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Relationship between glycemic control and metabolic implications of type 1 diabetes in children and adolescents

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Abstract

The objective of our work is to study the relationship between glycemic control and metabolic outcomes (severe hypoglycemia and ketoacidosis).

Material and Methods: Among 538 diabetics, we identified 69 patients with hypoglycemic or ketoacid comas. The HA1c assay was performed on a DCA 2000 analyzer.

Result: The incidence of acidotis coma is 0.93% and the incidence of hypoglycemic coma is 12%. The patients who had an acidotis coma had an HbA1c level between 6.5 and 11.5% with major hyperglycemia (3g/L to >5g/L). 63 diabetics have a hypoglycemic coma with duration of diabetes < 6 years. The number of hypoglycemic comas is inversely proportional to the duration of diabetes. One is more likely to have hypoglycemic comas for HbA1c levels < 7.5%, compared with HbA1c levels 7.5% and 8 or HbA1c levels > 8%. 45% of patients increased their HbA1c levels versus 35% who decreased it in the last quarter compared to the previous quarter.

Conclusion: This original work shows that there is an inverse relationship between the incidence of severe hypoglycemia and quarterly HbA1c values. A low HbA1c level exposes the T1DM child to a high risk of hypoglycemic coma. Thus, the fear of severe hypoglycemia would be at the origin of an alteration of the patient's glycemic balance and the high HbA1c values. Thus, multidisciplinary management (adequate treatment and initial therapeutic education) will help avoid metabolic complications in diabetics.

Keywords: insulin-dependent diabetes, ketoacidosis, hypoglycemic comas, glycated hemoglobin, glycemic equilibrium

Introduction

Diabetes is a leading cause of death in most developed, developing and newly industrialized countries1. Diabetes is the 1st pandemic of non-communicable diseases in the world. In 2019 it is estimated that 463 million people worldwide will have diabetes1. According to the World Health Organization (WHO) and the International Diabetes Federation (IDF), diabetes will affect 550 and 642 million people in 2025 and 2040 respectively [1]. An estimated 96,000 children under the age of 15 develop type 1 diabetes each year worldwide [2]. In Morocco, the prevalence of diabetes has increased considerably. In 2000, according to statistics from the Ministry of Health, more than 2 million people had diabetes 6.6% of the population (2.26% in 1976), 10 to 15% of whom were young and insulin-dependent [3]. In 2009, there were 3 million diabetics, of which 100,000 to 150,000 were insulin-dependent, including 10,000 children under 5 years of age. The number has tripled since 1990, and it is estimated that in the Rabat-Sale region alone, more than 1,000 children have type] T1DM [4] is a common metabolic disorder compared to other types of diabetes (Moddy, Neonatal, Mitochondrial) [5], induced by autoimmune destruction of insulin secreting β-cells via anti-islet antibodies [6]. The diagnosis of diabetes includes a clinical pathway through the appearance of clinical signs (polydipsia, polyuria, polyphagia, asthenia...), and a biological pathway based on the measurement of biological parameters: glycemia, glucose testing (glycosuria) and ketene bodies in urine [7].

The study of glycemic control in diabetic patients, the monitoring of diabetes (daily self- monitoring and glycated hemoglobin measurement) for the prevention of acute and chronic complications is recommended. Therefore, in T1DM, glycemic control depends on the only exogenous insulin provided to the body by treatment (insulin therapy), and the appropriate dietary regimen.

The goal of diabetes treatment is to achieve near-normal blood glucose values in order to avoid metabolic impacts (hypoglycemic coma and ketoacid coma) due to their short-term effects on quality of life and to prevent the risk of chronic complications of diabetes.

The aim of our work is to demonstrate the relationship between HbA1c levels, severe hypoglycemia and acidotic comas. The subjects of our study are T1DM patients who presented at least one hypoglycemic or acidotic coma during the three months preceding the HbA1c test.

In order to highlight the severity of metabolic incidences (severe hypoglycemia and acidotic comas), their effects on the life of diabetics and their relationship with the quarterly HbA1c level, this two- month study was carried out in the specialized pediatric diabetes center.

The objective is to study the metabolic impact, risk factors, and patient and caregiver challenges in achieving optimal glycemic control without risk of acute metabolic

complications in children and youth with diabetes.

