ORIGINAL ARTICLE

Transitioning to Insulin Analogs in Tunisian Children with Type 1 Diabetes: Efficacy and Safety

Transition vers les analogues de l'insuline chez les enfants tunisiens atteints de diabète de type 1: Efficacité et sécurité

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Abstract

Introduction: there is a lack of research evaluating the impact of therapeutic switching from human insulin to analogues, particularly in paediatric populations from low- and middle-income countries.
Aim: The study aimed to retrospectively assess the effectiveness and safety of transitioning from human insulin to insulin analogs in Tunisian children with diabetes.
Methods: This retrospective descriptive study included children with type 1 diabetes who changed their insulin therapy protocol after at least one year of treatment with human insulin. Clinical, therapeutic, and glycaemic homeostasis parameters were assessed following the transition from human insulin (NPH + rapid-acting insulin) to the Basal-Bolus insulin analog- protocol.
Results: The study included 60 patients. Following the switch, all patients showed a significant reduction in mean fasting blood glucose levels (11.11 mmol/l vs. 8.62 mmol/l; p=0.024). Glycated haemoglobin A1C levels decreased notably in children who adhered to their diet (from 9.93% to 8.38%; p=0.06) and/or engaged in regular physical activity (from 10.40% to 8.61%; p=0.043). The average number of hypoglycemic events per year decreased from 4.03 events/year to 2.36 events/year (p=0.006), along with a decrease in the rate of patients hospitalized for acid-ketotic decompensation (from 27% to 10%; p=0.001). Financial constraints led to 82% of patients reusing microfine needles ≥2 times per day, and 12% were compelled to revert to the initial insulin therapy protocol due to a lack of access to self-financed microfine needles or discontinued social coverage.
Conclusions: Although insulin analogues offer clear benefits, their use poses challenges as a therapeutic choice for children with diabetes in low- to middle-income countries. These challenges hinder the achievement of optimal glycemic control goals.

Key words: Children; Type 1 Diabetes; Tunisia, Human Insulin; Insulin Analogs; Risk Factors.

Résumé

Introduction: Le passage thérapeutique de l'insuline humaine aux analogues fait l'objet de peu de recherches, en particulier chez les enfants diabétiques des pays à revenu faible à intermédiaire.
Objectif: Cette étude vise à évaluer rétrospectivement l'efficacité et la sécurité de ce changement chez les enfants tunisiens atteints de diabète type1.
Méthodes: Cette étude descriptive rétrospective a inclus les enfants atteints de diabète de type 1 ayant modifié leur protocole d'insulinothérapie après une durée d'au moins un an sous insuline humaine. Les paramètres cliniques, thérapeutiques et l'équilibre glycémique ont été évalués après le passage de l'insuline humaine (NPH + insuline rapide) au protocole Basal-Bolus d'analogues d'insuline.
Résultats: L'étude a colligé 60 patients. Après le changement, tous les patients ont eu une réduction significative de la glycémie à jeun (11,11 mmol/l vs 8,62 mmol/l ; p=0,024). Les niveaux d'hémoglobine glyquée A1C ont diminué chez les enfants respectant leur régime alimentaire (de 9,93% à 8,38% ; p=0,06) et/ou pratiquant une activité physique régulière (de 10,40% à 8,61% ; p=0,043). Le nombre moyen d'événements hypoglycémiques par an a diminué (4,03 événements/an à 2,36 événements/an ; p=0,006), tout comme le taux d'hospitalisation pour décompensation acidocétosique (27% à 10% ; p=0,001). En raison de contraintes financières, 82% des patients ont réutilisé des aiguilles microfines ≥2 fois par jour, et 12% ont dû revenir au protocole initial faute d'accès à des aiguilles microfines autofinancées ou en raison de la cessation de la couverture sociale.
Conclusions: Malgré les avantages des analogues d'insuline, leur utilisation pose des défis en tant que choix thérapeutique pour les enfants diabétiques dans les pays à revenu faible à intermédiaire. Ces défis entravent l'atteinte des objectifs de contrôle glycémique optimal.

Mots clés: Enfants ; Diabète De Type 1 ; Insuline Humaine ; Analogues D'insuline ; Facteurs De Risque; Tunisie.

