SOMATO PUBLICATIONS

Archives of Diabetes

Review Article

Diabetic Children's Dietary Evolution Since the Discovery of Insulin: Personal Experience and Opinion

Harry Dorchy*

Université Libre de Bruxelles, Past Head, Diabetology Clinic, University Children's Hospital Queen Fabiola, Avenue JJ Crocq 15, 1020 Brussels, Belgium

***Address for Correspondence:** Harry Dorchy, Université Libre de Bruxelles, Past Head, Diabetology Clinic, University Children's Hospital Queen Fabiola, Avenue JJ Crocq 15, 1020 Brussels, Belgium, E-mail: hdorchy@ulb.ac.be

Received: 11 November 2019; **Accepted:** 21 November 2019; **Published:** 22 November 2019

Citation of this article: Dorchy, H. (2019) Diabetic children's dietary evolution since the discovery of insulin: personal experience and opinion. Arch Diabetes, 1(2): 015-019.

ABSTRACT

Over the years, various diets have been proposed often without scientific evidence. Restriction in calories, carbohydrates, or lipids was advocated, but also a high intake of the same nutriments or of proteins. "Free diet" as well as "anarchic" eating habits as opposed to "restricted" and "weighed" diets (thanks to "sliding scales" or "exchange lists") have been proposed. Slowly there was an evolution towards a normal and flexible diet. Both insulin therapy and diet are inseparable. The number of daily insulin injections, 2 or ≥ 4 or the use of pumps, by itself does not necessarily give better results. Because recent multicenter studies, even those performed in developed countries without financial restriction, show that treatment of childhood, adolescent and young adults diabetes is inadequate in general and that levels of HbA1c are very different, diabetes treatment teams should individually explore the reasons for failure, without any prejudice or bias. Any dogmatism must be avoided.

Keywords: Diabetic children, Diet, Insulin therapy, HbA1c

The Age of Dogmatic Diets without Scientific Evidence

Diet has traditionally played an important role in diabetic therapy. Before the discovery of insulin, a restrictive diet, yielding more or less positive results in 80% of diabetic subjects, was the only therapy available. Later, it became evident that diet, as such, is the ideal treatment for obese diabetics of middle age (now called type 2 diabetes that is beginning, however, to be encountered in children and adolescents with the rising rate of obesity) [1] since the problem is not based on a lack of insulin. In children and adolescents, diabetes is most often associated with a genetically determined predisposition, the presence of autoimmune markers, aggressive beta-cell destruction leading to severe insulin deficiency (type 1 diabetes), and the urgent need for insulin replacement therapy. Until insulin was made available, a diagnosis of diabetes in children was a death sentence within weeks or months.

Many researchers had tried to isolate insulin from animal pancreas. In 1921, the Romanian Nicolae Paulescu, who studied pancreatic secretion in Paris, developed an aqueous pancreatic extract that was injected into a diabetic dog, reducing hyperglycemia and ketonuria. Paulescu published his experience in the August 1921 issue of the Archives Internationales de Physiologie [2]. In 1922, Canadians Frederick Banting and Charles Best, under the direction of Macleod, with the help of the biochemist James Collip, have prepared clearer insulin free from impurities. This extract was injected successfully to Leonard Thomson, a ketotic diabetic child aged 14 years old [3]. He had a high-fat diet and died in 1935. The 1923 Nobel Prize in Physiology and Medicine was attributed to the Canadian team, ignoring the pioneering work of Paulescu.

Over the years, various diets have been proposed often without scientific evidence. Restriction in calories, carbohydrates, or lipids was advocated, but also a high intake of the same nutriments or of proteins. "Free diet" as well as "anarchic" eating habits as opposed to "restricted" and "weighed" diets (thanks to "sliding scales" or "exchange lists") have been proposed [4,5]. A total caloric restriction inhibits growth and, associated with a lack of insulin, leads to the Mauriac syndrome [6].

One of the main errors was (is! cf "carbohydrate counting") to speculate that there exists a direct linear correlation between the injection of x units of insulin and the utilization of y grams of glucose [7]. If it was true, one should give more insulin to practice physical activity! In reality, it is the reverse! The reason is that the affinity of the muscular insulin receptors, as well as the activity of GLUT-4, is increased during (and even after) muscular work, but it is not the case for the hepatic insulin receptors. Moreover, the regulation of glucose is dependent on a number of factors such as counter-regulatory hormones, gluconeogenesis, the relative use of glucose and non-esterified fatty acids as energy for muscular exercise, psychological factors (stress), and other mechanisms that are beyond our control [8,9]. It has been shown that a decrement in glucose per se or a signal elicited by a moderate decrement in glucose, but largely independent of glucagon and hepatic catecholamine action, stimulates glucose releasefrom the liver during exercise [10].

