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Relationship between retinopathy and glycated heamoglobin in insulin dependent diabetic children and adolescents

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Abstract

Background: This work is to evaluate the frequency of diabetic retinopathy, and to assimilate its impact in young diabetics followed at the endocrinology-diabetology department at the Children's Hospital of Rabat. Thus, patients with this complication were compared to patients without it, in order to demonstrate the various parameters that influence the appearance of diabetic retinopathy: age of diagnosis, duration of evolution, glycemic balance

Material and Methods: 200 children and young people with type 1 diabetes, aged between 5 and 28 years, who are followed up in the Department of Diabetology and Endocrinology at the C.H.U -Rabat. We analyzed their clinical and biological parameters during 12 months. Their glycemic control was evaluated by the determination of glycated hemoglobin by DCA 2000. The patients underwent a fundus examination followed by angiography to screen for retinopathy.

Results: 28% of patients had good glycemic control with HbAlc < 7.5%; 16% had a of HbA1c: 7.5 % - 8.31% have an average HbA1c: 8% - 9%; 24% have a poor glycemic balance: HbA1c between 9 - 14% and 2% have an HbA1c > 14%. The duration of diabetes is the best predictor of the occurrence of retinopathy, the prevalence of which increases with the duration of diabetes. 50% of the patients, i.e. half of the male community, belong to the age of onset group > 5 years and up to 10 years. 57% of the patients with a duration of diabetes > 6 years up to more than 15 years have a retinopathy. There is a predominance of the male sex with a frequency of 65% who have retinopathy. The frequency of diabetic retinopathy increases with the length of diabetes, from 14% before 10 years of diabetes to 31% after 10 years. After 17 years of diabetes, 100% of patients have diabetic retinopathy, often accompanied by other complications. The majority of patients with DR have a poor average glycated hemoglobin between 8 and 9% and a very poor glycemic control with a rate between 9 and 14%.

Conclusion: This original work shows that the frequency of diabetic retinopathy is influenced by two factors: the length of diabetes and the level of glycated hemoglobin. A too high level with a duration of evolution of more than 10 years increases the incidence of this pathology

The implementation of educational programs and the follow-up of hygienic and dietary measures within the framework of an organized management of diabetes has made it possible to significantly reduce the intensity and severity of complications, the cost of the disease and to improve the daily comfort of diabetics.

Keywords: type 1 diabetes, children, Glycated heamoglobin, retinopathy

Introduction

Diabetes is a chronic disease that occurs when the body can no longer effectively use the insulin it produces; due to an autoimmune reaction that destroys all or part of the beta cells of the pancreas. Hyperglycemia, a common effect of uncontrolled diabetes, over a long period of time, damages many of the body's systems, especially the nerves and blood vessels [1]. There are several types of diabetes that differ in age of onset and treatment. Type 1 diabetes (also known as insulin-dependent, juvenile or childhood diabetes) is characterized by insufficient insulin production and requires daily insulin administration [2]. The major cause of type 1 diabetes is currently unknown, but studies on the subject have established a link with heredity. A genetic predisposition would seem to be more and more certain; in addition to environmental factors and exposure to certain foods or drugs likely to cause the disease [3]. The diabetic subject suffers from excessive urine secretion (polyuria), thirst (polydipsia), and constant hunger, weight loss, vision changes and fatigue. Symptoms that may appear suddenly [4]. Mature diabetes (type 2), as its name indicates, affects older people, it is more frequent, it is said to be non- insulin-dependent, so its treatment is different, it is often associated with obesity. On the other hand, gestational diabetes appears during pregnancy in some women and is defined by a metabolic disorder. This chronic disease constitutes a real worldwide epidemic, according to the World Health Organization (WHO). According to the latest estimates, there are 371 million diabetics in the world. Among them, 78,000 children (0-14 years) are diagnosed with insulin-dependent diabetes every year [5]. The number varies according to geographical and socioeconomic criteria.

