Targeting glycaemic control in children and young people with type 1 diabetes: Getting it right from day one

Wendy Watts, Harshan Lamabadusuriya, Julie Edge

There is now clear evidence that achieving good glycaemic control in type 1 diabetes reduces the risk of diabetic complications. However, despite more intensive diabetes management, less than a fifth of children in the UK achieve current HbA_{1c} target levels. This review summarises recent evidence about the importance of HbA_{1c} targets, including HbA_{1c} tracking and "metabolic memory", and discusses the experience of one UK clinic in attempting to achieve better control of blood glucose levels from the point of diagnosis. It emphasises the need for clear and consistent messages to be given by all members of the diabetes team in order to achieve good glycaemic control. Targeting normal blood glucose levels (4–7 mmol/L) allows teams to set HbA_{1c} targets as low as 50 mmol/mol (6.7%) from diagnosis.

The landmark DCCT (Diabetes Control and Complications Trial) was a multicentre randomised controlled trial that compared complication outcomes in people with type 1 diabetes treated with intensive (insulin pump, three or more insulin injections per day) and conventional (usual care) diabetes regimens (DCCT Research Group, 1993). The trial proved that the use of intensive therapy, with the aim of maintaining blood glucose concentrations as close to the normal range as possible, effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy. There was a direct relationship between incidence and progression of all complications and HbA_{1c} levels, with a continuous risk gradient at any HbA_{1c} level >42 mmol/mol (>6%; *Figure 1*).

Within the DCCT there was a small group of adolescents (215 of 1441 participants) whose HbA_{1c} level was generally higher by around 1% compared with the adults in both groups, but in whom better control was still related to complication incidence and progression. In the UK, the ORPS (Oxford Regional Prospective Study) of children with diabetes has also shown that for every 1% rise in HbA_{1c} level, the risk of microalbuminuria increases by around 10% (Amin et al, 2005).

Metabolic memory

At the end of the DCCT, the mean HbA_{1c} level was still significantly lower in the intensive treatment group than in the conventional treatment group (57 mmol/mol vs 76 mmol/mol [7.4% vs 9.1%]; $P<0.0001$). Following closure of the trial, participants were encouraged to maintain or begin intensive treatment and were invited to take part in a prospective observational study, the EDIC (Epidemiology of Diabetes Interventions and Complications) study.

Within a year, the difference in HbA_{1c} levels between the intensive and conventional treatment groups had narrowed, and by 5 years there was no longer a significant difference (65 mmol/mol intensive versus 66 mmol/mol conventional [8.1% versus 8.2%];

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1. The lower the target HbA_{1c} level set by diabetes teams, the better the levels achieved in children and young people in that centre.
2. Children who achieve good HbA_{1c} levels within 3 months from diagnosis are much more likely to maintain good levels in the long-term.
3. Clear, consistent messages from team members will help parents to adjust insulin doses to achieve target blood glucose levels.

Key words

- Children and young people
- Diabetic complications
- Glycaemic control
- HbA_{1c} tracking
- Metabolic memory
- Targets
- Type 1 diabetes

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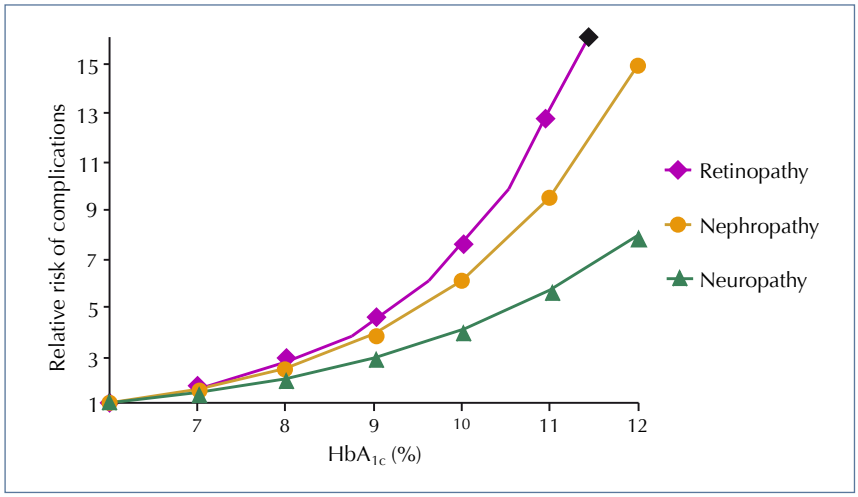

Figure 1. HbA_{1c} level and relative risk of diabetic complications. Adapted from Diabetes Control and Complications Trial Research Group (1993).

