

The meaning of the A1c blood test result

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INTRODUCTION

An important effect of the disease *diabetes mellitus* ("diabetes", for short), as untreated, is that the concentration of glucose (sugar) in the person's blood rises to an undesirable level. This in turn can lead to serious and often disastrous physiological effects.

Management of this disease in part emphasizes, through various therapy (perhaps the administration of insulin), maintaining the glucose concentration "most of the time" within a desirable range.

An important tool in monitoring and managing this therapy is a blood test called for short the "A1c test", which measures the effect of blood glucose on the blood's hemoglobin. The result of this test is often simplistically described as indicating "the person's average glucose concentration over the past several months".

Sadly, this is inaccurate as applies to the general situation. In this article, insight is given into how this test result arises and its real significance.

The author emphasizes that he is not a healthcare professional, and that this discussion is done from an scientific and mathematical perspective.

1 BACKGROUND

1.1 Hemoglobin

Hemoglobin is a complex protein, which, among other things, is responsible for the transport of oxygen through our body.

1.2 Red blood cells

Red blood cells, technically called *erythrocytes*, make up a large portion of human blood, and most of the hemoglobin in the blood is carried by these erythrocytes.

Erythrocytes have a short life span (typically 120 days or so), but new ones are continuously formed so as to replace the dead ones. This death and replacement process plays an important role in the model of the formation of the A1c value.

1.3 Glucose

Glucose (a type of sugar) exists in the plasma¹ of the human bloodstream as a result of the metabolism of the food eaten. The concentration of glucose in the blood plasma varies continuously over time, even within a day, as a result of the ingestion (and then metabolism) of various foods and the exercise that the person does (even walking from the dining table to the office is exercise!).

As mentioned in the Introduction, the concentration of glucose in the blood plasma is an important factor in the management of diabetes.

The plasma glucose concentration of the blood (from here on I will mostly say just “glucose concentration”) at any one time is denominated (in US practice) in units of *milligrams* [of glucose] *per deciliter* of blood (mg/dL). In Canada, and typically in Europe, the glucose concentration is denominated in a different unit, based on the concept of a *mole* of a substance (symbol mol).² That unit is *millimols* [of glucose] *per liter* (mmol/L).

Just to get some idea of the range of numbers involved here, it is said that for non-diabetic persons, the typical plasma glucose concentration upon arising (“fasting”) is in the range 50–80 mg/dL.³

1.4 Glycation of the hemoglobin

The hemoglobin in the blood continuously takes on glucose from the blood plasma. We can think of this as individual hemoglobin molecules taking on molecules of glucose, a process called *glycation*. The fraction of all the hemoglobin molecules that are glycated advances at a rate that is basically proportional to the concentration of glucose in the blood plasma.

Running counter to this increase in glycation is that the erythrocytes that are the containers of the hemoglobin die off. Their ingredients are then “recycled”, and so the molecules of hemoglobin they carry leave the “counting field”.

¹ The plasma is the “vehicle” of blood (to use a metaphor from paint), the liquid that carries the various types of cells, platelets, and so forth. Sometimes this parameter is spoken of as the “serum glucose concentration”. There is a subtle difference between blood serum and blood plasma, which need not concern us here.

² One mole of a compound (symbol: mol) is, simplistically, the amount of it whose mass in grams is numerically equal to the molecular weight of the compound. One mole of any compound always comprises the same number of molecules (Avogadro’s number, about 6.02×10^{23} , in fact).

³ This is not intended to be a basis for anyone to evaluate their own plasma glucose concentration.

2 THE HbA1c TEST

2.1 Introduction

A person's glucose concentration can be measured (or estimated) in various ways. The person himself can measure the glucose concentration in a small sample of capillary blood drawn with a "finger stick" lancet and picked up by an expendable test strip in a small test instrument.

Or the person may be fitted with a continuous glucose monitor (CGM) system, in which a small sensor on the skin, having a detector probe that extends into the interstitial fluid, measures the glucose concentration there (perhaps at one-minute intervals) and records that.

