Annotations

Diabetes

I Measuring adequacy and lability of control

Parents of diabetic children may read widely and bombard paediatricians with questions. Two concepts they are likely to have gleaned from British Diabetic Association literature are that good control is important if their child is to avoid complications, and that urine testing is an inaccurate and old fashioned way of monitoring control. The first proposition is broadly correct.^{1 2} The second may only be judged in the context of what information is needed to manage the child's diabetes on a day to day basis and assess overall control. Ideal control implies blood glucose concentrations within the normal range throughout the 24 hours.² In real life, diabetic children fluctuate wildly from hyper- to hypoglycaemia with few short interludes of stable blood glucose concentration. Monitoring can be used to measure either the level of attainment—how close on average blood sugar concentrations are to normal throughout the 24 hours—or lability—the frequency and magnitude of blood glucose changes. The former is necessary for long term audit of treatment and is primarily the province of the doctor, while the latter, of equal interest to parents and doctor, is essential to devise individual treatment regimens, solve day to day problems of control, and avoid excessively frequent hypoglycaemia.

Urine tests

In theory urine tests may be used to measure both overall control and lability, but have several major drawbacks reviewed in detail elsewhere.^{3 4} 'Spot' urine tests reflect simultaneous blood glucose concentrations poorly because of the lag between secretion of urine and testing, variation in renal threshold for glucose, and the semiquantitative nature of the tests. Parents are disconcerted by and find it difficult to grasp the concept that a negative urine test cannot distinguish between normal and abnormally low blood glucose concentrations, a particularly important consideration because so much hypoglycaemia is asymptomatic.³ To aim for continuously negative urine tests usually leads to frequent hypoglycaemia and, if set this target, parents may decide to play safe and 'keep a little

sugar in the urine at all times'. Divided 24 hour urine collections give more information and can not only be used to measure attainment but also to detect nocturnal hypoglycaemia or cheating.⁵ They are unpopular, however, with patients, and incomplete collections are the rule.⁶ One group among whom urine tests of any type are particularly inaccurate is teenage girls, although whether this is a short coming of the tests or the girls is uncertain.⁷

Home blood glucose monitoring

Soon after its introduction in 1978, home blood glucose monitoring was hailed as the ideal way to improve diabetic control, measure attainment, and solve problems.⁸ In theory, it should be better than urine tests because it provides instant reliable information, enables realistic targets to be set, and can detect hypoglycaemia. Home blood glucose monitoring, however, will not lead to better control unless it is backed up by intensive support and education;^{8 9} neither will control be improved unless sufficiently frequent blood tests are done, probably at least five times a day.¹⁰ A similar frequency of testing is also necessary to document attainment and tests have to be done not only before meals, when blood glucose concentrations are at their lowest, but also postprandially. It has been reported that young people can be persuaded to test six or more times a day,¹¹ but I think this is unreasonable and will inevitably lead to non-compliance. Given that most youngsters are unlikely to test sufficiently frequently and to document accurately their attainment, what is needed is an objective test to measure control between three monthly clinic visits. There are only really two contenders, height velocity and glycosylated haemoglobin, which are complementary rather than mutually exclusive.

Objective tests of control

It is well known that growth is retarded in children with grossly uncontrolled diabetes (the Mauriac syndrome), although it is often thought that moderate control does not affect growth. When control was measured with urine tests, there was either no

correlation between control and growth¹² or retardation only with really bad control as shown by more than 40 g glycosuria per day.⁵ More recent work in which near perfect blood glucose control has been obtained and documented has shown that growth velocity is in fact a highly sensitive index of blood glucose control. Rudolf *et al*¹³ were able to obtain near normoglycaemia with a pump in nine diabetic adolescents in whom growth velocity increased from 5.3 to 9.4 cm per year in only six months. Growth velocity has also been shown to correlate well with the level of control as measured by the other objective index, glycosylated haemoglobin.¹⁴