Materials and Methods

Our study is carried out in the department of pediatric diabetology at the children's hospital of Rabat - CHU Ibn-Sina. Our work consists in interviewing diabetic patients in quarterly consultation, and who presented hypoglycemic or acidocetosis comas, and to note all the related information, namely, the causes, the clinical biological signs and the treatment. This on the one hand and, on the other hand, to measure the HbA1c level thanks to a capillary blood sample at the fingertip, the result of which is obtained in 6 minutes by immunological method on the DCA 2000 device.

The aim of this study is to demonstrate the relationship between glycemic control (quarterly glycated hemoglobin values) and metabolic outcomes: hypoglycemic coma and acidotic coma in a population of children and adolescents with T1DM.

These are 69 selected patients who are aged 1 to 19 years during the two months of the study. They are divided into two groups:

- Patients who have had at least one acidotic coma in the last trimester.
- Patients who have had at least one hypoglycemic coma in the last trimester.

Self-Monitoring of Blood Glucose Levels

It is a simple technique that consists of pricking the tip of the finger, taking a drop of blood, and placing it on the end of the reactive electrode of the meter (the strip). The results appear in a few seconds on the screen of the glucometer, which displays the level of glucose in the bloodstream [8]. The blood glucose meter was used for this purpose.

Determination of Glycated Hemoglobin by Immunological Method (DCA 2000)

The specific HbA1c concentration and the total hemoglobin concentration are measured separately. The ratio is expressed as a percentage of HbA1c.

An agglutinate causes agglutination to latex coated with a mouse monoclonal antibody specific for HbA1c [9]. This agglutination reaction results in increased light scattering, which is reflected by an increase in absorbance at 531nm. The HbA1c molecules present in the whole blood sample then compete to bind to the binding site of the latex antibody complexes, which are limited in number, resulting in an inhibition of agglutination and a decrease in light scattering. This decrease can be measured. It corresponds to a decrease in absorbance at 531nm. The HbA1c concentration is then quantified using a calibration curve of the absorbance established in relation to the HbA1c concentration.

The percentage of HbA1c in the sample is calculated according to the following relationship:

$$\text{HbA1c (\%)} = \frac{[H\text{bA1c}]}{\text{Total Hemoglobin}} \times 100$$

- DCA 2000 analyzer: this is the device used to make the quantitative immunological determination of glycated hemoglobin from 1µl of whole blood. When the capillary tube is filled with the blood sample the analysis should start within 5 minutes.

Results

Among 538 diabetic patients who presented for quarterly HbA1c testing during the two-month study period. We identified 69 patients who presented with at least one acidotic or hypoglycemic coma.

5 patients had acidotic comas with a frequency: 5/538: 0.93% (Group I) and 64 had hypoglycemic comas with a frequency: 64/538: 12% (Group II).

The frequency of acidotic comas: 1% is negligible compared to the 87% of the rest of the population free of acute complications. These values show that the patients benefit from a good follow-up and a good management by the multidisciplinary medical team of the department.

Acidotic Coma

5 patients presented at least one acidotic coma: these are children who presented an inaugural DKA (discovery of the disease). Or children who have either an infection, or following a deviation from the diet or a lack of injection or adaptation of insulin doses. The treatment depends on the severity of the coma and the degree of dehydration. A rapid insulin injection is started at home followed by an infusion in hospital. The coma phase is always preceded by vomiting, abdominal pain.... symptoms of hyperglycemia and the ketosis phase (urine acetone breath). On the other hand, severe hypoglycemia can be calm or silent due to the non-perception of the symptoms of hypoglycemia.

Patients who presented with an acidotic coma had HbA1c levels ranging from 6.5% to 11.5% and major hyperglycemia ranging from 3g/L to >5g/L. The HbA1c level does not depend on the frequency of acidotic comas.

Hypoglycemic Coma

64 people of 538 diabetics had hypoglycemic comas during the last trimester. The frequency of hypoglycemic coma is: 64 /538 = 12%.

Age de Distribution

The 52 fall into two groups:

- **Group I:** includes children (< 12 years) with a frequency of (24/64): 46.15%.
- **Group II:** includes adolescents (< 19 years) with a frequency equal to (28/64): 53.85%.

