

# Seeking a low value of HbA<sub>1c</sub> may be dangerous under recurrent episodes of hypoglycaemia: A short report

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**Abstract.** During the last decades, HbA<sub>1c</sub> became a standard assay in the control of risks for diabetic complications. Epidemiological studies and clinical trials have explored and determined the relationship between HbA<sub>1c</sub> and mean blood glucose. However, for patients and health care providers, a clear understanding of this relationship is necessary for setting appropriate day-to-day blood glucose testing goals aiming to achieve specific HbA<sub>1c</sub> targets while avoiding hypoglycaemia.

Keywords: Diabetes, glycaemia, HbA<sub>1c</sub>, hypoglycaemia, control, complications

## 1. Background

The effect of intensive treatment of diabetes on the development and progression of long-term complications of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) was considered by the Diabetes Control and Complications Trial Research Group (DCCT) [1] and the U.K. Prospective Diabetes Study Group (UKPDS) [2]. The two studies established the relationship between the glycated haemoglobin (HbA<sub>1c</sub>) levels and risks for diabetic complications in T1DM and T2DM.

Consequently, the HbA<sub>1c</sub> assay became widely accepted and used for assessing chronic glycaemia [3]. More precisely, different epidemiologic studies and clinical trials have explored the relationship between HbA<sub>1c</sub> and the mean blood glucose (MBG) [4, 5]. Using a linear regression on data of DCCT ( $n = 1439$  patients), Rohlfing et al. found that HbA<sub>1c</sub> and mean plasma glucose (MPG) were correlated ( $r^2 = 0.82$ ) and hence determined the following relationship between HbA<sub>1c</sub> and MPG [4]:

$$\text{MPG (mmol/l)} = 1.98 * \text{HbA}_{1c} - 4.29 \text{ or } \text{MPG (mg/dl)} = 35.6 * \text{HbA}_{1c} - 77.3 (*)$$

The A<sub>1c</sub>-Derived Average Glucose (ADAG) study concluded that HbA<sub>1c</sub> can be expressed as estimated average glucose (eAG) for most patients with T1DM and T2DM [5]. Again, the linear regression analysis ( $R^2 = 0.84$ ) provided the following relation:

$$\text{eAG (mmol/l)} = 1.59 * \text{HbA}_{1c} - 2.59 \text{ or } \text{eAG (mg/dl)} = 28.7 * \text{HbA}_{1c} - 46.7 (**)$$

The quasi-totality of biological laboratories which carry out HbA<sub>1c</sub> tests worldwide, stress that a good control of diabetes requires an HbA<sub>1c</sub> < 7% while an HbA<sub>1c</sub> > 10% indicates a very bad control of diabetes. However, very

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few of them indicate that seeking a low value of HbA<sub>1c</sub> (<7%) may expose insulin-dependent patients and especially those with T1DM to high risks of hypoglycaemia and its consequences.

Nonetheless, the values of measured and computed HbA<sub>1c</sub> may be in very good agreement while the daily blood glucose may show large variations with dangerous recurrent mild and severe episodes of hypoglycaemia. An illustration is provided by the following case.

## 2. Case presentation

Although the guidelines given by diabetes associations worldwide, and the recommendations generally provided by doctors advise people with diabetes to avoid hyperglycaemia as well as hypoglycaemia, we think that the case presented here is interesting for the following reasons:

1. The 27 old patient (B.W) is a doctoral student living with T1DM since the age of one year,
2. B.W is a citizen of a low-medium income country where students have no medical insurance and cannot afford insulin pumps nor continuous self-monitoring systems,
3. She is convinced that avoiding high levels of blood glucose is the main rule to avoid complications of diabetes or at least to delay them as far as possible,
4. The link between daily high blood glucose and complications has constituted a psychological fear of hyperglycaemia and consequently pushed her to undergo recurrent episodes of hypoglycaemia,
5. With time, the patient has become unaware of hypoglycaemia and her family has noticed that a hypoglycaemia from which B.W used to recover after ten to fifteen minutes if a 15–20 g sugary drink was taken, is now needing one hour and a huge quantity of sugar. During the last three months, unawareness represented around 75% of all hypoglycaemia episodes (for capillary glucose <70 mg/dl).

## 3. Data collection

Using a self-monitoring glucometer, the patient performed nearly 700 finger stick capillary glucose tests over three months, representing an average of 7 to 8 measurements per day. Figure 1 below shows that during the three months period, the average blood glucose was ideally situated between 70 mg/dl and 180 mg/dl. On the other hand, the patient has excessively suffered from recurrent mild and severe hypoglycaemia (over the three months period, the number of hypoglycaemia episodes was 115 of which 15 (13%) were severe episodes).