Alas nowadays carbohydrate counting, even if disputed [11] is still widely used without proving best HbA1c levels [12,13]. Explanations on diet should focus on quality rather than quantity of foodstuffs and should be given by a multidisciplinary team, taking into account the insulin regimen (two daily insulin free-mixed, basal-bolus, CSII) and the traditional food habits varying tremendously from one country to another as well as the allocation and the time schedule of meals.

Evolution to a Normal and Flexible Diet

In the 70s, clinical studies by Henri Lestradet in France [14], and by our group in Belgium [15], demonstrated that diabetic children, receiving an adequate and flexible dose of insulin according to self monitoring of urine glucose at that time, benefited from a normal "spontaneously balanced and adapted diet". The best glycemic control was not obtained by totally free or rigid diets, but by appropriate daily adjustments of insulin and adequate distribution of normal food intake [5,13]. Diabetic children have no fixed energy requirements because they grow and have variable physical activities. Energy intake may fluctuate from day to day without mandatory changes in the need for insulin or in the degree of glycosuria [14,15]. To impose a weighed and measured diet is undesirable both for diabetic control and for psychological reasons. Moreover, the notion of "measuring" leads to rejection of the entire therapeutic regimen and to emotional problems. A restricted diet that controls only carbohydrate intake and thus favors fat intake is potentially dangerous for the vascular system.

On the other hand, even in the seventies we observed a too high fat consumption in Belgian diabetic children (42% of the total caloric intake) [16], persisting later [17], and we had/have to concentrate our efforts on emphasizing fat rather than carbohydrate restriction, which is the case nowadays in many industrialized countries. Nearly after introduction of clinical use of glycated hemoglobin, we noted a positive correlation between the blood levels of HbA1c and those of total cholesterol and of triglycerides [18], which we confirmed later adding the LDL-cholesterol and apolipoprotein B [19]. There was no relationship between HbA1c and HDL-cholesterol or its subfractions [19,20]. This was confirmed by other studies [21]. Moreover we observed the lack of relation between HbA1c levels and oxidized LDL [22] or serum lipoprotein (a) [23]. However, using multiple linear regression analysis, we have shown an independent positive correlation with daily energy intake, saturated fat intake and apolipoprotein B levels [24].

The Insulin-Diet Couple

Too many proposals for managing the diets of diabetic children were/are not related to insulin regimens. Both insulin therapy and diet are inseparable. Modern insulin regimens for the treatment of type1 diabetes are highly individualized. The concept of an individually tailored medicine accounts for a broad variety of different applied insulin regimens. Flexible, personalized insulin preparations and fixed premixed preparations are in use. Despite clear recommendations for insulin management in children and adolescents with type 1 diabetes there is little distinctiveness about concepts and the nomenclature is confusing. However, in 2015, Neu et al have proposed a classification in order to offer the opportunity to compare therapeutic strategies [25].

In 1993, according to the diabetes control and complications trial research group (DCCT), HbA1c levels must be, in adults, under 7% (53 mmol/mol), if the upper normal limit is about 6% (42 mmol/mol) [26]. The DCCT obtained such results utilizing targeted blood glucose (BG) treatment decisions usually with multidose insulin (MDI) (≥ 3 shots/d) and/or insulin pump treatment (called "intensive" treatment), compared to a relatively fixed insulin dose schedule (1 or 2 shots/d) and daily self-monitoring of urine or BG in the control group (called "conventional" therapy). Apart from insulin regimens, the 2 groups differ mainly by education and follow-up. The patients in the intensive-therapy group visited their study center each month and were contacted even more frequently by telephone to review and adjust their regimens.Unfortunately, in this study, diet was not defined. In the subset of adolescents with "intensive" treatment, mean HbA1c was only 8.5% (69 mmol/mol)! [27].