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1. Review of the HbA_{1c} levels of more than 360 children for up to 15 years revealed that individual levels were significantly correlated from year to year, and the correlation remained significant for up to 9 years post diagnosis.
2. Only 4 of 49 children with poor control at 6 months post diagnosis (HbA_{1c} >75 mmol/mol [9%]) achieved a median HbA_{1c} of <64 mmol/mol (8%) over the next 2–3 years.
3. Tracking of HbA_{1c} levels within individuals suggests that if good control can be achieved early on it can be maintained, resulting in good glycaemic control over the long term.
4. It follows that poor control in the first 6 months should be recognised and acted upon as early as possible by providing additional support.

P=0.11). When these subjects were followed for a further 8–10 years, the group previously receiving intensive treatment had a lower cumulative incidence of nephropathy and retinopathy than the conventionally treated group, despite having identical HbA_{1c} levels for many years (DCCT/EDIC Research Group, 2003; White et al, 2010). This long-term beneficial effect of prior tight glycaemic control has been termed "metabolic memory".

When metabolic memory was compared between adolescents and adults in the EDIC study, it was found that the benefits of prior tight glycaemic control on development or progression of retinopathy persisted for 4 years in both adults and adolescents, but only in adults at 10 years. The majority of the difference in effect at 10 years was explained by the higher average HbA_{1c} level during the DCCT in the adolescents (White et al, 2010).

The mechanisms for metabolic memory are currently poorly understood, but the message from the EDIC study is that a reduced risk of complications can outlast the period of good glycaemic control. It is likely that this would last for longer in adolescents if better control were achieved.

Tracking of HbA_{1c} levels within diabetes centres

The Hvidøre Study Group compared glycaemic control internationally across 21 paediatric diabetes centres in 1995 and found substantial differences in glycaemic control between centres that could not be explained by treatment regimen or staffing structure (Mortensen and Hougaard, 1997). Ten years later, the group found that the differences between centres persisted (mean HbA_{1c} range [57–77 mmol/mol [7.4–9.2%]; *P*<0.001) despite major changes in insulin regimens, attempts to improve service provision and an overall improvement in metabolic control (de Beaufort et al, 2007). Furthermore, mean HbA_{1c} levels seemed to show tracking within diabetes centres, with individual centres maintaining the same relative position within the group as a whole.

Tracking of HbA_{1c} levels within individuals

We postulated that if levels track within centres, then they might also track within individuals. Review of the HbA_{1c} levels of more than 360 children for up to 15 years revealed that individual HbA_{1c} levels were significantly correlated from year to year, and that this correlation remained significant for up to 9 years post diagnosis (Edge et al, 2010). Only 4 of 49 children with poor control at 6 months post diagnosis (HbA_{1c} level >75 mmol/mol [>9%]) achieved a median HbA_{1c} level of <64 mmol/mol (<8%) over the next 2–3 years.

This tracking of HbA_{1c} levels within individuals suggests that if good control can be achieved early on (within 6 months of diagnosis) it can be maintained, resulting in good glycaemic control over the long term. It follows that poor control in the first 6 months should be recognised and acted upon as early as possible by providing additional support.

HbA_{1c} targets

There is much debate around appropriate HbA_{1c} target levels in children. Most diabetes organisations internationally have aimed for an HbA_{1c} level of <58 mmol/mol (7.5%), based on the outcomes of the DCCT, although some paediatricians, particularly in the US, have argued for higher target levels because of fears around hypoglycaemia.