Eating properly is a true treatment for diabetes, as are physical activity and medication; monitoring glycated hemoglobin helps to avoid significant changes in blood glucose levels and prevent the onset of diabetes-related Complications. Glycated hemoglobin is the best biochemical marker for monitoring diabetes and should be

considered a diagnostic tool [6]. It represents a retrospective and cumulative index of blood glucose levels for the 3 to 4 months preceding the blood test, whereas blood glucose provides information at a given time [7]. Undetected, untreated or uncontrolled, diabetes can lead to long or short term disabling and fatal complications (nephropathy, neuropathy, visual disturbances, ketoacidosis, and severe hypoglycemia), the sudden development of which constitutes a daily threat for diabetic subjects [8]. Diabetic retinopathy is the most specific microangiopathy complication related to diabetes and remains one of the first causes of blindness and acquired blindness in the world, its prevalence increases with the duration of the evolution of diabetes in addition to the poor metabolic balance [9]. The seriousness of this pathology requires a perfectly controlled knowledge of these risk factors for prevention and treatment.

The interest of this work is to evaluate the frequency of diabetic retinopathy, and to assimilate its impact in young diabetics followed at the endocrinology-diabetology department at the Children's Hospital of Rabat. Thus, patients with this complication were compared to patients without it, in order to demonstrate the various parameters that influence the appearance of diabetic retinopathy: age of diagnosis, duration of evolution, glycemic balance.

Materials and Methods

We conducted a cross-sectional study among young diabetics 200 patients aged 5 to 28 years who are followed at the Department of Diabetology and Endocrinology at the C.H.U. Children's Hospital Rabat. We analyzed the clinical and biological parameters during 12 months.

The blood tests for glycated hemoglobin, and could be in direct contact with these young diabetics.

The main goal of my research was to highlight the frequency of diabetic retinopathy in this T1DM community.

Patients with this complication were compared to patients without it, in order to demonstrate the causal factors and the different parameters influencing this dysfunction.

Patients

During a consultation, the diabetic patient must be equipped with a:

Watchbook

To note simultaneously the daily blood sugar level, that is to say 3 values per day in the morning (before breakfast) the afternoon (after lunch) and the evening (before bedtime). The blood sugar level should not exceed the range of (0.6g/L-1.2g/L), and note, at the same time, the presence or absence of acetone in the urine.

The capillary blood sugar is checked with a blood glucose meter, by taking a drop of blood from the fingertip. In this booklet we also find the daily dosage of insulin, the patients or their relatives can vary these doses according to the glycemia. If the glycemia is high, they increase the measurement of 1 to 1.5 units each time and on the contrary if the glycemia is judged to be too low, they decrease the measurement also by the same process.

The booklet also includes basic information and guidelines (foods to avoid, first aid measures, etc.), a sort of diabetic charter.

It represents a 3-month record of two consultations, and thus reports the attitude adopted by the patient during this period.

Medical File

It gathers all the Information Concerning the Patient

First of all, an identity form: name, date of birth, address, date of hospitalization, information on the Parents, etc... A medical form: family history, medical history, allergies, etc...

An archive of the patient's medical history: all clinical data, from the first day of diagnosis to the last Date of consultation.

In addition to all the check-ups carried out: ionogram, thyroid check-up, NFS, angiography, ultrasound, radio plates, reports of ophthalmologist of gynecologist of radiologist or other specialists according to the proscribed controls...

Methods

Glycated Hemoglobin Assay

Before seeing the doctor, the patient must absolutely take a blood sample for the quarterly glycated hemoglobin measurement to ensure his glycemic status and to see the fruits of his efforts or, on the contrary, suffer the consequences of his excesses. Glycated hemoglobin is measured using the DCA 2000 analyzer.

The patient pricks his or her finger with the self-piercing pen and a drop of blood is taken from the glass capillary tube. Once the tube is filled with 1µl of blood, the analysis begins. The result is displayed as a percentage after 6 minutes.

F.O., Angiography, or Urinalysis

In some cases a fundus examination is requested to ensure the presence or absence of an abnormality leading to diabetic retinopathy, followed by an angiography. These examinations are usually requested after 5 years of diabetes and repeated annually after this period.