But even if this is done, a diabetic person's healthcare provider will likely have the person periodically have a laboratory test formally known as the "hemoglobin A1c" test (but for short, just "HbA1c", or sometimes "HgbA1c", and for shorter yet, "A1c"; I will use the latter moniker from here on). The test result (stated in percent) essentially tells, over all the hemoglobin molecules in the blood at the time of the test, what fraction of them are glycated.⁴

2.2 Time weighting

Consider that over a certain day, in which the subject's glucose concentration had a certain average value, the fraction of the hemoglobin molecules in his blood that are glycated increases, the rate of that increase at any time being approximately proportional to the glucose concentration at that time.

For our exercise, consider that there was no earlier glycation of that hemoglobin, and there is no further glycation of that hemoglobin in later days. And there are no further newly-born erythrocytes in the story, thus no further hemoglobin molecules. (All this very fanciful, of course, but handy to make the story progress well.)

If we were to measure (with an A1c test) the average fraction of the hemoglobin molecules that were glycated at the end of that day, we would get a certain number (say, 0.04%).

Now say that 30 days later we make the test again. By that time, 1/4 of all the erythrocytes that were alive on that first day would have died (thus their hemoglobin molecules have left the "counting field"). They have been replaced by newborn cells (which had not yet had any exposure to glucose, and we will assume that they have no initial

⁴ The name comes from the designation of one "fraction" of the glycated hemoglobin that is easy to isolate in testing.

glycation)⁵. So this time the A1c result would be only 3/4 of what it was earlier, 0.03%.

Now, 30 days later yet, we take the test again. By this time, a total of 1/2 of all the erythrocytes that were alive on that first day would have died, and been replaced by newborn cells (whose hemoglobin molecules, we assume for now, had not yet been glycated). So this time the A1c result would be only 1/2 of what it was earlier, 0.02%

Next, 30 days later yet, we take the test again. By this time, a total of 3/4 of all the erythrocytes that were alive on that first day would have died, and have been replaced by newborn cells. So this time the A1c result would be only 1/4 of what it was earlier, 0.01%.

Thus we see that the impact of glycation of the hemoglobin on a given day will have an effect on an A1c measurement that will decline (linearly) with time to when the A1c test is done.

Now of course in reality, there will be some glycation of the hemoglobin on each day. Nonetheless, the effect of the glycation on each day on the result of an A1c test done at some later time depends on the time from that day of glycation until the A1c test is taken.

So the glucose concentration on some day "90 days ago" will have less influence on today's A1C value than the glucose concentration on some day "30 days ago". That is because today, of the hemoglobin molecules that were glycated 90 days ago, 3/4 of them have died, while of those that were glycated 90 days ago, only 1/4 of them have died.

2.3 Typical range

Just to get some idea of the range of numbers involved here, it is said that for non-diabetic persons of age 40-59 years, the typical range of the A1c value is 4.1%–6.2%.⁶

2.4 A special case

There is a special case of some interest: when the daily average glucose concentration remains essentially constant for at least 120 days. In that case the A1c test result will in fact be about proportional to that constant average glucose concentration, just as the "simple" description suggests.

⁵ In reality, erythrocytes newly entering the bloodstream are already partially glycated, but for the sake of simplicity, I will ignore that for the moment.

⁶ This is not intended to be a basis for anyone to evaluate their own A1c value.

There are equations (and tables) that relate a certain plasma glucose concentration to a certain A1c value (in either direction) (see Section 5). But we must keep in mind that these relationships are strictly only applicable to the situation in which the plasma glucose concentration has remained nearly constant over perhaps a 120-day period.

2.5 The more general case

Now consider a diabetic person who, perhaps as a result in some ongoing adjustment of his diabetes therapy, has a daily average glucose concentration that steadily decreases significantly over, say, a 120-day period. And the overall average of the glucose concentration over that period would have a certain value.

But the earlier days of (higher) glucose value will have a lesser weight on the A1c result than the more recent days of (lower) glucose value. Thus the A1c result will suggest a lower glucose value than the actual overall “average” over that 120-day period.

3 IMPACT ON CLINICAL EVALUATION

So, given that the A1c test does not in fact indicate the overall average plasma glucose concentration over some prior time period (perhaps 4 months), is it not a “meaningful” indication? That is a matter far out of my lane.

But it seems that the practical reality is that this is a valuable indicator, if interpreted by the clinician in the light of what is known about changes in the subject’s diabetic therapy and of lifestyle changes (perhaps in diet) that may effect his plasma glucose concentration.