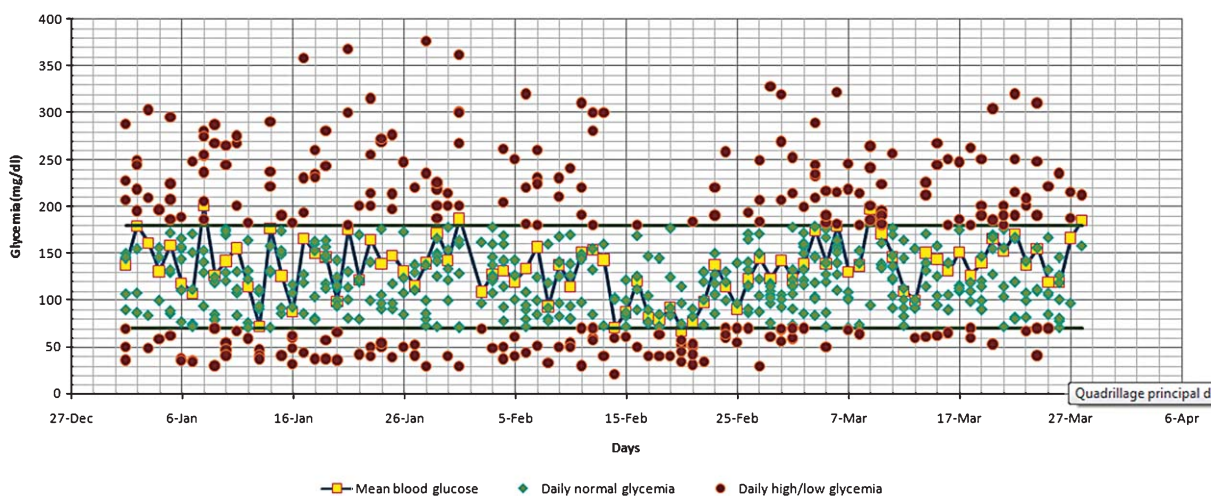


Fig. 1. Daily variation and mean of blood glucose during three months.

#### 4. Comparison of computed and measured HbA<sub>1c</sub>

The measured value of HbA<sub>1c</sub> was obtained through a Biological Laboratory using a HPLC, D-10 HbA<sub>1c</sub> Technics. At the end of the three months period, measured HbA<sub>1c</sub> was: 7.2%.

Using  $MPG = 1.1 \text{ MBG}$  and the inverse of relations (\*) and (\*\*) to compute HbA<sub>1c</sub> as a function of MPG ( $HbA_{1c} = 2.6 + 0.03 * \text{MPG}$  and  $HbA_{1c} = 1.63 + 0.035 * \text{MPG}$ ), provided the calculated HbA<sub>1c</sub> = 7.3% and HbA<sub>1c</sub> = 7.1% respectively. The measured and computed HbA<sub>1c</sub> appear in a good agreement.

#### 5. Discussion

Ogawa et al. showed that glycaemic standard deviation is not associated with A<sub>1c</sub>, but has a significant positive correlation with fasting plasma glucose, glycated albumin(GA) and GA/A<sub>1c</sub> ratio [6]. Kilpatrick et al. established that HbA<sub>1c</sub>, MBG and glucose variability measurements each have an independent role in determining an individual's risk of hypoglycemia in type 1 diabetes [7]. Ceriello et al. reported that hyperglycaemia after recovery from hypoglycaemia worsens cardiovascular risks in healthy subjects and subjects with T1DM [8].

As stressed by diabetes associations worldwide, HbA<sub>1c</sub> is a “must” for diabetes control but its traps should be kept in mind. For instance, a patient may be falsely reassured by a low HbA<sub>1c</sub> obtained by alternating episodes of hypo-hyperglycaemia [9]. In this direction, the present case illustrates clearly the insufficiency of the measured value of HbA<sub>1c</sub> as a criterion of good glycaemic control because this value reflects only the average blood glucose and does not capture the glycaemic variations. In the case of a diabetic suffering from recurrent hypoglycaemia (as our case), there may be a compensating effect between lower and higher glycaemic values, leading to a MBG corresponding to an ideal HbA<sub>1c</sub>. In such a case, the patient may be very happy with his or her achievement when he or she must be very careful about the danger of repetitive episodes of low blood glucose. Indeed, many studies have shown that hypoglycaemia constitutes a high risk of morbidity and mortality [10–14]. McCoy et al. followed a cohort of 1,013 patients with T1DM and T2DM and found that after 5 years, patients who reported severe hypoglycaemia had 3.4-fold higher mortality compared with those who reported mild/no hypoglycaemia [10]. A similar rate of mortality (4%) was reported by Patterson et al. in EURODIAB population-based cohorts of T1DM [11]. Higher rates (6%, 7% and 10%) of deaths caused by hypoglycaemia among patients with T1DM were reported by Jacobson et al. [12], Feltbower et al. [13] and Skriverhaug et al. [14].

#### 6. Conclusion

While recalling that HbA<sub>1c</sub> constitutes a standard assay in the control of risks for diabetic complications, it should also be stressed that HbA<sub>1c</sub> may be insufficient or even misleading in the case of patients suffering from hypoglycaemia. Moreover, treatment of hypoglycaemia is generally accompanied by high levels of blood glucose but the two adverse events are not seen in HbA<sub>1c</sub>. The 2015 ADA's diabetes guidelines indicates that a less stringent target ( $HbA_{1c} < 8$ ) should be sought in case of hypoglycaemia [4]. Interpreting HbA<sub>1c</sub> as a measure of MBG is meaningful only in the case of stable glycaemia, and a clear understanding of the relationship between MBG and HbA<sub>1c</sub> is necessary for achieving low HbA<sub>1c</sub> levels while avoiding hypoglycaemia. Finally there should be more sensitisation about the danger of hypoglycaemia for patients who seek a  $HbA_{1c} < 7$ , especially for people with T1DM living in developing countries where specialists of diabetes give more importance to the value of HbA<sub>1c</sub> since the majority of patients have few or no self monitoring data.

For patients and health care providers, a clear understanding of the relationship between MBG and HbA<sub>1c</sub> is necessary for setting appropriate day-to-day BG testing goals with the expectation of achieving specific HbA<sub>1c</sub> targets while avoiding hypoglycaemia [6].

#### Consent

The authors confirm that the patient has given her consent for the Case Report to be published.

## Competing interests

The authors affirm that there is no competing interest.

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