After publication of the conclusions of the DCCT and of my own results, causing some debate about "Dorchy's recipes" [28,29], The Hvidoere Study Group on childhood diabetes (HSG) evolved in 1994, during a workshop, to discuss strategies that could be important in improving quality of pediatric and adolescent diabetes care and, therefore good HbA1c levels. Four international comparisons of metabolic control (1995, 1998, 2005, 2009) have been performed in about twenty pediatric diabetology centers from industrialized countries in Europe, North America, Japan and Australia. Cameron, et al. [30] have reviewed these studies and note that "The one center that has consistently had the lowest HbA1c values from 1995 to 2009" is my center in Brussels with a mean HbA1c (upper normal limit: 6.3% or 45 mmol/mol) of 7.3 and 7.4% (56 and 57 mmol/mol) [13]. They comment: "The Hvidoere member in question is highly charismatic and has a very prescriptive, "recipe"-based approach to managing diabetes in his clinic. He prescribes mostly twice-daily free mixing injections of insulin and eschews, a flexible approach to dietary intake. This does not appear to be at the expense of either hypoglycemia or QOL in his patient group. Although many aspects of his practice are shared by other Hvidoere members, it has proved very difficult to translate this total approach into other contexts for a variety of reasons. However, this experience is emblematic that consistently excellent outcomes can be achieved by simple, "non-intensive" insulin regimens that are underpinned by a strong philosophy of care. Perhaps the conclusions relating the best clinical practice drawn from the entire body of work of the Hvidoere studies can be best summarized as -be dogmatic about outcome but flexible in approach". This is true for the couple insulin-diet.

What Are Our "Recipes" Concerning the Insulin-Diet Couple? [13,31,32]

Two daily insulin free-mixed regimen in children or even teenagers: Two daily insulin free-mixed regimen with an human rapid-acting insulin or a fast-acting analogue and NPH (*i.e.,* 4 insulins per day as in the basal-bolus regimen) in children < 15-16 years is easy and effective in countries where the meal schedule allows correct allocation of diet. The first injection (and insulin dose alteration) is done before going to school and the second injection (and insulin dose alteration) after returning from school, before dinner, with the facultative help of the parents. Diabetic children have to eat a snack in the middle of the morning and afternoon periods with their friends, without the need to give an additional insulin injection or to measure blood glucose. This reduces the risk of insulin omission. The doses of the 4 insulins are adjusted according to the results of 4 daily blood glucose measurements (or better with Continuous Glucose Monitoring (CGM), i.e. the FreeStyle Libre® which is available, costless for the patients, in Belgium since August 2016) of the preceding days (retroactive analysis) and not only to the present glycemia (reactive responsitivity). A third injection with a fast-acting analogue may be done to allow a greater snack or to correct hyperglycemia.

Basal-Bolus regimen in adolescents but more complicated: Basal-bolus regimen in adolescents gives increased flexibility in daily life and dietary freedom, but is more complicated; no simplistic sliding scales according to the present glycemia; insulin dose alteration must be triple: (1) retrospective, according to previous BG analysis, trial and error experiments, in order to enjoy more freedom for meals, sports, etc; (2) prospective according to programmed changes in meals and sports (*i.e.,* add more insulin if overeating or temporarily reduce insulin dose to prevent activity-related expected hypoglycemia); and (3) with only a "touch" of compensatory adaptation (reactive dose changes) according to the present glycemia. This needs psychological maturity and ongoing education support and teaching of child, adolescent and family members, otherwise the multiple injection system leads to anarchy, "cheating" and obesity, especially but not only in adolescent girls. Before or after meals, there is an injection of rapid human insulin or fast-acting analogue, and before sleeping, an injection of a stable long-acting analogue. The doses of the 4 insulin injections are adjusted according to analysis of the results of at least 4 daily blood glucose measurements if three meals (or a lot better with CGM).

