INSULIN REGIMENS AND INSULIN ADJUSTMENTS IN DIABETIC CHILDREN, ADOLESCENTS AND YOUNG ADULTS: PERSONAL EXPERIENCE*

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SUMMARY - Because recent multicenter studies, even those performed in developed countries without financial restriction, show that treatment of childhood diabetes is inadequate in general and that levels of glycated hemoglobin (HbA1c) are very different, diabetes treatment teams should individually explore the reasons for failure, without any prejudice or bias.

The "good" treatment is signed by good HbA1c associated with good quality of life, and is not necessarily exportable without adjustment to the local way of life. HbA1c must be under 7%, if the upper normal limit is about 6%, which is possible, in our experience, even in diabetic children and adolescents. Our "recipes" are summarized.

The number of daily insulin injections, 2 or 4, by itself does not necessarily give better results, but the 4-injection regimen allows greater freedom, taking into account that the proper insulin adjustment is difficult before adolescence.

Successful glycemic control in young patients depends mainly on the quality and intensity of diabetes education. Any dogmatism must be avoided; only the objective result is important.

Key-words: type 1 diabetes mellitus, diabetic children, insulin therapy, glycated hemoglobin.

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The principal aims of therapeutic management of the child, adolescent and adult with type 1 diabetes are to allow good quality of life [1, 2] and to avoid long-term complications (retinopathy, neuropathy, nephropathy, etc.) by maintaining blood glucose concentrations close to the normal range [3, 4].

Clinical studies conducted since the 1970s by our team [5-8] have demonstrated that screening for subclinical retinopathy, neuropathy, and nephropathy should be started at puberty and three years after diagnosis, as also shown by the Berlin’s group [9], with the goal of detecting early abnormalities responsible for functional disorders that can be reversed by improved metabolic control, thus preventing the occurrence of potentially irreversible incapacitating lesions [8].

Repeated determinations of glycated hemoglobin levels (HbA1c) provide a good criterion of overall control. They must be under 7% [3], if the upper normal limit is about 6%, which is possible, in our experience, even in diabetic children and adolescents [7, 10-12]. The number of daily insulin injections, 2 or 4, by itself does not necessarily give better results, but the 4-injection regimen allows greater freedom, taking into account that the proper insulin adjustment is difficult before adolescence. Successful glycemic control in young patients depends mainly on the quality and intensity of diabetes education. Any dogmatism must be avoided [13].

The purpose of this paper is to propose some “recipes” [10], concerning the choice of insulin regimens and the criteria for insulin adjustments, in order obtain good HbA1c levels. Because recent medical literature show that treatment of type 1 diabetic patients is inadequate in general and that levels of HbA1c are often too high (Fig. 1 from reference 13), diabetes treatment teams should individually explore the reasons for failure, without any prejudice or bias [7, 10, 11, 14-18]. In 1998, Rosilio et al. [17] have summarized, in a table, the main aspects of major studies of glycemic control in children with type 1 diabetes since 1981. The best results, in terms of HbA1c, are obtained by our team in Brussels [11].

Details on our way of treating diabetic children and adolescents have been published elsewhere, in our textbook on pediatric diabetology, edited with Paul Czernichow in Paris [19], and in updated papers [20, 21], taking into account that the major improvements in the field of practical insulin treatment were above all acquired in the 1980s [13]. The 1990s have only brought the insulin analogs, which represents progress but not a medical revolution [21, 22]. The integration of physical activity into treatment has been reviewed elsewhere [23, 24]. This is also the case for the role of diet, which in fact must follow the same recommendations as those for non diabetic subjects [25, 26], taking into account that the allocation of carbohydrates throughout the day may be influenced by the choice of insulin regimen. A normal diet for diabetic children was proposed for more than 40 years in France by Henri Lestradet [13], and is now accepted by mainly guidelines as those of the American Diabetes Association since 1986 [27] and of the International Society for Pediatric and Adolescent Diabetes (ISPAD) [28], but not always implemented even by pediatric endocrinologists, without documented explanation.