In any case, it is common in practice to consider that an A1c result less than some established “bogey” indicates that the “glucose control” for the diabetic person is “successful”.

4 MORE DETAILED INFORMATION

Appendix A discusses, from a “scientific” standpoint (no higher mathematics involved, though), the development of the A1c value and the working of the “time weighting” factor.

Appendix B discusses why the notion that the A1c value tells us “the average glucose concentration over the past three or four months’ is inaccurate.

Appendix C discusses a simple mathematical function that relates the A1c value to glucose concentrator.

5 RELATING THE A1C VALUE TO THE PLASMA GLUCOSE CONCENTRATION

Various researchers, working from actual clinical data over large cohorts of subjects, have fit a linear function to the relationship between mean plasma glucose concentration and the ensuing A1c value.

The following table follows one widely-cited function ⁷. Note that this is only valid for an assumed constant plasma glucose concentration over a 120-day period.

A1c value (5)	Plasma glucose concentration (mg/dL)
5	101
6	137
7	172
8	208
9	244
10	279
11	315
12	350

I note that the plasma glucose concentration is linear with the A1c value but not strictly proportional to it. That is because the rate of glycation of the hemoglobin is linear with, but not exactly proportional to, the glucose concentration in the blood (even though for simplicity my earlier descriptions suggested that it is).

6 SIMPLE EXPLANATIONS OF THE TIME WEIGHTING

I mentioned earlier that the simple description of the A1c value as indicating “the average glucose concentration over the past three or four months” is not in general accurate. (See Appendix B for a further discussion of this.)

We often see slightly more detailed explanations of the meaning of the A1c value of the form, “The average glucose concentration over the prior W days accounts for X% of the A1c value; the average plasma glucose concentration over the earlier Y days accounts for X% of the A1c value.”

⁷ Described in Section Appendix C in Appendix A.

Again, that might be true in the case of a constant glucose concentration, but probably not if that concentration has changed any significant amount over each of the intervals mentioned.

The following table <p style="margin:0px 40px">[Text]shows the theoretical situation assuming a constant glucose concentration over each of the mentioned 30-day periods.

Time period (days before A1c taken)	Fraction of A1c value affected (%)
120–90	3.1
90–60	9.4
60–30	15.6
30–0	21.9

This is based on the fiction followed earlier in this article, that the glycation of the hemoglobin proceeds proportionally to the glucose concentration. That is not strictly true.

7 ACKNOWLEDGEMENTS

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Many thanks to my wife Carla C. Kerr for her insightful copy editing of this tedious manuscript.

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Appendix A

The development of the A1c value in a bit more detail

A.1 INTRODUCTION

In this appendix, I will discuss in a little more detail the workings of what is considered to be the underlying mechanism that leads to an A1c result. Although the presentation is mathematically oriented, no advanced mathematics is involved.

A.2 CAVEAT

The biological mechanisms that underlie this matter are extraordinarily complex. I will often ignore many of these complications in the interest of most clearly presenting the important concepts here.

A.3 REVIEW

We recall the following things (accepting some simplifying assumptions):

- The life of an erythrocyte (red blood cell) is 120 days.
- The hemoglobin molecules in living erythrocytes are *glycated* at a rate that is approximately proportional to the plasma glucose concentration.
- The hemoglobin A1c (“HbA1c” or just “A1c”) test reports the fraction of those molecules that are glycated (stated in %).

A.4 GRAPHIC ILLUSTRATIONS

A.4.1 Example 1

I will start with Figure 1.