Often accompanied by a renal examination (micro albuminuria, 24h diuresis, creatinine or urea) Doubting diabetic nephropathy.

The Consultation Process

The consultation takes place at the end of each 3 months at least (except complications).

It starts with a weight, height and blood pressure measurement.

Once the value of glycated hemoglobin is verified, the physician pays attention to the daily values of blood sugar recorded on the monitoring booklet. This way, the doctor is sure of the patient's health status and the dietary and sanitary behavior adopted by the patient.

According to these values and the level of glycated Hemoglobin, the doctor can control the evolution of Diabetes in the subject and prescribe new dosages or advise a better lifestyle.

For emergency hospitalization (acute hypoglycemia or high HbAlc >14%), the patient is admitted either directly to the unit after advice from the doctor in charge, or to the emergency room, depending on bed availability.

Methods

The French Society of Clinical Biology (SFBC) and the French Association for the Study of Diabetes and Metabolic Diseases (ALFEDIAM), as well as the French Society of Endocrinology (SFE), have decided to issue recommendations that will allow the assay techniques to

evolve towards standardization.
All glycated hemoglobin results should be reported as HbAlc expressed as a percentage of total hemoglobin.
The methods used must measure HbAlc alone, or be able to calculate an HbAlc level.
The determination must be performed using standardized techniques and certified against reference systems recognized by the scientific societies N.G.S.P/D.C.C.T or I.F.C.C.

ANAES Recommendations
"...For a given patient, the HbAlc assay should be performed in the same laboratory, so that successive results can be compared.
The laboratory report should specify the technique used, whether the technique has been certified by the international standardization societies, the range of normal values and the intra- and inter-laboratory coefficients of variation. The technique used should preferably measure HbAlc alone..."

Method for the Determination of Glycated Hemoglobin: DCA 2000
It is an NGSP certified method, an immunological method, based on the inhibition of agglutination (monoclonal antibody specific to HbAlc).

- The specific glycated hemoglobin concentration and the total hemoglobin concentration are measured separately. The ratio is expressed as a percentage of hemoglobin Alc [10]

All reagents involved in both reactions are contained in the Glycated Hemoglobin Reagent Cartridge [11]. For the determination of total hemoglobin, potassium ferricyanide is used to oxidize the hemoglobin in the sample to methemoglobin, which then binds to thiocyanate and forms a complex of thiocyaniate and methemoglobin. It is this complex that is measured. The increase in intensity of the staining at 531nm is proportional to the total hemoglobin concentration in the sample. For the specific determination of Hb Alc a latex agglutination inhibition method is used [12] . An agglutinator (synthetic polymer containing multiple copies of the immunoreactive part of Hb Alc) causes agglutination to the latex coated with a mouse monoclonal antibody specific for Hb Alc. This agglutination reaction results in increased light scattering, which is reflected by an increase in absorbance at 531nm. The Hb Alc molecules present in the whole blood sample then compete for the binding sites of the limited number of antibody-latex complexes, resulting in inhibition of agglutination and a decrease in light. This decrease can be measured at 531nm absorbance.

Calculation of the Percentage of Glycated Hemoglobin
The HbAlc concentration is then quantified using an absorbance calibration curve established against the Hb Alc concentration. The percentage of Hb Alc in the sample is calculated as follows:

HbAlc (%) = [HbAlc]/ [Total Hemoglobin] x100

HbAlc in mmol/mol = (HbAlc in mmol)/ (Total Hemoglobin in mol)
All measurements and calculations are performed automatically by the DCA analyzer and the display shows the HbAlc percentage at the end of the assay. The values shown in the package insert are expressed in % HbAlc according to the NGSP, and where they appear in parentheses, in mmol/mol HbAlc according to the IFCC**.**

Materials and Dosing Procedure
The kit contains reagents consisting of antibody-latex, agglutinator, buffer solution and oxidant after taking 1µl of whole blood from the patient's fingertip via a glass capillary tube, the latter is slid into the existing holder on the cartridge, the analysis can finally start.
The result of the analysis is displayed as a percentage after six minutes [13].