PERSONAL “RECIPES” MAKING GOOD HbA1c EASIER

Critical mass of patients; personalized long-term follow-up

– A critical mass of patients is mandatory in order to get the indispensable experience for the multidisciplinary team. More than 400 diabetic children, adolescents and young adults are followed-up at the Diabetology Clinic of the University Children’s Hospital Queen Fabiola, by the same pediatric diabetologist (HD), and the same specialized nurse (M-P R), with about 30 years experience. The team also comprises a dietician, a social worker, a psychologist and a pedopsychiatrist.

– Friendly and personal contacts with a large dose of psychology are indispensable in the long-term relationship of a patient with a chronic disease. At the onset of follow-up, the technical problems are important, but after a few months the patient or the family knows more about practical diabetology than the general practitioner in their vicinity. If diabetic young people have problems with their diabetes, there are many causes outside the ability to self-management: diabetes is never on holiday, there are problems with
the brother or the sister, with the boy- or girlfriend, etc. Therefore, the diabetologist must know the whole story of the life of his patients, and must adapt his psychology to the psychology of the patients and of their families, and not the reverse. It is not so necessary for an endocrinologist because the treatment of other endocrine diseases doesn’t need the constant participation of the patient. The diabetologist is not interchangeable, as it can be the case for some other pediatric specialties.

– I am a diabetologist and not an endocrinologist giving consultations at the out-patient clinic during certainly 4 complete days per week, and personally taking in charge the follow-up and education of the hospitalized patients. It becomes very difficult to cumulate these 2 specialties because of a lack of time to master the exponential scientific knowledge and the clinical experience in too many fields. The education at the onset of diabetes (hospitalization of about 10 days) needs 10 to 20 hours, involving also the nurse and the dietician.

– In my office, at the outpatient clinic, there are no observers: neither temporary assistants nor students, especially with adolescents, in order to not disrupt the mutual trust and to preserve private life. Patients need privacy in order to explain their intimate problems that are often the causes of bad control.

– In a pediatric diabetology clinic of a Belgian public hospital, recognized by the Social Security, medical consultations and material necessary for treatment are nearly without cost. Personally, I have no private practice and I never ask honorarium supplements. Everybody is equal. Nearly 50% of my diabetic patients are immigrants, mainly of Moghrabin origin. Because of the cultural and social differences, the education must be made-to-measure.

– I continue to follow my patients largely above the upper pediatric limit. The mean age of my patients now reaches nearly 20 years. It is their decision because of the privileged contacts. To follow adult diabetic patients, at the age where clinical complications are possible, gives the so-called pediatric diabetologist more motivation to require good control. The pediatrician who abandons his diabetic children at 16 or 18 years knows complications only through books and is often too lax.

High frequency of long-duration consultations; HbA1c and subclinical complications

– Good metabolic control is, among other things, significantly related to the frequency of out-patient clinic attendance, 6 to 9 per year on average, in our 2 studies on the levels of HbA1c which can be obtained in unselected diabetic patients [7, 11]. In the majority of diabetes centers, this frequency is reduced to 3 or 4 times per year. A high frequency of visits is important for motivating the patient.

– The mean duration of a visit is 35 minutes in my nurse office and, afterwards, 35 minutes with me. Patients are not undressed... They are not ill... It is important on a psychological point of view, mainly in adolescents. If they are nearly naked, they are not prompt to express their secrets. Moreover, there could be a religious problem with Muslims. They have no clinical complications at adolescence and what is the importance of determining exactly their Tanner’s stage of puberty? If there is delayed or precocious puberty, the parents themselves ask for a check-up.

– HbA1c is measured at each visit and the patient knows the result and the target. It is also important for the motivation of the patient and the doctor.

– If necessary, other members of the team interact during the consultation. The dietician never gives rigid meal plans or exchange lists. Diet is never prescribed. The dietician builds up a picture of the family’s and child’s usual eating habits and life style. When possible, the family is encouraged to adopt a similar and normal eating pattern so that the diabetic child does not have to eat specially prepared meals. The main problem with the twice-daily insulin regimen is the allocation of carbohydrates in 6 meals. The dietician must know perfectly the actions of the insulins and their adjustment.