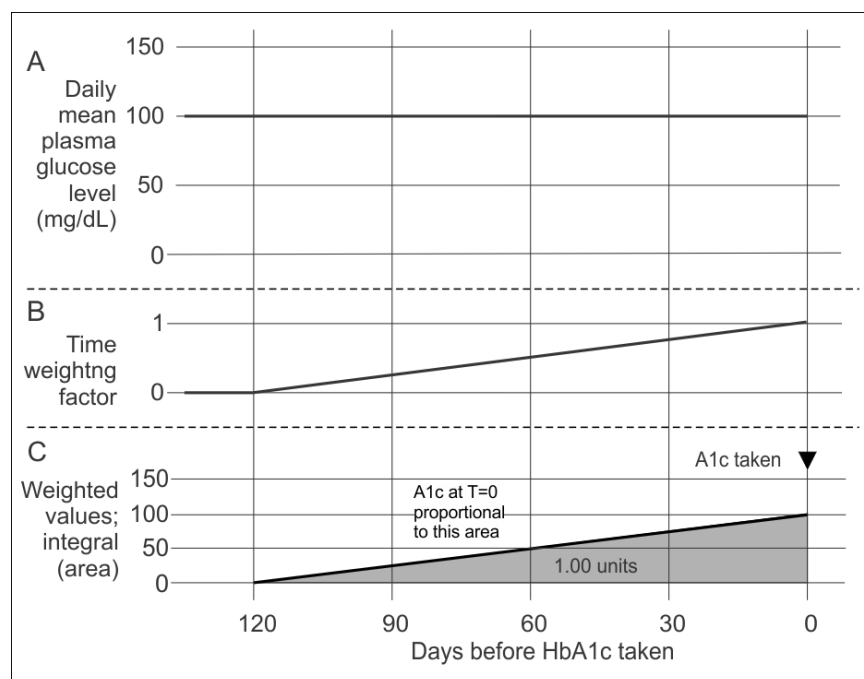


Figure 1. Development of A1c value for constant plasma glucose concentration

The time axis here is in terms of days before the time an A1c value is taken.

In panel A we see the profile of the daily mean value of the subject's plasma glucose concentration, which we assume to be constant at 100 mg/dL.

Panel B shows the "time weighting" function, which will be used to reflect the effect of the erythrocytes that carry the hemoglobin molecules dying after a lifetime assumed to be 120 days, thus diluting the effect of earlier glycation on the A1c value..

We see that for an exposure to glycation earlier than 120 days before the time the A1c value is taken, that glycation will have zero effect on the A1c value (since all the erythrocytes carrying hemoglobin molecules glycated then will have died before the A1c value is taken).

We then consider hemoglobin molecules glycated on a day 119 days before the A1c value is taken. By the time the A1c value is taken, 119/120 of the erythrocytes carrying hemoglobin molecules glycated on that day will have died. Therefore, the glycation that occurred that day will have only 1/120 of its potential effect on the A1c value.

We then consider hemoglobin molecules glycated on a day 50 days before the A1c value is taken. By the time the A1c value is taken, 50/120 of the erythrocytes carrying hemoglobin molecules glycated on that day will have died. Therefore, the glycation that occurs that day will have only 70/120 of its potential effect on the A1c value.

We finally consider hemoglobin molecules glycated on a day just before the A1c value is taken. By the time the A1c value is taken, none of the erythrocytes carrying hemoglobin molecules glycated on that day will have died. Therefore, the glycation that occurs that day will have 120/120 of its potential effect on the A1c value.

This varying fraction of the “impact” of glycation at various times on the A1c value (the “time weighting factor”) is plotted in panel B.

In panel C, the curve is the product of the plasma glucose concentration and the time weighing factor.

The total area under that curve taken reflects the fraction of the hemoglobin that is glycated at the time the A1c value is taken. And so the A1c value that is measured is proportional to that area.

The area in this case (in arbitrary units) is 1.0.

A.4.2 Example 2

The second example is shown in Figure 2.