Performance Liquid Chromatography: HPLC
Principle
The principle is based on the fact that the net charge of HbAlc on the N-terminus of the ß-chains is more negative than that of neutral Alc.The hemolysate is deposited on a column filled with negatively charged resin.
First, the fast hemoglobins: HbAla, HbAlb, and HbAlc, and then the main fraction HbA0, are elected. The percentage of the different fractions is determined by spectrophotometric measurement [14], this technique is the most widespread.

Results
Average Glycated Hemoglobin
200 patients were studied, aged 5 to 28 years, with type 1 diabetes for more than 5 years, treated with insulin and followed by the department's specialist physicians. Glycated hemoglobin was measured over a 12-month period (with a frequency of 1 measurement per 3 months mandatory). The 3 or 4 measurements were added together and then divided to obtain an average HbAlc value. We subdivided the patients into 5 groups according to their HbA1c level all sexes combined and then according to their sex:

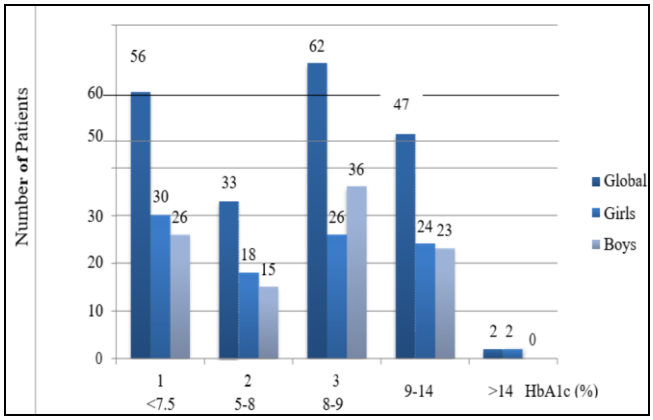

Fig 1: Distribution of glycated hemoglobin levels in the T1DM population

Studied

- **Group 1:** 28% of patients with Alc Hb less than 7.5%.
- **Group 2:** 16% with good glycemic control: HbA1c between 7.5% and 8%.
- **Group 3:** On the other hand, 31% of diabetics exceeded this limit with a mean HbA1c between 8% and 9%.
- **Group 4:** A large proportion of diabetics with very unbalanced blood sugar levels showing 9% to 14% hemoglobin levels or 24% of all subjects studied.

- **Group 5:** 2% of cases exceed the threshold of 14 and are at risk of complications diabetes.

This distribution was developed in the male and female communities in percentages and proportions:

- Ideal glycemic control is in the majority in girls at 30% of cases.
- Note a significant percentage of more than 24% of patients with an HbAlc between 9% and 14.
- Then 2 girls out of 100 have an average high hemoglobin above 14%.
- Nevertheless, we note the predominance of poor glycemic status, i.e. an average glycated hemoglobin between 8 and 9%, which occupies 36% of the male community studied.

Age of Diabetic Patients

The age of the type 1 diabetics studied ranged from 5 to 28 years and the frequencies were distributed as follows for both sexes:

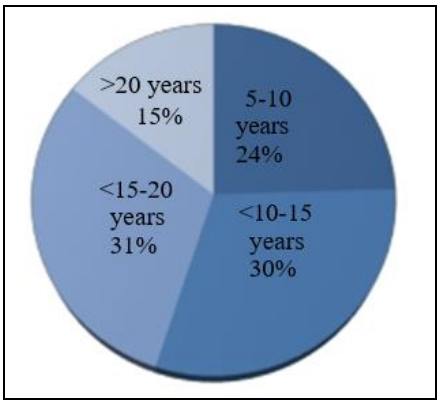

Fig 2: Frequency of age in diabetics

- Among the 200 type 1 diabetics only, those whose disease duration exceeded 5 years were retained.