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Introduction

Considerable progress has been made in the treatment of pediatric T1DM, offering multiple choices regarding not only molecules but also insulin therapy protocols (1). This diversity in insulin therapy for children with T1DM provides greater flexibility and adaptation to their physical, psychological and socioeconomic conditions (2). In low- and middle-income countries, the management of children with T1DM remains a complex issue (3). After more than a century since the discovery of insulin and despite numerous advances, inequalities in access to different forms of insulin persist (3). Therapeutic choice in insulin therapy for diabetic children remains difficult in low- and middle-income countries (4). What is the efficacy and safety of transitioning from human insulin to insulin analogues in children with diabetes? Are there any challenges and precautions to consider during the transition from human insulin to insulin analogues in children with diabetes living in a developing country? Few studies have answered these questions.
The study aimed to retrospectively assess the effectiveness and safety of transitioning from human insulin to insulin analogs in Tunisian children with diabetes.

Methods

This was a retrospective descriptive analytical study. Data collection took place in January 2020 in the pediatric ward of Ben Arous in Tunisia.
The patients included in the study were children under 18 years of age followed for T1DM in the pediatric ward, initially treated with human insulin protocol two injections per day and then with insulin analog protocol Basal-Bolus for a duration of at least one year for each type of insulin. Patients with less than one year of follow-up on insulin therapy or analogs were excluded.
Initial insulin therapy: all children started their treatment with a mixture of semi-slow NPH insulin and fast human insulin in the same syringe delivered in two subcutaneous injections per day. Insulin therapy with insulin analogs: Insulin injections were made through a pen-injector following the Basal-bolus protocol.
Blood glucose monitoring was done via self-monitoring of pre-prandial and postprandial capillary blood glucose levels by the patient, quarterly fasting venous blood glucose and glycated hemoglobin (HbA1c).
Staturo-weight growth was assessed according to the The WHO Growth Charts: Assessing Child Growth and Development for boys and girls. Body mass index (BMI) was interpreted according to the WHO BMI-for-age table (girls and boys).
Epidemiological, clinical, therapeutic parameters and glycemic homeostasis of each child were analyzed before and after change of insulin therapy. All data were entered and analyzed using SPSS 18.0 software. Analysis was based on Student t test and $\chi 2$ test.

Results

Epidemiological description of patients

A slight male predominance was noted (57%) (34 boys vs 26 girls). The mean age at the time of discovery of diabetes was 7.21 years. At the time of switching from HI to insulin analogues, the average age of the patients was 10.9 years and the average history of diabetes was 3.7 years. The average socioeconomic class represented 86% of the patients. All patients had a social security coverage allowing them to be reimbursed for insulin analogs, glucometers, and blood glucose strips, as well as free access to hospital care. The microfine needles necessary for the use of insulin analogs were not reimbursed. Children from a lower socioeconomic background have limited opportunity to make choices in their insulin therapy. Their social coverage only allows them access to human insulin (Table n°1).

Table 1. Epidemiological characteristics of patients at the time of insulin therapy switch.

Patients	60
Girls	26
Boys	34
Average age	10.9 years (4 - 16.5 years)
Average history of diabetes	3.7 years (1 – 6.2 years)
Socioeconomic class	
Upper social class	9 (14%)
Middle class	51 (86%)
Lower social class	0

Insulin therapy

Intensive insulin therapy based on insulin analogs was initiated according to the Basal-Bolus protocol using fast analogs (Aspart 95% or Gluisine5%) and slow analogs (Detemir 45% or Glargine 55%). Due to their high cost and the absence of social security coverage, the majority of patients (82%) used the same needle more than twice a day.
After one year of protocol change, the mean annual used insulin dose increased significantly from 0.73 IU/kg/d of human insulin to 0.87 IU/kg/d ($p<0.001$) under the Basal-Bolus protocol.

Dietary education and sports activity

All children had dietary education sessions on average 2/year. The rate of compliance with the diet varied non-significantly before and after introduction of the analogs (19% vs. 21%, $p=0.8$). Due to lack of financial means, before or after the introduction of analogs, the majority (32) of patients did not practice sports : 53% versus 51% ($p=0.752$).

Clinical follow-up

Growth and trophicity
During their follow-up, both before and after the use of the analogs, there was no significant difference in the patients' height growth evolution.