– The help of the psychologist is not often solicited... Indeed, the diabetologist has to do a large part of the psychological work. The patient must not be cut in slices like salami... One slice for the diabetologist, one slice for the educator in diabetology different from the diabetologist in some teams, one slice for the psychologist, etc. Diabetic children and adolescents often detest psychologists or psychiatrists because they are associated with the notion of madness.

– The social security system allows each member of a recognized pediatric diabetes team, namely the specialized nurse, to go to the patients’ places of life: home, school, etc. This is particularly useful in the underprivileged classes and partially explains the good results even among the diabetic immigrants.

– As repeated, the motivation of both the patient and the doctor is fundamental in order to obtain for life good glycemic control. After age 13 and 3 years of diabetes, we perform every year: retinal angiography, measurements of motor and sensitive conduction velocities (which is different from a painful electromyography), sympathetic evoked potentials, and dosage of microalbuminuria [5-8]. The majority of my colleagues use only the dosage of microalbuminuria and the observation of the eye fundus at regular opthalmoscopy. It is important to be able to say to the patient, for example, “you have no complaint, but, as you can see on this photograph, there are 2 leakages of fluorescein in your left eye; it is reversible if you improve your HbA1c; otherwise, that will become an irreversible lesion leading later to overt complications”. The same message for the slow-
ing of conduction velocity or the presence of abnormal microalbuminuria.

- A high frequency of home blood glucose monitoring (HBGM) is also significantly associated with better HbA1c levels [7, 11]. Whatever the number of daily insulin injections, 2 or 4, four daily blood glucose measurements (sometimes a urinalysis may replace a glycemia) are necessary to adjust the 4 daily insulins injected twice daily with mixtures, or separately in the basal-prandial system. However, in my experience, non-compliance with HBGM occurs in 2/3 of the patients, being more frequent in adolescents [29]. If one stops this phenomenon, using, for example the Sensorlink system as a tool for retrieving the results of HBGM stored in the glucose meter, their is a dramatic fall in the frequency of cheating and a reduction of HbA1c levels in patients with insufficient metabolic control.

Two daily insulin injections in children < 15 years; easy and effective

- The proper use of the 2 injection regimen, in countries where the meal schedule allows correct allocation of diet, may lead to “intensive conventional therapy” and good metabolic control [7, 10, 11]. It is inadequate to systematically assimilate the multiple-insulin injection regimen to intensified insulin therapy, and the “conventional” 2 injection regimen to a non-intensified insulin therapy. Indeed, a multiple-injection regimen not associated with an intensified and complete education, as well as with the application of the consecutive knowledge, may have deleterious effects on HbA1c, as shown within the Hvidøre study group [15, 16]. The number of daily insulin injections, 2 or 4, by itself does not necessarily give better results.

- The first injection (and insulin dose alteration) is done before school and the second injection (and insulin dose alteration) after school with the help of the parents, if necessary; before lunch at school, the young children may use urine monitoring. Diabetic children may eat a snack in the middle of the morning and afternoon periods with their friends, without he obligation of giving a shot of insulin.

- This system works well if dinner is eaten between 6 and 7 PM. If dinner is too late, there is a risk of hyperglycemia before it. A solution is to introduce a third injection of rapid-acting or monomeric insulin before the afternoon snack.

- An individualized mixture of rapid-acting (type 1) and intermediate-acting insulins (type 2) in a syringe gives better results, in terms of HbA1c, than the use of premixed insulins with a pen injector [16]. The reason is that with premixed insulins, one cannot adjust separately the 2 insulins of the mixture and therefore to realize a made-to-measure adaptation.

- Mixtures of rapid-acting insulins with zinc insulins must be avoided for 2 reasons: the excess of zinc delays the activity of the rapid-acting insulin, and intermediate- and long-acting insulins without protamine sulphate as retarding factor are complement activators [30].