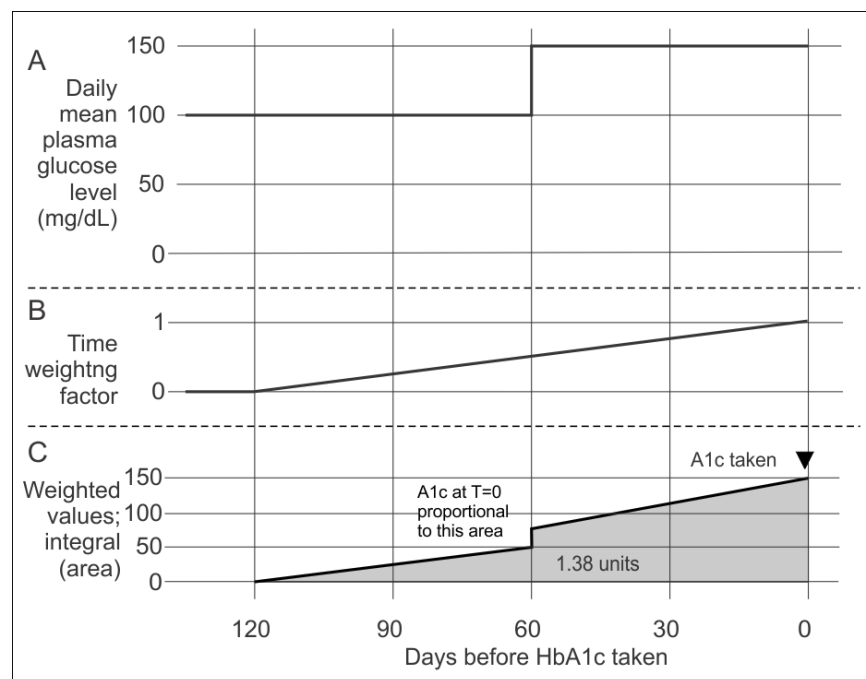


Figure 2. Development of A1c value for varying plasma glucose concentration

Here the assumed glucose concentration is not constant. Rather (as shown in Panel A), we assume that up to 60 days before the time the A1c value is taken, the daily mean glucose concentration is 100 mg/dL, but at that time, it changes suddenly to 150 mg/dL.

The description of the action here is the same as in Section A.4.1.

We see that, as a consequence of the increase of the daily mean glucose concentration at T-60 days, at that time the curve jumps and its slope increases.

The total area under the curve is greater than in the earlier example, and thus the A1c value will be greater.

The area in this case (in arbitrary units) is 1.38.

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Appendix B

The “average glucose” fallacy

In his exercise I will demonstrate that the A1c value does not indicate “the average plasma glucose concentration over the last 120 days”, as is often said.

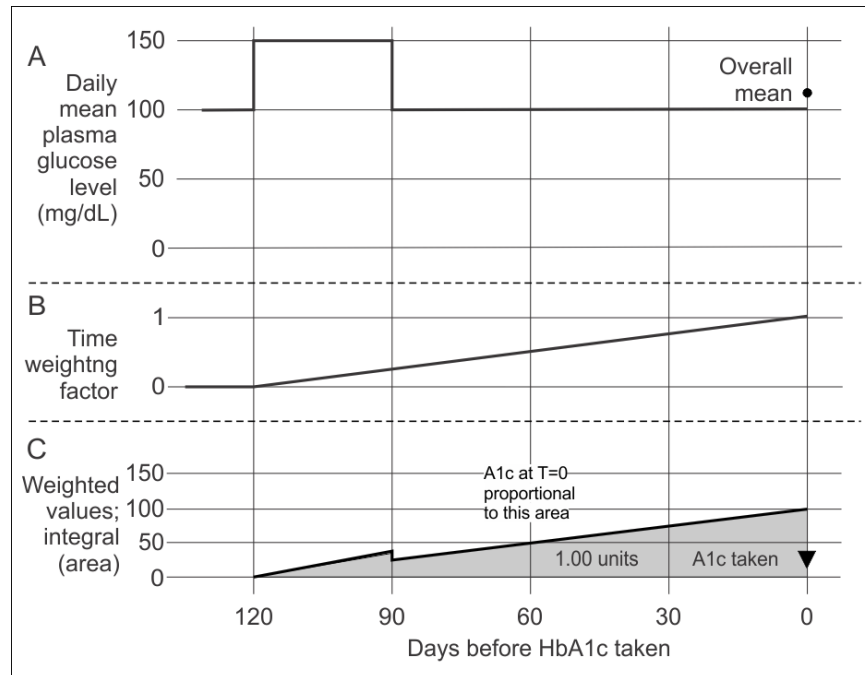


Figure 3. Development of A1c value for a 30-day long increase in plasma glucose

Figure 3 shows a situation in which we only consider the daily mean plasma glucose concentration over a period of 120 days. That concentration is 150 mg/dL for the first 30 day interval of that period and 100 mg/dL for the rest of the period. This is of course a rather fanciful scenario, but is used here so the point being made will be evident graphically.

We can easily determine that the overall mean of the plasma glucose concentration over the time period of interest in this situation is 112.5 mg/dL.

The various panels work the same as previously.