Although the DCCT did demonstrate an inverse

Table 1. Percentage of team members in the Hvidøre study who identified specific HbA_{1c} levels as their target. The final column shows the centres' mean HbA_{1c} levels. The greater the percentage of healthcare professionals who targeted lower HbA_{1c} levels at a clinic, the better the results were.*

Percentage of healthcare professionals						Centre mean HbA_{1c} (%)
	Target HbA_{1c} level (%)					
	<7.0	7–7.4	7.5–7.9	8.0–9.0	No specific target	
	100.0					7.40
	100.0					7.58
	20.0	40.0	40.0			7.68
		100.0				7.74
	16.7	83.3				7.80
			57.1	42.9		7.89
	52.4	42.9	4.8			8.00
		100.0				8.02
		100.0				8.08
		60.0	40.0			8.18
		40.0	40.0	10.0	10.0	8.23
	33.3	44.4	22.2			8.24
	20.0	60.0		20.0		8.27
		60.0	20.0	20.0		8.36
		80.0	20.0			8.45
		20.0	20.0	60.0		8.59
		33.3	44.4	22.2		8.76
				100.0		8.82
			75.0	25.0		8.83
			60.0	20.0	20.0	8.98
		20.0	60.0	20.0		9.05

* Adapted from Swift et al (2010), with thanks to Carine de Beaufort.

relationship between HbA_{1c} level and incidence of severe hypoglycaemia, it has to be remembered that the study was carried out before analogue insulins were available. Recent evidence generally shows that better control with multiple daily injections (MDI) and insulin pumps is generally associated with a lower incidence of severe hypoglycaemia (O'Connell et al, 2011; Rosenbauer et al, 2012).

Despite an HbA_{1c} target of <58 mmol/mol (7.5%) being in use for many years in the UK, data from the *National Paediatric Diabetes Audit Report 2011–2012* in England and Wales (Royal College of Paediatrics and Child Health, 2013) show that glycaemic control has hardly changed since 2007, with only 17.4% of children and young people achieving HbA_{1c} levels in the target range. Clearly, therefore, improvements in control need to be made, and should start from diagnosis and continue throughout childhood and adolescence.

Given that there was no threshold in the DCCT below which complications do not occur, it would be logical to suggest a new recommendation for all children to aim for the lowest achievable HbA_{1c} level that can be sustained without problematic hypoglycaemia.

Achieving targets

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1. Although the Hvidøre Study group found no relationship between glycaemic control and staffing, insulin regimen or other treatment factors, a later study found a close association between HbA_{1c} targets set by diabetes teams and levels achieved in the clinics.
2. A close relationship was also found between the targets set by professionals and those understood by adolescents and parents.
3. Target setting therefore appears to play a significant role in explaining the differences in metabolic outcomes between centres and is an important part of successful management.

Box 1. Altering insulin doses to keep good control: "Ten Top Tips". Provided to patients at a New Patient education session at 4–6 months from diagnosis.*

1. Blood glucose (BG) level targets are 4–7 mmol/L first thing in the morning, before all meals and before bed.
2. Keep a record book (BG diary) and try to fill it in at least twice a week with all the BG levels from your child's meter.
3. Look at the book every week with your child and compare their BGs to target levels. That way they will learn with you about how to change doses.
4. Always give your child's usual correction dose if BG levels are more than 8.0 mmol/L before a meal, and more than 12 at snack times.
5. Look for patterns of high BG levels and increase insulin doses if BG levels are high 4 days or more in a week (more than 7.0 mmol/L).
6. If your child has **high BG levels in the mornings** (more than 7.0 for 4 days or more in the week), and these are not because of high levels before bed, increase Lantus or overnight basal rates.
7. How to increase Lantus doses (or basal doses if your child is on a pump):
   a. If your child has less than 10 units, increase by unit at a time (you will need to ask your nurse for a -unit pen).
   b. If your child has 10–20 units, increase by 1 unit at a time.
   c. If your child has more than 20 units, increase by 2 units at a time.
   d. On a pump, basal rates can go up overnight by 0.05–0.1 unit per hour for 10 hours (total 0.5–1.0 extra unit).
8. If your child has **high BG levels before bed,** increase the evening meal dose by 0.5 to 1 unit from now on. Either add on this amount to your child's usual carbohydrate ratio, or increase the insulin to carbohydrate ratio (ICR) if your child has a pump or Expert meter.
9. If your child has **high BG levels** for 4 or more days in a week **before a particular meal**, increase the insulin dose for the meal eaten earlier in the day BEFORE the high levels (e.g. if your child's level is high at lunchtime, increase the breakfast dose.)
10. **If you are not sure what to change, or would like some discussion, then please don't hesitate to call your nurse.**

* With thanks to Bruce King, Newcastle, NSW, Australia, for the concept and some of the text.

study (Swift et al, 2010) asked what HbA_{1c} targets were being used by diabetes teams, adolescents and parents. A close association was found between HbA_{1c} targets set by diabetes teams and levels achieved in the clinics (*Table 1*). Furthermore, there was also a close relationship between the professionals' targets and those understood by adolescents and parents (Swift et al, 2010).