The patients were thus divided into 4 age groups:

- Between 5 and 10 years: 24% of T1Ds
- More than 10 years and up to 15 years: 30% of T1D
- More than 15 years and up to 20 years: 31% of patients
- Finally, T1DM aged over 20 years: 15% of the 200 subjects selected

In order to give a more precise analysis of this age frequency, the individuals were subdivided according to their sex:

1. Among 100 girls, 26% are between 5 and 10 years of age, including 9 girls under 6 years of age who were diagnosed with diabetes at 1 year of age or younger.
- In 28 cases their age was over 10 years and up to 15 years.
- 33 cases with an age between 16 and 20 years.
- Only 13 patients were older than 20 years.

2. The boys are divided into age groups as follows:

- Age group between 5 and 10 years old: 23
- Age group over 10 and up to 15 years: 33
- Age over 15 and up to 20 years old: 28
- Age over 20 years old: 16

Age of Diagnosis

- We could not talk about the age of the patients without talking about their age of onset of diabetes. The following diagram shows the frequency of age of diagnosis of the female and male communities studied:
- 38% of girls with early onset diabetes between 1 and 5 years of age with 9 girls diagnosed with diabetes at age 1.
- Others have seen their disease appear a little longer after the age of 5 years or 43% of patients.
- 50% of the patients or half of the male community belong to the age group onset > 5 years up to 10 years.
- Only 19% of them discovered diabetes at an advanced age, i.e. more than 10 years.
- Among the group of individuals diagnosed between 1 and 5 years of age, which occupies 39% of the votes, 2 elements had their disease at the age of 6 months.
- Only 11% of boys are older than 10 years of age at diagnosis.

Diabetic Retinopathy

The duration of diabetes is the best predictor of the occurrence of retinopathy, the prevalence of which increases with the duration of diabetes. Proliferative retinopathy is rare before ten years of diabetes. Among the parameters studied, it was obvious to analyze the frequency of the duration of diabetes, the following diagrams show the distribution of this elementary factor:

Frequency of diabetes duration in males

- Frequency without significant difference, but the least abundant group is the one with duration of evolution beyond the 15-year threshold.

Frequency of diabetes duration in females:

- Predominance of the group whose evolutionary duration is between 5 and 6 years, Same frequency as in the male community in the group with more than 15 years of service

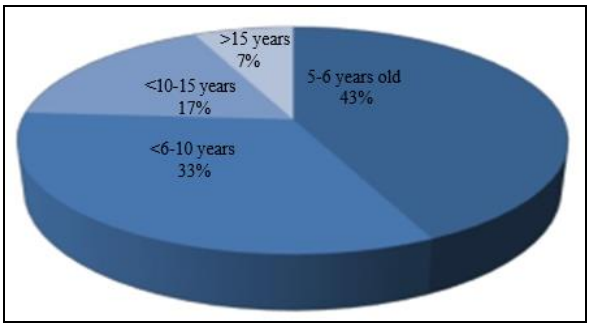

Fig 3: Frequency of diabetes duration in the entire T1D population.

- Among the 200 patients selected, a majority of individuals with a duration of diabetes between 5 and 6 years, i.e. 43% of the population.
- 33% with a duration of diabetes of more than 6 years and up to 10 years.
- On the other hand, 17% of cases have been diabetic for more than 10 years and up to 15 years less abundant, patients with diabetes for more than 15 years are at 7% of the votes, they represent the group most exposed to the complications of diabetes, and thus the risk of diabetic retinopathy among others.

Frequency of Diabetic Retinopathy

The diagnosis of diabetic retinopathy is made by

angiography, which is done after 5 years after the onset of diabetes. Out of 200 patients with more than 5 years of evolution, only 162 were able to undergo angiography at request of the attending physician, the other 38 did not undergo this control because of lack of means, lack of time, or sometimes the assessment was simply not requested: of the 162 individuals, or 81%, who performed angiography

- 20 have diabetic retinopathy, which represents 12% of the 162 individuals selected
- 142 have normal angiography, 88% of the retained community.

Gender Distribution

- 7 female patients have this pathology for 13 male patients, with Frequencies of 35% and 65% respectively.

Patients with normal angiography were compared as controls with diabetics with retinopathy:

As a result some remarks were raised:

- The frequency of diabetic retinopathy increases considerably with the evolution of the disease. It appears in subjects whose diabetes is older than 8 years and up to 17 years.
- Uninfected individuals with the same duration of diabetes have a mean normal glycated hemoglobin <7%, or they did not have the angiography test.
- This shows the role of age in parallel with good glycemic control in the development of this pathology.