The results are shown in the following table: Using the statistica software, we tested the difference in the frequency of hypoglycemic comas between adolescents and children, for which we performed the U test (Mann-Whitney), which gave us a p value = 0.73 (> 0.05). Therefore, we can see that the difference is not significant. This result shows that children and adolescents are equally likely to present hypoglycemic comas.

The Student's t-test shows that there is no significant difference in the frequency of hypoglycemic comas in girls and boys. The 52 selected patients were subdivided into 5 groups according to the duration of diabetes: ≤ 3 years (47 cases); 4 and 6 years (16 cases) between 7 and 9 years (8 cases) between 10 and 12 years (6 cases); > 12 years (3 cases).

According to the results obtained, the number of hypoglycemic comas is inversely proportional to the duration of diabetes. As the duration of diabetes increases, the number of hypoglycemic comas decreases (Figure.1). Thus, the risk of hypoglycemic comas decreases with the

duration of diabetes. This decrease is related to the ability of the child and adolescent to perceive and understand the symptoms of hypoglycemia and to obtain immediate treatment. The factors favoring and causing hypoglycemic coma are multiple and can be associated at the same time. In the studied sample these factors can be related to diet, physical activity, insulin misuse, and other factors (psychic, associated diseases). We can see that the most common factor is diet, followed by physical exercise. These two factors are linked. Glucose intake through diet, exercise and insulin doses. Among the most frequent errors made by patients causing severe hypoglycemia are: delay or insufficiency of dietary glucose intake, failure to adapt treatment before and after unusual physical activity. The incidence of hypoglycemic comas may be due to psychiatric disorders (refusal of the disease and/or treatment...). The association of other diseases (epilepsy, gastroenteritis) whose treatment or deviation from the diet may cause severe hypoglycemia (Alfediam recommendations on hypoglycemia in the diabetic patient 1997) [10]

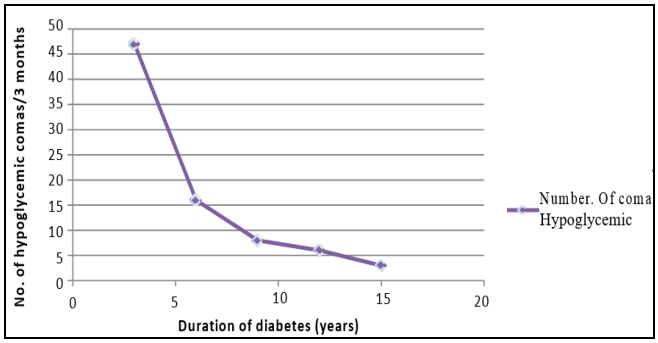

Fig 1: Variation of hypoglycemic coma cases according to the duration of diabetes

It is noted that 85% of hypoglycemic comas are treated by immediate natural resucration. While 8.75% of cases are hospitalized and treated with serum glucose, a minority (6%) use glucagon by intramuscular injection at home.

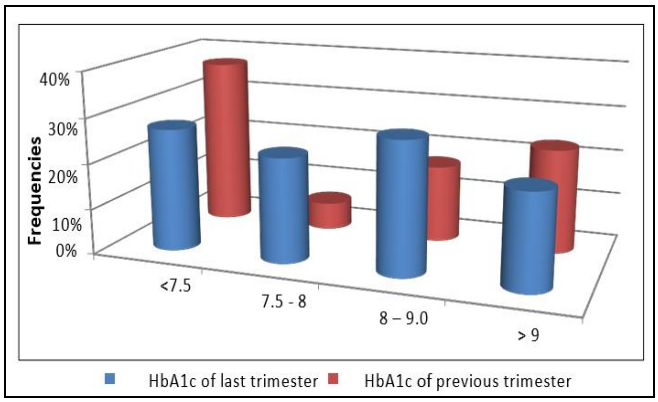

Fig 2: Change in HbA1c levels from last trimester and previous trimester

The HbA1c values < 7.5%, which reflect very good glycemic control, decreased during the last trimester. While HbA1c levels between 7.5% and 8% have increased. There is also a decrease in the frequency of HbA1c levels above 9% (Figure 2).
The increase in HbA1c levels between 7.5% and 9% is due to the fear of severe hypoglycemia, which leads patients to maintain blood glucose values above normal.