CSII is not often recommended: In our experience, CSII is very rarely recommended and used in about 10% of our patients. We do not promote use of expensive insulin pump regimens (In Belgium treatment of type 1 diabetes is nearly costless for the patients, but the use of an insulin pump has a overhead cost of ±200€/month for the national Social Security) and believe that patients and their family members can do as well with pens and syringes. Pumps in children and adolescents have not been associated with significant improvements in daily BG results or in A1c according to results of the HSG [30] and also by the PedPump study in 30 centers of 17 countries. In that study, the use of less than 6.7 daily boluses was a significant predictor of an HbA1c level > 7.5% or 58.5 mmol/mol, despite increasing blood glucose measurements and the added expense that this entails [33]. Fortunately the use of CGM solves the problem of multiple pricks at fingertips. In a Belgian retrospective cross-sectional study among 12 pediatric centers, A1c was higher among patients with insulin pump therapy [34]. Comparing the median HbA1c levels obtained with the different insulin regimens, the freemix 2 regimen (7.5 % or 58 mmol/mol) was significantly lower than the basal-bolus (7.7 % or 61 mmol/mol) and the CSII (7.9 % or 63 mmol/mol) regimens. However, using multiple linear regression, only CSII remained associated with higher HbA1c levels. In a French study including 4293 children and adolescents (12.9 ± 2.6 yr, diabetes >1 yr) attending AJD (Aide aux JeunesDiabétiques) summer camps between 2009 and 2014, the percentage of youth treated with insulin pumps increased up to about 45%, basal bolus stabilized around 40%, and other regimens decreased majorly. HbA1c was higher with premixed insulins only regimens (9.05 ± 2.43%), but there was no difference between pump (8.12 ± 1.09%), basal bolus (8.32 ± 1.33%) and two to three injections (8.18 ± 1.28%) [35]. It should be noted that the results of HbA1c in the Belgian study are better regardless of insulin therapy.

No carbohydrate counting: The dietician never gives rigid meal plans or exchange lists. "Diet" is never prescribed. No carbohydrate counting is recommended because there is no linear correlation between the metabolization of X grams of glucose by Y units of insulin (see above). The dietician builds up a picture of the family's and child or teen's usual habits and life style. When possible, the family is encouraged to adopt a similar and normal eating pattern so that the child and adolescent with diabetes 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 according to the cumulated action of the insulins [31,32]. The dietician must know perfectly the actions of the insulins and their adjustment. While being criticized for this being too difficult, our glycemic control and A1c results certainly prove that this is feasible to accomplish with large numbers of children, adolescents and young adults. In addition, all members of the professional diabetes team must have the same treatment philosophy to provide the same message and same target BG and A1c goals [36].

Confusion between conventional and intensive therapy

The team that I have created in Brussels believes it is inappropriate to automatically designate the term "intensive treatment" only to imply insulin pumps or multidose insulin regimens when, in fact, it is the goals of glycemic control and A1c achievement that should define intensified treatment not the manner or number of insulin doses each day. It is inadequate to systematically assign the multiple injection regimen, or the pump therapy, to "intensive" treatment, and some forms of the twice-daily injection regimen (Freemix+ at Brussels in the HSG) abusively called "conventional" to a non-intensified therapeutic category of insulin therapy. Indeed, a multiple injection regimen, or the use of pumps, not associated with a good intensified and complete education, as well with the application of the consecutive knowledge, may have deleterious effects on HbA1c, as shown by the HSG [30]. The confusion between "conventional therapy" and "intensive therapy" was born from misinterpretation of how the DCCT was structured in 1993 [26].

General Conclusion

Because recent multicenter studies, even those performed in developed countries without financial restriction, show that treatment of childhood, adolescent and young adults diabetes is

inadequate in general and that levels of HbA1c are very different, diabetes treatment teams should individually explore the reasons for failure, without any prejudice or bias, in their own centers especially when center average A1c results are over 8% (64 mmol/mol). The number of daily insulin injections, 2 or ≥ 4 or the use of pumps, by itself does not necessarily give better results. Merely increasing the number of daily insulin injections or encouraging insulin pump treatment does not automatically produce better results although may offer greater flexibility for the patient and family. Diet has traditionally played an important role in diabetic therapy. Over the years, various diets have been proposed often without scientific evidence. Dietary recommendations issued over the last few years are the same for diabetic and non-diabetic individuals in order to avoid degenerative diseases. In many industrialized countries, the intake of fat is too high, and of complex carbohydrate too low. Explanations on diet should focus on quality rather than quantity of foodstuffs, and must be dependent of the insulin regimen (inseparable insulin-diet couple). Prescription of a highly rigid diet has proved ineffective in producing adequate metabolic control, and increases the risk of deviations from the diet.

Key remains unified education by a team of diabetes professionals (at least pediatric diabetologists, nurses, dieticians) who know their patient and his/her family as well as insulin action and equilibrated diet, and mutually sets goals known and agreed upon by not only the entire team providing such care but also the patient and his/her family. Treatment cost *vs* results must also be taken into account.