Haemoglobin A is the major normal adult haemoglobin and, in the presence of high glucose concentrations, undergoes accelerated glycosylation whereby glucose is bound non-enzymatically to the N-terminal valine of one or both beta chains. A number of glycosylated products are formed of which haemoglobin A1c is the most abundant. Most methods, however, measure total glycosylated haemoglobin which is referred to as either haemoglobin A1 or glycosylated haemoglobin. The rate of glycosylated haemoglobin formation depends on the average blood glucose concentration to which the red cell is exposed and also on the life span of the red cell, usually 120 days. Normal levels of glycosylated haemoglobin are below 9%. The advantages of glycosylated haemoglobin as a test of diabetic control are that it is objective, independent of the patient's cooperation, independent of the time of the last meal, and reduces diabetic control to a single number which reflects average blood glucose concentrations during the previous four to six weeks.¹⁵ An early study showed that when patients with juvenile onset diabetes were brought under control in a metabolic ward, it took four to six weeks for their glycosylated haemoglobin concentrations to return to normal. Glycosylated haemoglobin correlated not only with the degree of glycosuria, but also with six blood glucose determinations before and one hour after meals, a testing technique which is sometimes referred to as 'glucose brackets'.¹⁶ More recently its value as an objective index of control has been emphasised in a study¹⁷ which showed a linear correlation between mean blood glucose concentrations calculated from concentrations of glycosylated haemoglobin and mean blood glucose measured by self monitoring at home. In the same study, assessment of control by symptoms, home urine tests, or single clinic blood glucose measurement were shown to be highly inaccurate. Nevertheless, glycosylated haemoglobin is far from a perfect test. A major difficulty in interpreting results is that short periods of poor control lead to a

disproportionate increase in glycosylated haemoglobin concentration which then takes four weeks of good control to expunge.¹⁸ This is encapsulated in the epigram that glycosylated haemoglobin is, 'more sensitive to sin than to repentance': a rise in blood glucose of 20 mmol/l for as little as six hours can increase its proportion by as much as 2%.¹⁹

A further problem with the use of glycosylated haemoglobin is that there are at least five different ways of measuring it, each with advantages and disadvantages.^{20, 21} Standards are not available and the results with different techniques cannot be directly compared. In routine practice the coefficient of variation of any method is between five and seven per cent but, even when conditions are carefully standardised, errors can arise from the way the samples are handled and stored, the temperature at which the assay is carried out etc. At present there is no inexpensive, foolproof assay for use in a routine chemical pathology laboratory.

The main value of glycosylated haemoglobin in clinical practice is when results are unexpectedly high or low. For example, children, especially those on once daily insulin, may seem well controlled on the basis of preprandial tests but have a high glycosylated haemoglobin concentration which makes sense when postprandial blood sugar peaks are measured and found to be extremely high. Children who produce sheets of negative urine tests or normal blood sugars but have glycosylated haemoglobin concentrations of 20% are almost certainly cheating.²² An unexpectedly low glycosylated haemoglobin concentration—unexpected in the sense that the child has high day time blood sugars—may indicate an abnormal haemoglobin such as HbS or HbC²³ or alternatively may alert one to the presence of prolonged nocturnal hypoglycaemia.^{24, 25} Glycosylated haemoglobin determination is also the only way of assessing treatment in the postpubertal child or adolescent who refuses to do any tests.

The main problem with glycosylated haemoglobin is that, by and large, it usually only confirms what one can guess from other evidence: this is usually that a child is rather poorly controlled with values of 14% or higher. Tests are only really of practical value if they lead to corrective action and what is disappointing is that it has proved extremely difficult, if not impossible, to lower glycosylated haemoglobin values in individual children in spite of intensive attention to diet, education etc.^{26, 27}

Conclusions

No method of monitoring a child's diabetic control is entirely satisfactory. For objective measurement of

attainment both height velocity and glycosylated haemoglobin are objective but retrospective. Both give a warning of poor control but give no indication of its cause. To measure lability and guide day to day diabetic management, some form of self monitoring is necessary. Home blood glucose monitoring gives more useful information than urine tests and is generally preferred by teenagers.

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