The mean BMI was 18.04% for a mean duration of human insulin use of 3.7 years. It had significantly increased to 19.20% after a mean duration of 1.7 years of analogs use (p=0.026). When analyzing the change in BMI we found: a decrease in the rate of obesity (9% vs. 8%; p=0.51), a decrease in malnutrition (31% vs. 15%; p=0.012) and an increase in overweight (11% vs. 24%; p=0.038).

Glycemic homeostasis

• *Preprandial blood glucose:*

All patients significantly lowered their mean fasting blood glucose. It decreased from 11.11mol/l vs. 8.62 mmol / l; (p=0.024).

• *Postprandial blood glucose (PPG)*:

Mean PPG decreased from 20.17 mmol /l under HI to 18.07 mmol /l under analogs. The rate of patients with a mean PPG >15 mmol/L decreased from 35% to 22% (p=0.573) after introduction of the analogs.

• *HBA1c*:

On insulin analogs, adherence to the diabetic regimen improved the mean HbA1c from 9.93% to 8.38% (p=0.06). In patients who regularly practiced sports, the use of analogs significantly lowered the mean annual HbA1c from 10.40% to 8.61% (p=0.043). However, the mean annual HbA1c increased from 9.62% to 10.09% after a mean duration of 1.7 years of using analogs (p=0.709). Children over 10 years of age significantly increased their mean HbA1c with the change in insulin therapy (9.47% vs. 10.3%, p=0.038). Regardless of treatment with human insulin or analogs, patients experienced an increase in annual HbA1c as the duration of diabetes lengthened and as children approached puberty, both of which negatively impacted diabetes control (p=0.05).

The results of this study did not demonstrate a significant difference regarding the choice of insulin analogue, whether it be detemir or glargine.

Acute complications

After the introduction of the analogs, the average number of hospital admissions of patients / year had significantly decreased from 0.35/year to 0.23 hospital admissions/ year (p=0.001).

• *Hypoglycemia*:

After the introduction of analogs, the rate of patients with one or more episodes of hypoglycemia / year decreased from 41% to 27% (p=0.067). Symptomatic hypoglycemia was significantly reduced from 45% with human insulin to 18% with analogs (p=0.034).

• *Keto acidosis de-compensation*:

With human insulin, 27% of patients (16) had at least one ketotic or ketoacid de-compensation versus (12) 20% after switching to insulin analogs (p=0.001). The factors of decompensation noted in the patients were: diet deviation (32% vs. 18% p=0.06), inter-current disease (32% vs. 27%), lipodystrophy (29% vs. 18%; p=0.08) and discontinuation of insulin therapy (7% vs. 37%; p=0.04).

Discontinuation of insulin analogs

Temporary discontinuation of intensive insulin therapy with analogs causing acid-keto de-compensation was due to: lack of financial means (22%), voluntary (78%).

The return to human insulin was marked in 12 patients after an average of 1.5 years of use. The definitive discontinuation of insulin analogs was due to the cessation of social security coverage (2) or to the difficulty in obtaining micro-fine needles which were self-financed (8). Two adolescents found a better quality of life with the twice-daily human insulin injection protocol.

The comparison of the most important epidemiological, clinical and therapeutic results is summarized in the Table n°2.

Table 2. Comparison of clinical, biological, and therapeutic parameters before and after introduction of intensive insulin therapy with insulin analogs.

Therapeutic characteristics	NPH+ rapid human insulin twice daily injection	Slow and rapid insulin analogs (Basal-Bolus)	p
Average duration of use in years	3.7	1.7	-
Average daily dose IU/kg/d	0.73	0.87	<0.001
Diet respected	11 (19%)	12 (21%)	0.8
Regular sports activity	7 (11%)	8 (13%)	0.75
Quarterly medical visits (%)	57	65	0.71
Average BMI (%)	18.04	19.2	0.026
Obesity	5 (9%)	4 (8%)	0.5
Overweight	7 (11%)	12 (21%)	0.04
Normal nutritional status	30 (49%)	33(52%)	0.
Malnutrition	18 (31%)	11(19%)	0.01
Average pre-prandial blood glucose mmol/l	11.11	8.62	0.024
Number of hypoglycemia / patient/years:			
Total	4.03	2.36	0.067
Girls	4.46	1.56	0.002
Boys	3.75	2.92	0.008
Average HbA1c (%)			
Total	9.62	10.09	0.79
Children adhered to diet.	9.93	8.38	0.06
Children practiced regular sports activity	10.4	8.61	0.04
Hospitalizations / year	0.35	0.23	0.001
Acid ketosis decompensations (%)	27.6	20	0.001

Discussion

The advent of rapid and slow insulin analogs has brought about a rapid and dramatic change in pediatric diabetes practices (1,2). In this study, after the introduction of the analogs, the insulin dose increased significantly. This dose escalation effect was confirmed by some authors (4,5) but refuted by others (6,7).

