CASE REPORT

Haemoglobin Marseille-Long Island and interpretation of HbA1c: which HbA1c result is the “right answer”?  

C M Florkowski, T A Walmsley, S O Brennan, P M George

A woman was screened for diabetes using glycated haemoglobin (HbA1c). Vastly different results were obtained by high performance liquid chromatography (4.5%) and immunoassay (2.9%), and affinity chromatography (4.2%) compared with the non-diabetic range of less than 6.4%. Mass spectral studies confirmed the presence of a haemoglobin variant, haemoglobin Marseille-Long Island which had confounded interpretation by all methods. Initial HbA1c analysis was undertaken by high performance liquid chromatography (HPLC) on the Bio Rad Variant (Bio Rad Laboratories Inc, California, USA) and gave a result of 45% (non-diabetic range up to 6.4%). This result was considered to be biologically implausible and HbA1c analysis was therefore undertaken by other analytical methods. HbA1c was therefore analysed by immunoassay on the DCA 2000 instrument (Bayer Diagnostics) and was 2.8%, which was considered to be implausibly low.

It was decided to arrange further HbA1c analysis by affinity chromatography on the Primus instrument (Primus Corporation, Kansas City, MO, USA) which gave a result of 4.6%. Haemoglobin was submitted to mass spectrometry (VG Platform; Micromass, UK) which confirmed the presence a haemoglobin variant, haemoglobin Marseille-Long Island (see fig 1) which confounds interpretation of these analytical methods.

DISCUSSION

The initial HbA1c of 45% by HPLC is implausibly high, especially in an asymptomatic woman with a low probability of diabetes. This raised suspicion of a possible haemoglobin variant. Haemoglobin electrophoresis on cellulose acetate (pH 8.6) gave a normal pattern. This prompted the decision to undertake mass spectrometry studies of HbA1c.

Mass spectrometry excluded a HbA1c of 45% and confirmed that the subject was heterozygous for haemoglobin Marseille-Long Island. This variant, originally termed haemoglobin Marseille was originally described in a diabetic Maltese woman, and subsequently termed haemoglobin Long Island.

Figure 1 Mass spectral analysis of control and patient lysate showing variant β chain (βMar) with a mass increase of 91 Da. This histidine to proline substitution decreases the mass by 40 Da and the addition of N terminal methionine results in a mass increase of 131.

Abbreviations: HbA1c, glycated haemoglobin; HPLC, high performance liquid chromatography

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Learning points

- Haemoglobin variants can interfere with most HbA1c methods and cause problems with interpretation.
- The possibility of haemoglobin variants should be considered when HbA1c results do not concur with clinical expectations.
- Haemoglobin variants may not always be revealed by electrophoresis.
- Analysis of HbA1c by alternative methods, in particular by mass spectrometry may help to elucidate the nature of confounding variants.
- It is occasionally necessary to consider alternative measures of glycation than HbA1c.

None of the obtained results therefore gives the “right answer” for glycaemic status. As indicated above, doubling of the DCA 2000 result may be argued as giving the “right answer” for glycaemic status. As indicated above, doubling of the DCA 2000 result may be argued as giving the “right answer” for glycaemic status. As indicated above, doubling of the DCA 2000 result may be argued as giving the “right answer” for glycaemic status.

Notwithstanding all of the above considerations, the predictive value of HbA1c for diabetes depends on the chosen cut off and is not usually recommended as a screening test.”

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REFERENCES

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