- In the twice-daily injection regimen, the allocation of carbohydrates throughout the day is essential. The proportion of carbohydrates of the mid-morning snack must be more important than that of breakfast. Indeed, the peak activity of the so-called rapid-acting insulin occurs only 1.5-3.0 h after injection, and cumulates its effect with the one of the intermediate-acting insulin mixed in the same syringe (Fig. 2). Not to do that is the most common error made in the twice-daily injection regimen. If the carbohydrate content of breakfast is higher than that of the snack taken at ~ 10.00, there is a risk of hyperglycemia after breakfast and of hypoglycemia at the end of the morning period. A good way to diagnose this situation is to measure, before lunch, glycemica that will be low, and glycosuria that will be very positive. This is one of the interests not to reject systematically the use of urine tests.

- The actions of the 4 insulins have to be assessed from the results of 4 daily measurements of blood or eventually urine glucose (at school or if a good HbA1c is easily reached).

Basal-bolus regimen in adolescents: more freedom but more complicated

- The proper use of the basal-bolus regimen, with increased flexibility in daily life and dietary freedom, cannot be applied successfully before adolescence. The adjustment of insulin dosage is more complicated because dose alteration cannot be done only according to sliding scales based on the glycemia measured immediately before the insulin injection. The simplistic use of these unphysiological sliding scales is the main error in the multiple daily insulin injection regimen. The number of daily insulin injections, per se, does not necessarily give better HbA1c levels both in our experience [7, 11] and in an international comparison [15].

- Insulin dose alteration must be triple: 1) retrospective, according to numerous previous experiments, in order to enjoy more freedom for meals, sports, etc.; 2) prospective according to programmed changes in meals and sports; 3) with only a “touch” of compensatory adaptation according to the present glycemia. This needs psychological maturity; otherwise, the multiple injection system leads to anarchy and obesity, mainly in adolescent girls [15, 30]. On the other hand, this more physiological regimen is the best choice in adolescents and adults having learned to cope alone.

- Figure 3 shows the basal-prandial regimen I use with an injection of intermediate-acting insulin (type 2; long-acting-insulins, type 3, having a too wide and unpredictable coefficient of absorption, and being complement activators [31]) at bedtime, and 3
shots of rapid-acting insulin (type 1) 1/2 h before the 3 meals if the patient eats 3 times daily. It is evident that, for example, if there is hyperglycemia before lunch, the solution is not only to increase the dose of rapid-acting insulin before lunch, but also to turn up the dose of the rapid-acting insulin injected before breakfast on the following day. It is possible to adjust the rapid-acting insulin according to the glycemia measured before the following meal (lunch and dinner), and at bedtime, because the total length of action of the rapid-acting insulin is 6 to 8 hours.

– This is not allowed with the fast-acting insulin analogs whose activity is twice shorter, if the duration between 2 meals exceeds 3 or 4 h (Fig. 4). One may need to measure postprandial glycemia, which is difficult at school or at work. This handicaps the advantage not to wait between the injection and the meal. Moreover, the systematic replacement of rapid-acting

Fig. 2. Twice-daily injection regimen with a mixture of rapid- and intermediate-acting insulins.

Fig. 3. Basal-prandial regimen with injection of intermediate-acting insulin at bedtime, and 3 shots of rapid-acting insulin an half-hour before the 3 daily meals.
insulins by fast-acting analogs may provoke preprandial hyperglycemia if the duration between 2 meals is more than 3 or 4 h.

Fast-acting analogs in the basal-prandial regimen: no systematic replacement of rapid-acting insulins