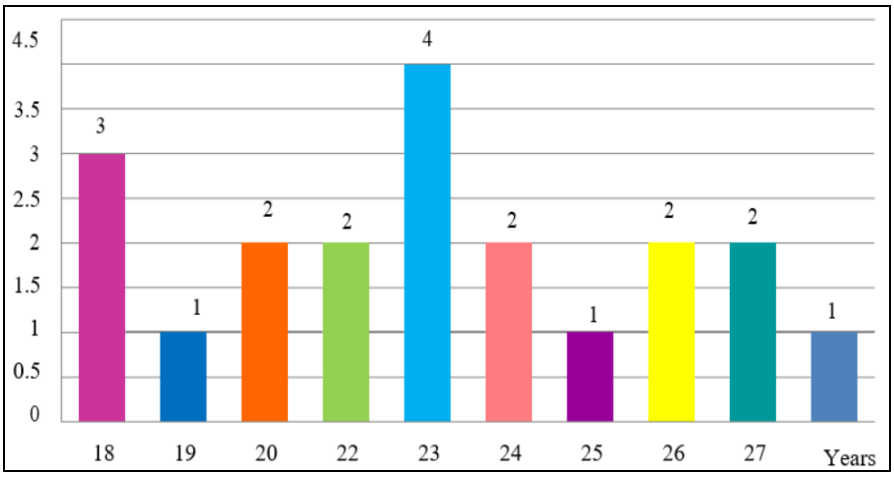

Fig 4: Age distribution of type 1 diabetics with retinopathy

- Of the unaffected individuals aged 18 years, 8 had a duration of diabetes of less than 10 years, 5 had normal glycated hemoglobin, and 2 had not had an angiogram**.**
- 7 of the control subjects, aged 19 years, had diabetes for less than 7 years, 4 had good glycated hemoglobin results, 2 elements combined these two criteria.
- The same remarks were noted for the 20-21 year old age group,
- Older individuals all showed discrete or more advanced signs of diabetic retinopathy in both the male and female communities.

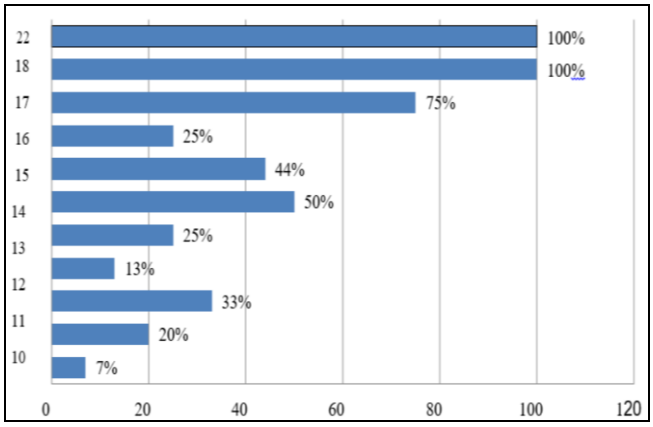

Fig 5: Distribution of time to first diagnosis of retinopathy

According to our study, the frequency of diabetic retinopathy increases in parallel with the age of diabetes, it increases from 14% before 10 years of diabetes to 31% after 10 years, and diabetics explored (having made an angiography) after 15 years of evolution has an abnormality in 60% of cases, beyond this period that is to say more than 17 years of duration of diabetes 100% of patients have diabetic retinopathy often accompanied by other complications

Distribution of Glycated Hemoglobin means among the Diabetic Retinopathy-Bearing Community

There is a strong correlation between HbA1c levels and the risk of microangiopathy complications including diabetic retinopathy (DR)**.** The average glycated hemoglobin of the 3 months preceding the diagnosis of diabetic retinopathy was calculated for the patients concerned, and the results were distributed as follows:

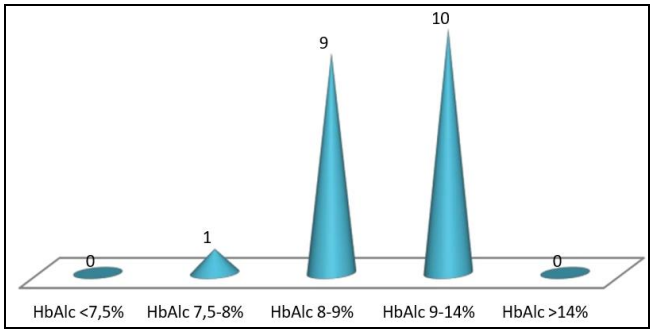

Fig 6: Distribution of mean glycated hemoglobin in diabetic carriers

Diabetic Retinopathy

The majority of patients with DR have a poor mean glycated

hemoglobin of 8-9% and very poor glycemic control with a level between 9-14%

This high rate accompanied by a significant duration of evolution (more than 10 years) explains the appearance of the pathology. Individuals with the same averages are less than 8 years old, and therefore the risk is less important.

Discussion

The work carried out shows that the frequency of diabetic retinopathy is influenced by two factors: the length of time diabetes has been present and the glycated hemoglobin level. After 3 years of diabetes evolution, the clinician prescribes to the patient an annual check-up among which a retinal angiography. A good glycemic balance <7.5% prevents the appearance of retinopathy. This rate seems comparable to that described by other authors (7.3%) [15].

The results are consistent with those of the literature. In fact, in the Goldstein study (performed on 420 young diabetics with retinopathy), 50% of diabetics had retinopathy after 9 years of diabetes, 90% after 15 years and 100% after 20 years [16].

Dorchy (study of 69 diabetics with retinopathy) found diabetic retinopathy in 50% of cases after 8 to 9 years of diabetes progression and nearly 100% after 15 years of progression. Several studies have demonstrated the influence of the age of diabetes on the appearance of the complication [17]. Large-scale studies have also shown that good glycemic control prevents the development of diabetes- related pathologies, however, even with a duration of evolution exceeding 10 years, an insulin- dependent diabetic, controlling his disease does not show signs of diabetic retinopathy and vice versa. Patients with retinopathy have an average HbA1c >8-14%.

In a meta-analysis of 35 epidemiological studies conducted between 1980 and 2002 and including 22,896 diabetics, the prevalence of Retinopathy was 34.6% [IC95%: 34.5- 34.8], that of Proliferative Retinopathy was 6.96% [CI95%: 6.87-7.04], diabetic macular edema was 6.81% [CI95%: 6.74-7.09], and vision-threatening forms of DR was 10.2% [CI95%: 10.1-10.3] [18].

Conclusion and Outlook

In the face of this epidemic, we cannot fail to mention the problems encountered by diabetic children whose care and treatment leave something to be desired, which has an impact on their growth, personality and schooling and exposes them to the dreaded diabetic complications in the more or less short term. In addition, the problems specific to puberty and later those related to the socio-professional integration of the young diabetic will only complicate an already precarious situation.

However, all these functional and/or vital complications with their dramatic socio-professional and economic consequences are no longer a threat as they were in the past, because they can be prevented if early structured care is provided. Indeed, the good control of the disease (self-monitoring and self- glycemic control), the fight against the risk factors (arterial hypertension, hyperlipidemia, smoking, obesity, sedentary lifestyle), the setting up of educational programs and the follow-up of hygienic and dietetic measures within the framework of an organized management of diabetes has made it possible to significantly reduce the intensity and the severity of the complications, the cost of the disease and to improve the daily comfort of the patient. In this context, the role of education, information and training of the diabetic and his entourage are essential to improve the results and reduce the metabolic and vascular risks. Specific objectives for each patient, the quality of the caregiver-patient relationship and the climate of security and trust that is established and developed are essential to raise awareness and motivate the diabetic. It is only through active participation and rigorous follow-up that diabetics can hope to avoid serious and unnecessary risks. This is why diabetic education must be considered and rightly so as one of the most important pillars for the treatment and management of diabetes in our country.

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