Patients are subdivided into 3 groups:
Group 1: includes those who have increased their HbA1c

Group 2: includes those who have lowered their HbA1c

Group 3: includes patients who have maintained the same HbA1c values

There were 45% of patients who increased their HbA1c levels versus 35% who decreased.
Elevated HbA1c levels always remain within the same ranges as the previous trimester values. In the limits of good control at values <8%. The difference is in the range of 0.2% to 0.4%. This increase is due to the coincidence of the last trimester with the periods of Ramadan, and successive holidays during which, some patients did not maintain their equilibrium.

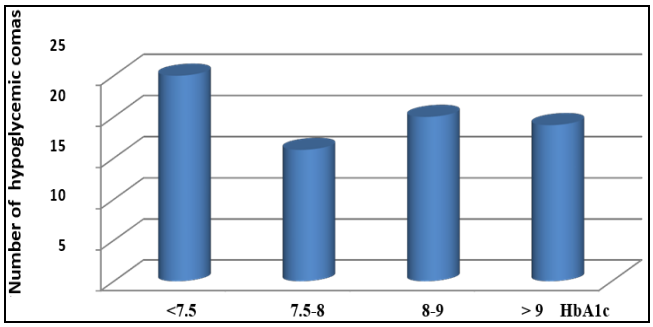

Fig 3: Variation in the number of hypoglycemic comas according to HA1c values.

It is noted that for intervals of HbA1c < 7.5%, there is a greater risk of hypoglycemic comas. This risk is more or less important for HbA1c levels > 8%. For patients who maintain their HbA1c levels between
7.5% and 8%, they have a lower risk of experiencing hypoglycemic comas (Figure 3). Being phobic about having severe hypoglycemia, patients end up with somewhat elevated HbA1c levels. Thus, the frequency of severe hypoglycemia does not affect the HbA1c level, which is related to the three-month blood glucose averages.

Discussion

Our work shows that the frequencies of severe hypoglycemia, and acid-fast comas, do not affect the quarterly HbA1c level. But the relationship is inversely proportional between low HbA1c levels and the frequency of metabolic events. It has been shown in several studies (DCCT research group...) [11] that the quarterly HbA1c level reflects the average blood glucose level of the three months preceding the test. Since HbA1c is calculated from both fasting and postprandial levels, it is important to monitor both 'types' of blood glucose. Large-scale studies have shown that lowering HbA1c levels reduces the development or progression of diabetes complications [12] .HbA1c is an important biomarker that is used in the diagnosis and monitoring of patients with diabetes. At each quarterly visit, diabetics are tested for HA1c to assess their glycemic control. In early 2020, the ADA recommended that strict glycemic control can prevent complications and reduce mortality in diabetics [13-14]. The association of average HbA1c levels with acidotic comas is due to the frequency of normal blood glucose values and minor nocturnal

hypoglycemia unperceived by patients. The incidence of ketoacidosis coma is often related to infections (intercurrent illnesses: fevers, angina, otitis) or to forgotten injections or poor adaptation of insulin doses during the ketosis phase without acidosis. Severe hypoglycemia is sometimes sudden and without clinical signs. This makes parents or caregivers more concerned, and more attentive. It is known that high postprandial blood glucose is an independent risk factor for cardiovascular disease. Therefore, if the HbA1c is low, postprandial glucose becomes the main element responsible for overall glycemic control [15] .

The incidence of severe hypoglycemia would be due to the frequency of minor nocturnal hypoglycemia which induces desensitization and non-perception of the clinical signs of hypoglycemia. Some patients have blood glucose levels < 0.30g/l but they do not perceive the signs of hypoglycemia (biological hypoglycemia), while other diabetics have hypoglycemic coma at blood glucose levels higher than those known as biological.

We report that, the incidence of hypoglycemic comas decreases with increasing duration of diabetes. This is explained by a good management of the patients themselves; they have obtained autonomy and a degree of maturity (ability to identify the signs of hypoglycemia with an adaptation of the treatment). In addition, the long duration of diabetes and the frequency of minor hypoglycemia weaken the adrenergic threshold for the secretion of counter-regulatory hormones that cause the clinical signs of hypoglycemia. Hypoglycemia represents the most frequent acute complication of T1DM. It is the consequence of an imbalance between insulin dose, food and physical activity. This leads to unpleasant clinical manifestations (anxiety and fear in patients and their relatives), which sometimes hinders optimal glycemic control [16].

