Monitoring (CGM)

Continuous glucose monitoring gives much greater insight into the direction, magnitude, duration, frequency and possible causes of glucose fluctuations in response to meals, insulin injections, hypoglycemic episodes and exercise throughout the day [7]. Compared to conventional SMBG measurements performed four to six times a day, results are provided every 5 to 10 minutes every day. Systems are now available that are factory calibrated which eliminates the need for fingerstick blood samples. For CGM, a tiny needle containing the glucose-measuring chemistry is inserted on the arm or abdomen and begins sending the interstitial glucose information converted into blood glucose values to a cell phone or other receiver. Millions of CGM systems are in use today. By connecting a CGM with an insulin pump, an artificial pancreas is possible [8].

## Non-Invasive Continuous Glucose Monitoring (NICGM)

One of the major problems with SMBG was the need to be constantly pricking your finger in order to get a blood sample for testing. Not only can it be painful, but it makes testing in public more of a concern, both emotionally and for the proper disposal of needles and test strips. Newer CGM systems have eliminated the need for fingerstick blood sampling, but they systems require that the needle used for the CGM measurement be inserted and changed weekly. This is not nearly as painful as a fingerstick, but does involve skin penetration. In order to eliminate skin penetration and needles, researchers have been working on NICGM for many decades, with no successful commercial products on the market today [9]. One product was FDA cleared in 2001 (the GlucoWatch), but taken off of the market because of poor performance [10].

Most of the attempts at NICGM have used spectroscopic techniques such as Raman or near and far infrared spectroscopy. Several new companies continuously report progress and keep the hope alive for this breakthrough.

## Hemoglobin A1c (HbA1c)

After the relationship between glycemic control and the HbA1c concentration was demonstrated, many tests have been developed to determine the HbA1c concentration [11]. HbA1c measures the average blood glucose over the previous 2-3 months, however several recent reports have shown that HbA1c changes can be seen as soon as 2 weeks after a change in treatment is made [12-16]. As an index of long-term glycemic control and a risk predictor, the HbA1c concentration is an indispensable part of routine management of diabetes. Formerly only a laboratory test, a home test for HbA1c (A1cNow®) is now available and allows people with diabetes to see how changes to their therapy effects their glycemic control [17]. Once again, the USA reports test results differently that the international community. The USA reports results as a percent of the total hemoglobin while the International results are presented as mmol/mol. There is a linear relationship between results from the two methods, and the “master equation” is used to convert results between the two methods:  $\text{HbA1c SI unit (mmol/mol)} = 10.93 \times \text{HbA1c NGSP unit (\%)} - 23.50$  [18].

## Current controversy over HbA1c and CGM

Recently there has arisen a controversy over the use of HbA1c compared to using CGM as the gold standard for monitoring glycemic control [19]. With CGM, it is possible to calculate an “estimated HbA1c” (eHbA1c). In addition, different individuals can have a wide range of mean glucose daily glucose concentrations and still yield the same HbA1c. While this is true, now is not the time to stop measuring HbA1c. The reasons to continue to measure HbA1c include the following:

- HbA1c measurements have stood the test of time and the ranges separating normal, prediabetes and diabetes are accepted and used to help diagnose diabetes and manage it (Figure 1).
- The number of people with diabetes who have CGM is a very small percentage of the population with diabetes.
- Exactly what parameters to use to optimize the CGM reports and their “optimum” range have not been established. For example, should it be “daily average glucose” or “time in range” or other measure for optimum guidance of therapy?
- Recent studies have shown that HbA1c can change rapidly when a change is made to the diabetes management of the patient. These changes include lifestyle changes (diet, exercise) and therapy using drugs or nutritional supplements [12-16].
- The availability of a home test for HbA1c allows patients to be more involved in their diabetes management using more frequent HbA1c home testing. This information can be used by the healthcare provider to make changes to management much more expeditiously.

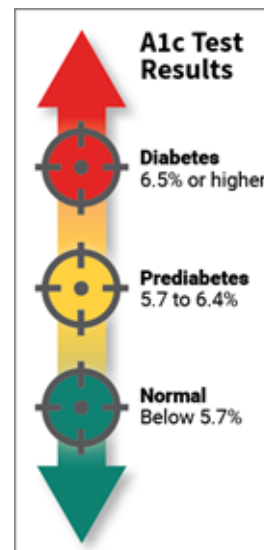


Figure 1: Interpretation of HbA1c test results.

## Conclusion

There has been tremendous progress in recent decades in the measurement of blood glucose with a goal of improving the management of diabetes. The advent of SMBG, CGM and home tests for HbA1c allow the person with diabetes to more rapidly make changes to improve their glycemic control and hopefully avoid the health consequences of uncontrolled diabetes. While

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CGM and non-invasive CGM may be the future of management, the tools exist today to help those suffering with diabetes.

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