– The use of fast-acting insulin analogs in the basal-prandial regimen improves post-prandial glycemia at the expense of an increase in pre-prandial glucose levels. The overall control is not improved as shown by many studies. Some authors have proposed an association of the fast-acting analogs with NPH that is administered 4 times daily [32]. This means 7 injections per day and 7 blood glucose measurements to adapt the 7 insulins! Another solution is the use of premixed analogs (fast-acting and intermediate-acting) before meals. In that case, the patient is unable to adjust separately the 2 insulins of the mixture if he uses a pen injector. Moreover, the postprandial glycemias are always necessary. In our experience, the fast-acting analogs are recommended in well defined circumstances:
  – To rapidly correct hyperglycemia, which is also valuable in the twice-daily injection regimen.
  – To allow to eat something between the main meals, which is also valuable in the twice-daily injection regimen. The injection may even be done after a snack. This is convenient when one is unaware of the amount of food that will be consumed, for example in children.
  – To allow a snack at 4 o’clock if the period between lunch and dinner exceeds 6 to 8 h, i.e. the length of action of the rapid-acting insulins. This can be also useful in the twice-daily injection regimen.
  – If the patient sleeps in, in order to avoid the superposition of the activities of the rapid-acting insulins injected before late breakfast and before lunch, the analog can replace the rapid-acting insulin before breakfast.
  – If dinner is near bedtime, in order to avoid the superposition of the activities of the rapid-acting insulin injected before dinner, and of the intermediate-acting insulin injected at bedtime, the analog can replace the rapid-acting insulin before late dinner. This reduces the risk of nocturnal hypoglycemia.

- PRACTICAL RECOMMENDATIONS FOR PATIENTS

Twice-daily injection regimen

– Relationship between insulins and analyses:
  - The midday analysis before lunch reflects the action of the rapid-acting insulin injected before breakfast.
  - The analysis before dinner reflects the action of the intermediate-acting insulin injected before breakfast.
  - The bedtime analysis reflects the action of the rapid-acting insulin injected before dinner.
  - The morning analysis reflects the action of the intermediate-acting insulin injected before dinner.
– Aims:
  • Blood glucose: minimum 70 mg/dl, maximum 160 mg/dl.
  • Urine glucose: 0.
    → same insulin dose.

– Glycemia < 70 mg/dl with or without signs of hypoglycemia, if:
  • No less food.
  • No more physical activity.
  → decrease of the insulin dose by 10%.

– Glycemia > 160 mg/dl or glucose in urine, for 2 or 3 consecutive days, at the same moment of the day, if:
  • No more food.
  • No less physical activity.
  → increase of the insulin dose by 10%.

**Basal-prandial regimen**

– Relationship between insulins and analyses:
  • The midday analysis before lunch reflects the action of the rapid-acting insulin injected before breakfast.
  • The analysis before dinner reflects the action of the rapid-acting insulin injected before lunch.
  • The bedtime analysis reflects the action of the rapid-acting insulin injected before dinner.
  • The morning analysis reflects the action of the intermediate-acting insulin injected at bedtime.

– Aims:
  • Blood glucose: minimum 70 mg/dl, maximum 160 mg/dl.
  • Urine glucose: 0.
    → same insulin dose.

– Hyperglycemia (check for ketones in urine or blood):
  • Without clinical signs: injection of a fast-acting insulin analog (dose \( \leq \frac{1}{10}\) of the daily dose) to repeat every 2 or 3 h, if necessary.
  • With clinical signs of hyperglycemia and ketones: injection of a fast-acting insulin analog (dose \( \leq \frac{1}{5}\) of the daily dose) to repeat every 2 or 3 h, if necessary.

**Particular circumstances**

– Sport:
  • Predictable sport: decrease of the insulin dose (working during or even after physical activity) by 10% or more and/or to eat more sugar, before, during, and even after physical activity.
  • Unpredictable sport: to eat more sugar, before, during, and even after physical activity.
  • Avoid injecting insulin near a muscle submitted to physical activity.

– Snack or extra meal:
  • Predictable snack: injection of a fast-acting insulin analog just before or even after.
  • Unpredictable snack: injection of a fast-acting insulin analog just after.

**CONCLUSION**

Because recent multicenter studies, even those performed in developed countries without financial restriction, show that treatment of childhood diabetes is inadequate in general and that levels of HbA1c are very different [7, 10, 11, 14-18], diabetes treatment teams should individually explore the reasons for failure, without any prejudice or bias [11, 18].

The good treatment is signed by good HbA1c associated with good quality of life, and is not necessarily exportable without adjustment to the local way of life.

No dogmatism! Only the objective result is important!

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