Target setting thus appears to play a significant role in explaining the differences in metabolic outcomes between centres and is an important part of successful management. The lessons from the Hvidøre studies are that successful cohesive diabetes teams provide an environment in which targets can be achieved through effective communication and family support, resulting in better glycaemic control (Cameron et al, 2013).

Importance of teamwork

King et al (2013) have further emphasised the importance of teamwork in the management of diabetes. In order to deliver clear and consistent messages to patients and their families, the multidisciplinary team (MDT) must first agree on defined treatment targets and use these as the basis for coordinated management plans. A common form of words then needs to be developed to explain to families in a clear, consistent way how these targets can be achieved. In this way, each member of the team can deliver the same message repeatedly to patients and their families. This repetition and reinforcement results in greater retention of information and allows families to have confidence in the management plan suggested (e.g. about blood glucose targets or exercise).

Where no coordinated plan exists, families receive conflicting advice, which results in confused messages and leaves families not knowing which advice to follow. This cohesive MDT approach has been shown to result in better glycaemic control without increased rates of hypoglycaemia (King et al, 2013).

So how should this approach be taken forwards in the UK, and is it possible to achieve better glycaemic control than is currently being achieved? We have recently looked at our own practice in the Oxfordshire Children's Diabetes Service from diagnosis to see if further improvements can be made.

Approach to new patients in Oxford

The Oxfordshire Children's Diabetes service is one of the larger diabetes clinics, with a total of 340 children and adolescents up to between 18 and 19 years of age. We have spent away-days each year and monthly team meetings discussing exactly how we will manage every aspect of diabetes care, so that we can be confident that new patients will receive exactly the same messages from all

members of the team, whether they are doctor, nurse, dietitian or psychologist.

Children newly diagnosed with type 1 diabetes are admitted to hospital the same day and, unless they are in diabetic ketoacidosis, are all started on an MDI regimen of insulin glargine, given once a day, and preprandial insulin aspart. Total daily doses have been 0.5 unit/kg/day in prepubertal children and 0.7 unit/kg/day during and after puberty, given as 50% glargine and 50% aspart. Doses are fixed until the families are taught how to count carbohydrate within the first week at home. Newly diagnosed children are seen by our dietitians before discharge, and the importance of a balanced diet, composed of regular starchy main meals, sugar-free drinks and healthy snacks, is emphasised. Children are admitted for the shortest possible time and most go home the following day, with regular follow-up to adjust insulin doses.

Parents and children are taught the principles of insulin physiology and the rationale for mimicking this by means of a basal-bolus regimen. Families are provided with age-appropriate education packs at diagnosis, and are taught to carbohydrate count and provided with scales within a week. At that stage, individual insulin to carbohydrate ratios are calculated by the dietitian from total insulin dose and carbohydrate intake.

Progress is reviewed daily initially with phone calls, at a home visit within 2 days, and in clinic at 2 weeks, 1 month and 3 months post diagnosis. Correction doses (using insulin sensitivity factors) are taught once blood glucose levels start to rise again after achieving target levels. We do not teach the management of severe hypoglycaemia until 2–3 months post diagnosis, and are consistent in emphasising the importance of aiming for "normal" blood glucose levels from day one.

As a result, parents gain confidence and familiarity in using higher insulin doses early on during the period of extreme hunger following the initiation of insulin. Families are encouraged to maintain a logbook of blood glucose levels, and taught to make appropriate changes to doses, both independently and following discussion with their diabetes nurse following a weekly review. We have also produced an information sheet for families on the best way to use their blood glucose data to adjust doses in order to keep blood glucose levels in target (*Box 1*).