Fortunately, since the costless use of CGM or more exactly Flash (every second) Glucose Monitoring in Belgium from 2016, one observes a reduction of severe hypoglycemia in real life [37]. However, in that study, the definition of severe hypoglycemia is unclear. Any dogmatism must be avoided!

References

1. Arslanian, S. (2002) Type 2 diabetes in children: clinical aspects and risk factors. Horm Res, 57 (Suppl 1): 19-28.
2. Paulesco N. (1921) Recherche sur le rôle du pancréas dans l'assimilation nutritive. Arch Int Physiol, 17: 85-109.
3. Karamitsos, DT. (2011) The story of insulin discovery. Diabetes Res Clin Pract, 93 (Suppl1): 2-8.
4. Lestradet H. (1953) Le problème du régime chez les diabétiques. Evolution des conceptions physiopathologiques. Incidences thérapeutiques. Presse Med, 61: 792-796.
5. Dorchy, H. (2003) Dietary management for children and adolescents with diabetes mellitus ; personal experience and recommendations. J Pediatr Endocrinol Metab, 16(2): 131-148.
6. Dorchy, H., Van Vliet, G., Toussain,TD., Ketelbant-Balasse, P., Loeb, H. (1979) Mauriac syndrome: 3 cases with retinal angiofluorescein study. Diabete Metab, 5(3): 195-200.
7. Sharp, A. (1999) Nutrition therapy for children and adolescents with diabetes. In: Franz MJ and Bantle JP, editors. Medical nutrition therapy for diabetes. Alexandria: American Diabetes Association, 211-228.
8. Dorchy, H., Mozin, MJ., Loeb, H. (1981) Unmeasured diet versus exchange diet in diabetics. Am J Clin Nutr, 34(5): 964-965.
9. Dorchy, H., Poortmans, J. (1996) Juvenile diabetes and sports. In: Bar-Or O and the International Olympic Committee, editors. The child and adolescent athlete. Oxford: Blackwell Science, 455-479.
10. Cocker, RH., Koyama, Y., Denay, JC., Camacho, RC., Lacy, DB., Wasserman, DH. (2002) Prevention of overt hypoglycemia during exercise. Stimulation of endogenous glucose production independent of hepatic catecholamine action and changes in pancreatic hormone concentration. Diabetes, 51(5): 1310-1318.
11. Davis, NJ., Wylie-Rosett, J. (2008) Death of carbohydrate counting? Diabetes Care, 31(7): 1467-1468.
12. Spiege, G., Bortsov, A., Bishop, FK., Owen, D., Klingensmith, GJ., Mayer-Davis, EJ., et al. (2012) Randomized nutrition education intervention to improve carbohydrate counting in adolescents with type 1 diabetes study: is more intensive education needed? J Acad Nutri Diet, 112(11): 1736-1746.
13. Dorchy, H. (2015) One center in Brussels has consistently had the lowest HbA1c values in the 4 studies (1994-2009) by the Hvidoere International Study Group on Childhood Diabetes: What are the "recipes"? World J Diabetes, 6(1): 1-7.
14. Lestradet, H., Dartois, AM., Machinot, S. (1974) L'alimentation spontanée de l'enfant et de l'adolescent diabétique traité par l'insuline. Ann Pediatr, 21: 667-676.
15. Dorchy, H., Mozin, MJ., Smets, P., Ernould, C., Loeb, H. (1977) Spontaneous variations in food intake and balance of diabetes. A covariance analysis. Acta Paediatr Belg, 30(1): 21-26.
16. Mozin, MJ., Dorchy, H., de Maertelaer, V., Ernould, C. (1978) Food habits of 215 diabetic children in Belgium. Acta Paediatr Belg, 31(1): 56-58.
17. Dorchy, H., Bourguet, K. (1997) Nutritional intake of Belgian diabetic children. Diabetes Care, 20: 1046-1047.
18. Dorchy, H., de Maertelaer, V., Toussaint, D., Loeb, H. (1981) Relations entre ingesta lipidiques (cholestérol, graisses saturées et polyinsaturées), cholestérolémie, contrôle métabolique (HbA1c) et rétinopathie des enfants diabétiques. RevPediatr, 17: 259-270.
19. Willems, D., Dorchy, H. (1990) Taux des lipoprotéines et des apolipoprotéines chez les jeunes diabétiques insulinodépendants. Relations avec l'hémoglobine glycosylée et la fructosamine. Presse Med, 19(1): 17-20.
20. Willems, D., Dorchy, H. (1991) Sous-fractions du HDL-cholestérol chez les jeunes diabétiques insulinodépendants. Press Med, 20: 86.
21. Virtanen, SM., Rasanen, L., Virtanen, M., Sippola, H., Rilva, A., Kaprio, EA., et al. (1993) Association of serum lipids with metabolic control and diet in young subjects with insulin-dependent diabetes in Finland. Eur J ClinNutr, 47(2): 141-149.
22. Willems, D., Dorchy, H., Dufrasne, D. (1998) Serum antioxidant status and oxidized LDL in well-controlled young type 1 diabetic patients with and without subclinical complications. Atherosclerosis, 137 (Suppl): S61-64.
23. Willems, D., Dorchy, H., Dufrasne, D. (1996) Serum lipoprotéin (a) in type 1 diabetic children and adolescents: relattionships with HbA1c and subclinical complications. Eur J Pediatr, 155: 175-178.
24. Messaaoui, A., Willems, D., Mélot, C., Dorchy, H. (2012) Risk markers for cardiovascular disease in young type 1 diabetic patients: lipoproteins, high-sensitivity C-reactive protein and adiponectin. Acta Clin Belg, 67(2): 79-82.
25. Neu, A., Lange, K., Barrett, T., Cameron, F., Dorchy, H., Hoey, H., et al. (2015) Classifying insulin regimens - difficulties and proposal for comprehensive new definitions. Pediatr Diabetes, 16(6): 402-406.
26. Nathan, DM., Genuth, S., Lachin, J., Cleary, P., Crofford, O., Davis, M., et al. (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med, 329(14): 977-986.