The area under the weighted curve will lead to the A1c value. In this case, that area is 1.00 units (that tidy value being just a coincidence).

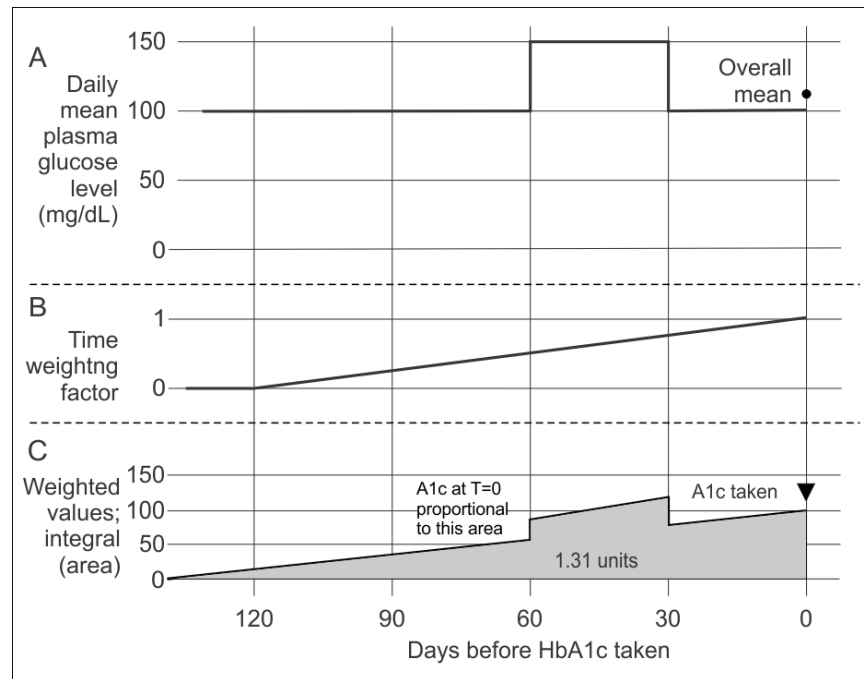


Figure 4. Development of A1c value for a different 30-day long increase in plasma glucose

Figure 4 shows a similar scenario, here with the 30-day period of a glucose concentration of 150 mg/dL at the third of the four 30-day intervals in our 120-day time window and 100 mg/dL in the rest of that period. Again the overall mean glucose concentration over the 120-day period is 112.5 mg/dL.

But now the area under the curve (which leads to the A1c value) is 1.31 units, 31% greater than in the prior case with the same overall mean glucose concentration.

Thus the two resulting A1c values would be quite different, despite the fact that the average glucose concentrations over the 120-day period are the same for both cases.

The reason is that, because of the time weighting, the later 30-day interval of greater glucose concentration weighs more heavily on the resulting area (and thus on the resulting A1c value) than would the same interval of increased glucose concentration occurring earlier..

Quod erat demonstrandum.

Appendix C

The relationship between the A1c value and glucose concentration

Earlier I showed how the area under the time-weighted curve of glucose concentration develops under different glucose concentration profiles, and mentioned that this area “led to” the A1c value. That cagey description allowed me to defer until now the fact that the A1c value is not exactly proportional to that area.

Several researchers have examined extensive clinical data to look for a general relationship between the A1c value and the time-weighted actual daily glucose concentration profile of many subjects.

They found that this relationship could, at least over the range of values of most interest, be closely modeled by a simple linear function fit to the actual data..

One such function that is widely cited is given by the following formula:

$$G = 35.6A - 77.3 \quad (1)$$

where G is the mean glucose concentration (in mg/DL) and A is the A1c value (in %). If in fact a person’s known glucose concentration is known to be essentially constant over a 120-day interval, we can use that to estimate that glucose concentration from the results of an A1c test.

If we solve that equation for A , we get:

$$A = \frac{G}{35.6} + 2.17 \quad (2)$$

which we can use to estimate the A1c value that will result from a know (constant) glucose concentration.

We note from the presence of a constant in these two equations that, while the relationship between glucose concentration and the A1c value is linear, it is not strictly proportional.

I suspect that this constant reflects the fact that newly-born erythrocytes are already partially glycated when they enter the bloodstream. But that is just conjecture on my part.