Table 2. Average insulin doses following diagnosis in the Oxfordshire New Patient audit

	TDD/kg	Lantus/kg	Lantus %
Day 2	0.66	0.31	47.93
Day 5	0.82	0.35	43.18
Day 10–14 clinic	0.97	0.36	37.31
1 month	0.75	0.31	40.36
3 months	0.60	0.26	41.37

TDD=total daily dose

Table 3. Initial blood glucose levels following diagnosis in the Oxfordshire New Patient audit

	Breakfast	Lunch	Dinner	Bed	Average
Day 1	10.67	15.63	19.26	20.2	17.6
Day 2	11.67	14.34	15.51	17.34	14.41
Day 5	9.84	14.72	14.40	13.23	13.07
Day 10–14 clinic	7.09	9.07	10.0	10.39	8.65
1 month	6.71	7.31	7.75	7.71	7.25

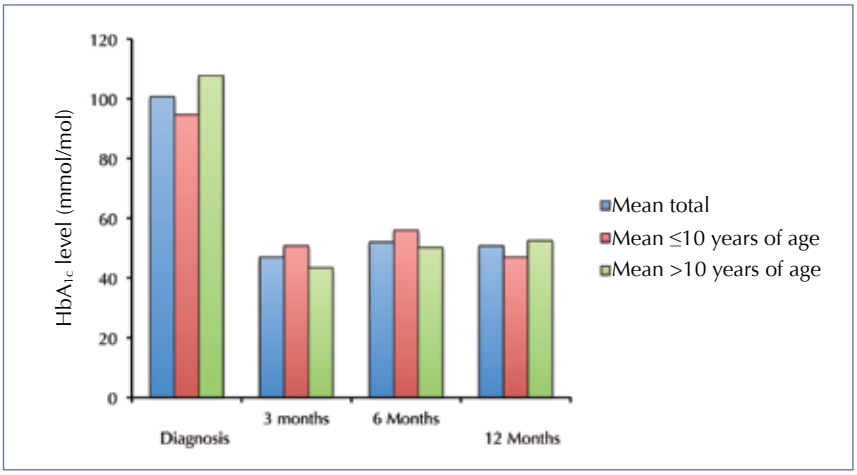

Figure 2. Mean HbA_{1c} levels (mmol/mol) from diagnosis in the Oxfordshire New Patient audit. Even at 12 months the majority of patients still had HbA_{1c} levels ≤57 mmol/mol (≤7.4%)

Oxfordshire New Patient audit

We recently conducted an audit of the initial insulin management and glycaemic control of

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newly diagnosed children with type 1 diabetes in the service. Of the 41 children diagnosed with type 1 diabetes in 2013 (with complete data), 35 were included in the audit; 19 (54%) were male and 16 (46%) were female. Average age at diagnosis was 9.3 years (range 1.1–16.8 years) and average weight was 33.3 kg (range 7.96–60.7 kg).

The initial average total daily dose of insulin was 0.66 unit/kg, comprising 48% glargine and 52% aspart. Doses were increased gradually to a total daily dose of 0.97 unit/kg (37% glargine, 63% aspart) 2 weeks post diagnosis, and subsequently declined to 0.6 unit/kg (41% glargine, 59% aspart) at 3 months (*Table 2*). Average blood glucose levels declined progressively from a peak of 17.6 mmol/L on day one to 7.25 mmol/L at 1 month post diagnosis (*Table 3*). High HbA_{1c} levels at diagnosis subsequently declined to 47–52 mmol/mol (6.5–6.9%) by 3–12 months (*Figure 2*). Twelve children had HbA_{1c} levels in the 30s (<5.7%) at 3 months post diagnosis without significant hypoglycaemia.

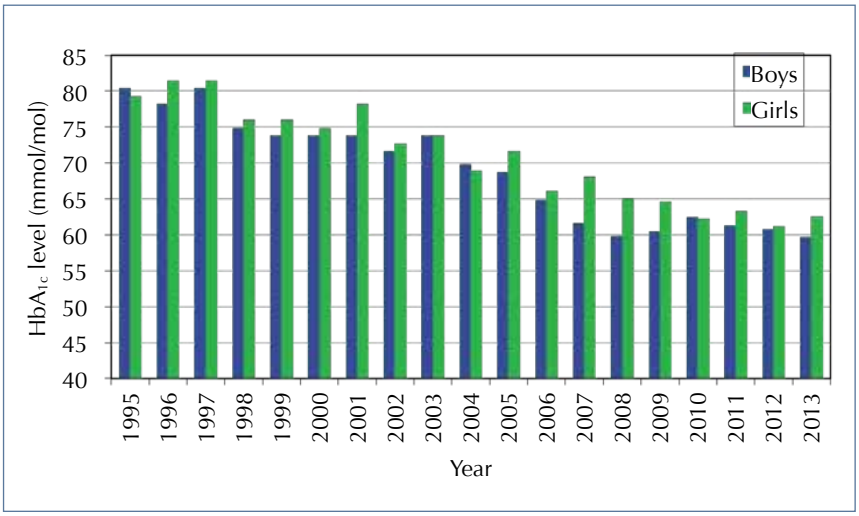

Figure 3a. Gradual improvement in HbA_{1c} levels in the Oxford clinic from 1995 to 2013. In 1995, most patients were using twice daily or three times daily insulin regimens. In 2003, we introduced multiple daily injections (MDI) for teenagers, and in 2006 made the change to start everyone on MDI at diagnosis. From 2010, there has been an increase in insulin pump use; 30% of our patients are using pumps.