27. The Diabetes Control and Complications Trial Research Group. (1994) Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. J Pediatr, 125(2): 177-188.

28. Dorchy, H., Roggemans, MP., Willems, D. (1997) Glycated hemoglobin and related factors in diabetic children and adolescents under 18 years of age: a Belgian experience. Diabetes Care, 20(1): 2-6.

29. Dorchy, H. (1994) Dorchy's recipes explaining the "Intriguing efficacity of Belgian conventional therapy". Diabetes Care, 17(5): 458-460.

30. Cameron, FJ., de Beaufort, C., Aanstoot, HJ., Hoey, H., Lange, K., Castano, L., et al. (2013) Lessons from the Hvidoere International Study Group on childhood diabetes: be dogmatic about outcome and flexible in approach. Pediatr Diabetes, 14(7): 473-480.

31. Dorchy, H. (2000) Insulin regimens and insulin adjustments in diabetic children, adolescents and young adults: personal experience. Diabetes Metab, 26(6): 500-507.

32. Dorchy, H. (2010) Stratégie thérapeutique dans le diabète de type 1 (insuline, alimentation, sport) "Dorchy'srecipes". Rev Med Brux, 31 (2Suppl): S37-53.

33. Danne, T., Battelino, T., Jarosz-Chobot, P., Kordonouri, O., Pánkowska, E., Ludvigsson, J., et al. (2008) Establishing glycaemic control with continuous subcutaneous insulin infusion in children and adolescents with type 1 diabetes: experience of the PedPump Study in 17 countries. Diabetologia, 51(9): 1594-1601.

34. Doggen, K., Debacker, N., Beckers, D., Casteels, K., Coeckelberghs, M., Dooms, L., et al. (2012) Care delivery andoutcomes among Belgian children and adolescents with type1 diabetes. Eur J Pediatr, 171(11): 1679-1685.

35. Keller, M., Attila, R., Beltrand, J., Djadi-Prat, J., Nguyen-Khoa, T., Jay, JP., et al. (2017) Insulin regimens, diabetes knowledge, quality of life, and HbA1c in children and adolescents with type 1 diabetes. Pediatr Diabetes, 18(5): 340-347.

36. Swift, PG., Skinner, TC., de, Beaufort, CE., Cameron, FJ., Aman, J., Aanstoot, HJ., et al. (2010) Target setting in intensive insulin management is associated with metabolic control: the Hvidoere childhood diabetes study group centre differences study 2005. Pediatr Diabetes, 11(4): 271-278.

37. Messaaoui, A., Tenoutasse, S., Crenier, L. (2019) Flash glucose monitoring accepted in daily life of children and adolescents with type 1 diabetes and reduction of severe hypoglycemia in real-life use. Diabetes Technol Ther, 21(6): 329-335.