Our diabetic children and youth are free of SARS-Cov2 infection. On the other hand, diabetics with an HbA1c > 9% are at increased risk of developing serious complications in case of COVID-19 infection with an increased mortality rate [17].

Conclusion

Controlling blood glucose levels is a fundamental element in the follow-up of the diabetic patient and in reducing the risk of long-term chronic complications. The objective of the management of children and young people with diabetes is to have a HA1c level <7.5%. This translates into an optimization of the glycemic balance level in which therapeutic education plays an important role: an adequate diet with corrections and adaptation of insulin doses in front of any transition of glycemic values and / or incidence of severe hypoglycemia and ketoacidosis.

There is an inverse relationship between the incidence of severe hypoglycemia and quarterly HbA1c values: a low HbA1c exposes the T1DM child to a high risk of hypoglycemic coma. Thus, the fear of severe hypoglycemia would be at the origin of an alteration of the patient's glycemic control and the high HbA1c values.

References

1. International Diabetes Federation. IDF Diabetes Atlas, Brussels, Belgium, 2019, (9). Available at: https://www.diabetesatlas.org
2. IDF Diabetes Atlas. Brussels, Belgium: International Diabetes Federation, 2017, (8).
3. Marouan Fatima. Diabetes a health challenge. Docti news. Professional magazine of medical Information. N°5.November, 2008, 25.
4. Samira Ezzel. The disease of the century. The morning,2009:13(11). (www.lematin.ma/Actualite/Journal/Article.asp?idr=116&id=122
5. Elizabeth J. Mayer-Davis, Anna R Kahkoska, Craig Jefferies, Dana Dabelea, Naby Balde et al. ISPAD Clinical Practice Consensus Guidelines: Definition, epidemiology, and classification of diabetes in children and adolescents Pediatr Diabetes,2018:19(27):7-19.
6. Marchand L, C Thivolet EMC - Endocrinology-Nutrition. 2016, 13 (4).
7. Martin Buysschaert. Clinical Diabetology. Boeck University, 2006, 3-7.
8. William V Tamborlane, Craig Kollman, Michael W Steffes, Katrina J Ruedy, Xing Dongyuan, Roy W Beck et al. Comparison of fingerstick hemoglobin A1c levels assayed by DCA 2000 with the DCCT/EDIC central laboratory assay: results of a Diabetes Research in Children Network (DirecNet) Study Pediatr Diabetes,2005:6(1):13-6.
9. Chico A, Aguilera E, Ampudia-Blasco FJ, Bellido V, Cardona-Hernández R, Escalada FJ et al. Clinical Approach to Flash Glucose Monitoring: An Expert Recommendation. J Diabetes Sci Technol,2020:14(1):155-164.
10. SFC/ALFEDIAM recommendations on the management of the diabetic patient seen by the cardiologist, 1997.
11. David M. Nathan for the DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview Diabetes Care,2014:37(1):9-16.
12. Konstantinos Makris, Loukia Spanou. Is There a Relationship between Mean Blood Glucose and Glycated Hemoglobin? Journal of Diabetes Science and Technology,2011:5(6):1572-83.
13. American Diabetes Association. Diabetes Technology: Standards of Medical Care in Diabetes-2020. Diabetes Care,2020:43(1):S77-S88.
14. Li Ying Zhang, Georges Krzentowski, Adelin Albert, Pierre J Lefebvre. Risk of Developing Retinopathy in Diabetes Control and Complications Trial Type 1 Diabetic Patients with Good or Poor Metabolic Control Diabetes Care,2001:24(7):1275-1279.
15. Kristine Færch, Marjan Alssema, David J. Mela, Rikke Borg and Dorte Vistisen. Relative contributions of preprandial and postprandial glucose exposures, glycemic variability, and non-glycemic factors to HbA1c in individuals with and without diabetes. Nutrition and Diabetes,2018:8:38
16. Thierry Mouraux, Sylvie Tenoutasse, Harry Dorchy. Severe hypoglycemia in children and adolescents with type 1 diabetes: risks factors and management. Rev Med Brux,2010:31:S65-70
17. Miriam E Tucker. Type 1 Diabetes Raises COVID-19 Risk in Kids if HbA1c Is High. Medscape, 2021.