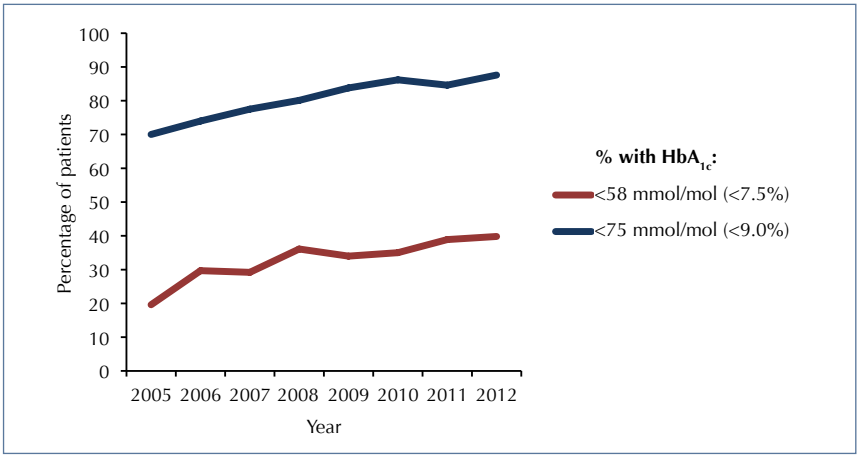

Figure 3b. Gradual improvement in HbA_{1c} levels in the Oxford clinic from 1995 to 2013. There has been a slow increase in the number of patients over the last 9 years achieving two target levels of HbA_{1c}.

Based on the results of this audit, we have now increased our starting insulin doses as follows:

- Prepubertal children receive a total daily insulin dose of **0.7 unit/kg/day**.
- Children in or past puberty are given a total daily dose of **1 unit/kg/day**.
- **One third** of the total daily dose is given as insulin glargine (previously 50%), with the remaining **two thirds** given as insulin aspart.
- We will be starting carbohydrate counting at diagnosis in the near future.

Our team target for HbA_{1c} level at 3 months from diagnosis is now <50 mmol/mol (<6.7%).

Targets – does this approach work?

For the past 10 years, we have aimed at 40% of our children and teenagers achieving HbA_{1c} levels of <58 mmol/mol (<7.5%), and have geared all our management policies and education towards this goal. There has been a slow but steady reduction in HbA_{1c} levels and the mean level in our clinic during the 2013–14 year was 61 mmol/mol (7.7%; *Figure 3a*). There has also been a reduction in the number of children and young people with very high HbA_{1c} levels (>75 mmol/mol [>9%]) to less than 10% of the total, and an increase in the number reaching the target of <58 mmol/mol (<7.5%) to 39.7% of the clinic population (*Figure 3b*).

Conclusion

We have provided the rationale for aiming for tight glycaemic control from diagnosis, based on tracking of HbA_{1c} levels and the effects of metabolic memory. Clear, consistent messages need to be given by all members of the diabetes team in order to achieve good glycaemic control;

blood glucose and HbA_{1c} targets should be to achieve as close to normal levels as possible from diagnosis.

However, it is the children and families who live with diabetes on a daily basis who need to be empowered and educated to make the regular changes necessary to maintain good control. Providing them with this knowledge and confidence as early as possible is likely to yield huge benefits in terms of a reduced risk of complications and better control over the long term.

If these improved outcomes can be achieved in one UK children's diabetes service, the approach can be replicated in other centres. The sharing of guidelines and protocols through the regional Paediatric Diabetes Networks in England should ensure that all services have access to educational material and guidelines that promote a target-driven approach. With all the resources that have been put into children's diabetes services in England, the main aim of our national strategy over the next 5 years must be to increase the number of children attaining target HbA_{1c} levels. ■

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