Switching from HI to analogs resulted in a significant increase in BMI (p=0.026). This increase was primarily related to the intensified insulin protocol (8,9). Optimizing diabetes management could limit weight gain to reduce overweight and obesity as well as comorbidities in children with T1DM (9,10). The observation of reduced malnutrition rates among diabetic children upon adopting insulin analogs suggests a potentially favorable impact on their nutritional status, potentially enhancing glycemic control and overall quality of life.

Diabetic children participate in fewer sports than their peers (11–13). The ease of use of insulin analogs allows children with diabetes to better organize themselves into regular physical activity. As a result, they will be able to better manage their disease by improving metabolic control, body composition, quality of life and mental well-being (12,14). In this study, glycemic control was improved mainly in children who adhered to their diets and those who engaged in regular physical activity. Therapeutic education of diabetic children should involve parents to encourage their children to engage in non-expensive physical activity to ensure continuity and regularity (13,14).

The role of analogs in improving preprandial blood glucose levels (15) has been confirmed in this study. Contrary to some authors (7), the improvement in postprandial glucose levels was not significant in this population, which could be due to the high rate of children not adhering to the diabetic diet before or after insulin analogs. In fact, analogs alone will not improve the metabolic balance of diabetic children without avoiding dietary mistakes (14). Therapeutic nutritional education should take into consideration the socio-economic conditions of the families and present adequate solutions to guarantee healthy and balanced meals according to international recommendations (16–18).

In this study, the switch from human insulin in twice-daily injection to analogues in Basal-Bolus protocol did not improve the level of HbA1c, as has been demonstrated by some authors (15). These results can be explained by the high rate of patients not respecting the diabetic diet (16,19), not practicing physical activity(20), and using the same microfine needle several times. The needle reuse can cause lip hypertrophy which is a preventable etiology of poor diabetic control (21,22). Type 1 diabetes incurs substantial out-of-pocket expenses (OOPE) on insulin and diabetes-related supplies (3,23,24). In developing countries, children with T1DM treated by analog in Basal-Bolus protocol, could not maintain this therapeutic choice in its optimal conditions. For manufacturers, technological feasibility and economic viability also need to be considered when developing injection devices (25,26).

This study has confirmed the major role of insulin analogs in reducing hypoglycemia in diabetic children (5,7). As previously shown (7,15), acidotic decompensations decreased after switching to analogs. During this study, the rate of temporary discontinuation of insulin therapy was significantly increased. Ensuring continuity in the use of safe insulin analogs appeared difficult in children with medium to low parental socioeconomic status. A significant linear relationship has been demonstrated between socioeconomic status and diabetes control (6,23,24). Therapeutic education of these children should be increasingly customized. The treating physician should anticipate situations of difficulty in accessing care or in obtaining the materials necessary for the adequate management of their diabetes by preparing scenarios with pre-established action plans as soon as insulin analogs are introduced to avoid the sometimes-fatal interruption of insulin therapy.

This study has inherent limitations as it is retrospective in design and was conducted at a single center dedicated to the management of pediatric diabetes. In order to further delve into the analysis of the impact of insulin therapy selection on glycemic control in diabetic children, taking into account both the socio-economic status of patients and their place of residence, it would be essential to conduct prospective multicenter studies.

Conclusion

Despite their value in reducing acute complications and improving glycemic control in diabetic children who adhere to their diet and regular exercise, switching to insulin analogs is a difficult therapeutic choice to maintain properly in diabetic children living in low- and middle-income countries. Therapeutic education should take into consideration the socio-economic conditions of these patients by encouraging the practice of the least expensive physical activities, by making the diet more personalized and by preparing personalized action plans in case of lack of access to care to prevent the discontinuation of insulin therapy. Until universal health coverage is achieved, equitable access to the best available treatments for people with diabetes should be the objective of the International Insulin Foundation.

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