Case Report

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Rising HbA1c in the presence of optimal glycaemic control as assessed by self-monitoring – iron deficiency anaemia

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Lesson
HbA1c can be affected by determinants other than glucose and an awareness of this is important to avoid unnecessary hypoglycaemia.

Keywords
HbA1c, type 2 diabetes mellitus, iron deficiency anaemia

A 54-year-old woman known to have type 2 diabetes was referred to the diabetes clinic by her General Practitioner who was concerned that HbA1c had risen to 85 mmol/mol from 57 mmol/mol over an eight-month period. This woman was concerned that her fasting blood glucose values checked on home blood glucose monitoring had remained unchanged (6–8 mmol/mol), but her HbA1c appeared to have significantly risen. Her other results showed a fall in haemoglobin from 120 g/L to 109 g/L (115–165) with an MCV of 80 fL (84–102) from a previous value of 85 fL. A new microcytic anaemia coincided with the rise in HbA1c (see Figure 1). Renal function was normal. Urine micro albuminuria was negative and normal TSH. Ferritin levels were 17 µg/L (12–300). She had a fructosamine level of 327 µmol/L (205–285).

Her comorbidities included hypertension, osteoarthritis and migraine headaches, and she was under the gastroenterologists for investigation of iron deficiency anaemia. She had a normal upper gastrointestinal endoscopy, colonoscopy and capsule endoscopy and had been told she had chronic iron deficiency anaemia of unknown cause. Her medication included lansoprazole, ramipril, topiramate, oxycodone, metoclopramide, atorvastatin, bendroflumethiazide, doxazosin, aspirin, rosiglitazone, metformin and gliclazide.

In the diabetes clinic, she was advised to continue to monitor her blood glucose levels at home, and no adjustments to her medication were made as she was due to have an iron infusion under the gastroenterologists. She was given contact details of the diabetes specialist nurse so that she could contact them if there was any change to her home blood glucose monitoring values. On review in clinic after three months, her Ferritin level had come up to 156 µg/L, haemoglobin 119 g/L and her HbA1c had come down to 62 mmol/mol as shown in Figure 1. Home blood glucose monitoring values remained unchanged from the initial clinic review.

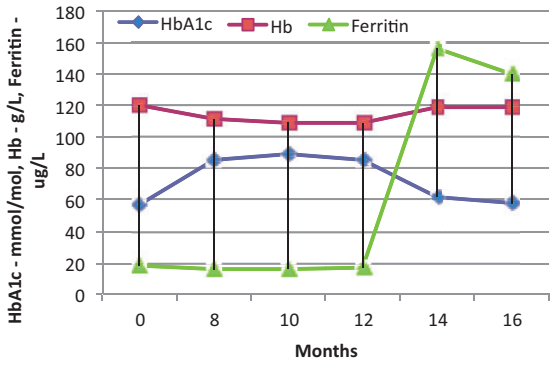
Discussion

Glycated haemoglobin is a form of haemoglobin formed in a non-enzymatic glycation of the terminal valine unit of the β-chain of haemoglobin after exposure to plasma glucose. The average plasma glucose levels are proportional to the fraction of glycated haemoglobin formed. This serves as a marker for average blood glucose levels over the previous three months prior to the measurement as this is the half-life of red blood cells.[1]

Once glycated, a haemoglobin molecule remains that way and this buildup of glycated haemoglobin within the red cell therefore reflects the average level of glucose to which the cell has been exposed during its life-cycle. Measuring glycated haemoglobin can be used to assess the effectiveness of therapy as this is more sensitive than home blood glucose monitoring levels.[2]

Measurement of HbA1c is dependent on the circulating haemoglobin being predominantly HbA. Shortened or altered red cell life span will cause a decrease in HbA1c levels. This may occur with haemoglobinopathies, splenomegaly, rheumatoid arthritis or as a side effect from drugs such as antiretrovirals and dapsone. Older non-diabetic subjects appear to have higher HbA1c values than younger individuals and differences in the HbA1c have also been found between individuals from different races, with Afro-Caribbeans and individuals of

Figure 1. Spatial relationship between HbA1c, haemoglobin and ferritin levels.



South Asian descent having values approximately 3 mmol/mol higher than Caucasians.[3]

Iron deficiency anaemia is associated with higher HbA1c and higher fructosamine levels.[4] It is believed to account for an inappropriate rise in HbA1c of 7–11 mmol/mol. Consistent with these observations, iron replacement therapy lowers both HbA1c and fructosamine concentrations in diabetic and non-diabetic individuals. Insight into the mechanism was recently obtained by the observation that malondialdehyde, which is increased in patients with iron deficiency anaemia, enhances the glycation of haemoglobin. Due to the unreliability of the HbA1c value in these circumstances, alternative measures of glycaemic assessment for example home blood glucose monitoring must be used, at least until the iron deficiency has been successfully treated.[5,6]

Both observational studies and controlled clinical trials demonstrate strong correlation between HbA1c and retinopathy, as well as other microvascular complications in patients with type 2 diabetes. It has been irrefutably proven that each 1% reduction in HbA1c is associated with reductions in the risk of complications, with the lowest risk being in those with HbA1c values in the normal range.[7]

Clinicians should be aware of the effect of iron deficiency anaemia on HbA1c when they make treatment decisions for their patients.[8] Extending set target HbA1c values to this group of patients may be erroneous due to potential risk of hypoglycaemia.[9]

Results of the Atherosclerosis Risk in Communities study (ARIC) suggest that fructosamine and glycated albumin could be useful as adjunctive tests when HbA1c might not be valid, or when assessing short-term glycaemic control. According to the study, HbA1c predicted incident diabetes better than fructosamine and glycated albumin. However, fructosamine and glycated albumin were strongly associated with retinopathy and predicted development of CKD nearly as well as HbA1c.[10]

Fructosamine is formed when glucose binds to total serum proteins, mostly albumin, whereas glycated albumin is produced when glucose binds to albumin alone. As neither fructosamine nor glycated albumin are affected by red cell survival or haemoglobin characteristics, they are reasonable alternatives to use in these circumstances. The half-life for serum proteins is 10 to 14 days faster than red cells (every 120 days). Therefore, these tests can be used to measure short-term glucose control over two to four week intervals.

Fructosamine tests are available in many countries but are not commonly used because of insufficient data about their usefulness in predicting long-term outcomes.[10]

Learning points

- Failure to appreciate the different influences for HbA1c may result in unnecessary hypoglycaemia in patients as they are over-treated to try to bring down the HbA1c to within set targets.

Declarations

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