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Persistently High Glycated Hemoglobin in a Subgroup of Type 2 Diabetic Patients Who Failed Usual Oral Antihyperglycemics and Insulin in Côte d'Ivoire

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Abstract

Background: Type II diabetes mellitus is associated with multiple metabolic derangements which can cause secondary pathophysiological changes in multiple organ systems. This in turn can impose a heavy burden of morbidity and mortality from micro- and macro-vascular complications. This study aimed to describe the metabolic and therapeutic profile of a subgroup of type 2 diabetic patients who have treatment failure with oral anti-hyperglycemic agents with persistent hyperglycemia despite insulin treatment. **Methods:** 60 type 2 diabetic patients in treatment failure with oral antidiabetics and under insulin treatment, aged 35 to 70 years, were recruited at the Diabetes Clinic of the University Teaching Hospital of Treichville in Abidjan, Côte d'Ivoire. Blood samples were collected in tubes containing Ethylenediaminetetraacetic Acid (EDTA) to determine glycated hemoglobin (HbA1c). **Results:** The average age of the population was 54 ± 9.38 years with a sex ratio (M/F) of 0.3, an average BMI of 30.25 ± 5 kg/m^2, and an average HbA1c of 10.1% ± 1.6% for an average diabetes duration of 11.8 ± 5.8 years. The average insulin dose was 74.556 ± 16.21 UI/day, and the average duration of insulin treatment was 5.4 ± 3.1 years. The average HbA1c value was 10.1% ± 1.87% in men against 10.03% ± 1.53% in women with no significant difference (p = 0.1). The mean HbA1c values according to patient weight were 10.08% ± 2.05% for normal weight, 9.55% ± 2.26% for overweight, and 10.57% for obese, with no significant difference between the three groups of patients (p = 0.1). **Conclusion:** This study showed a persistence increase in glycated hemoglobin regardless

of the treatment regimen, duration, and dose of insulin treatment in the subpopulation of type 2 diabetic patients.

Keywords

High Glycated Hemoglobin, Type 2 Diabetic, Insulin, Côte d'Ivoire

1. Introduction

Diabetes is defined as a group of metabolic disorders characterized by chronic hyperglycemia resulting either from a defect in the synthesis of insulin or the inaction of insulin by the defect of the receptors' signaling [1].

Nearly 537 million people have diabetes worldwide, including about 24 million in Africa [2]. In Côte d'Ivoire, more than 700,000 people have diabetes, with a prevalence rate of 6.2% in 2017, according to a survey by the National Program for the Fight against Metabolic Diseases [3].

There are four types of diabetes, but the most common form is type 2 diabetes, which accounts for 90% of diabetes cases [2]. The treatment is mainly based on oral antidiabetics. Insulin therapy only intervenes at an advanced stage of the disease or in patients whose glycemic control remains insufficient with oral treatment [4], but the clinical and therapeutic course of the disease in some cases suggests that the diagnosis of type 2 diabetes is clearly more complex [5]. Indeed, for a long time, diabetes was diagnosed based on glucose measurement alone, whereas hyperglycemia can occur due to multiple etiologic processes. Such heterogeneity in type 2 diabetes due to several genetic and acquired factors proves that the diagnosis could not only be based on the measurement of this single variable [5] [6].

Therefore, identifying diabetes subtypes with different risk profiles and etiologies becomes an important element for clinical care diagnosis [6].

In Côte d'Ivoire, a subgroup of type 2 diabetic patients who present hyperglycemia, "resistant" to the usual oral therapies and insulin therapy has been identified. This group has been referred to as "special profile type 2 diabetic patients."

Therefore, the general objective of this study was to describe the metabolic and therapeutic profile of this subgroup of type 2 diabetic patients with a particular profile. The secondary objectives are to evaluate the glycemic balance of patients by measuring glycated hemoglobin (HBA1c) and describe insulin treatment—the different regimens and the doses administered.

2. Materials and Methods

2.1. Study Setting, Study Site, and Study Population

This is a cross-sectional, descriptive, and analytical study carried out at the Diabetes Clinic of the University Hospital Center (CHU) of Treichville in Abidjan in Côte d'Ivoire and at the Department of Medical and Fundamental Biochemi-

stry of the Institut Pasteur of Côte d'Ivoire (IPCI) from January to August 2022. This study involved 60 type 2 diabetic patients.

The type 2 diabetic patients comprised 43 women and 17 men, aged 35 and above, who have failed oral antibiotics (combination Metformin, sulfonamides, DPP-4 inhibitors) and are under insulin treatment for at least 2 years with an average HBA1c value of ≥8.5% gave their informed consent. On the other hand, well-controlled type 2 diabetic patients under oral antidiabetics, patients with type 1 diabetes, chronic inflammatory pancreatic, hepatic, endocrine, hematological diseases, pregnant women, and breastfeeding patients were excluded from the study.

2.2. Biological and Technical Material

The collected blood samples in tubes containing the anticoagulant Ethylenediaminetetraacetic Acid (EDTA) were used to assay HbA1c on the COBAS C311 HITACHI.

2.3. Data Collection Method

Data collection included the questionnaires from the files of type 2 diabetics patients and the consultation registers available in the archives of the clinic. The observational survey for all patients focused on the following data: age, sex, duration of diabetes, glycemia, nature of the treatment, different types of insulin, different insulin therapy regimens used, and the commencement date of the initiation of insulin therapy. The insulin dose was calculated based on the 0.2 to 1 IU/kg (beyond 1 IU/Kg/day, we speak of exogenous insulin resistance). Metformin was maintained in all study patients for its action against insulin resistance.

2.4. Measuring Level of Glycated Hemoglobin

The glycated hemoglobin level was measured using the COBAS C311 HITACHI spectrophotometer. Its principle is based on the immunoturbidimetric method of the turbidimetric inhibition immunoassay (TINIA) type [7]. This method is based on using two reagents, R1 (buffer/antibody) and R2 (buffer/polyhapten). Glycohemoglobin (HbA1c) in the sample reacts with anti-HbA1c antibodies to form soluble antigen-antibody complexes. The polyhaptens form with the anti-HbA1c antibodies in excess insoluble antibody-polyhapten complexes, which are measured by turbidimetry. The result is expressed in HbA1c in mmol/mol or HbA1c in % and is calculated from the HbA1c/Hb ratio as follows: HbA1c (%) = (HbA1c/Hb) × 91.5 + 2.15.

In practice, 120 µL of R1, 180 µL of diluent (H_2O), and 24 µL of R2 are added to the tube containing 5 µL of serum sample and then placed on the "sample holder" rack. The analysis was carried out after validating the control, and the results appear in the "Results" window and are printed using an ordinary printer connected to the central unit of the machine. The normal HbA1c reference value is 4.7% - 6.2% (48 mmol/mol) [8].

2.5. Body Mass Index (BMI) Measurement

The weight was measured using a mechanical scale. BMI was calculated using the formula BMI = W/T^2, where W = weight, and T = height. In line with this, the WHO defines *overweight* and *obesity* as follows:

- Normal weight when the BMI is between 18.5 and 24.99 kg /m^2.
- Overweight when the BMI is between 25 and 29.9 kg/m^2.
- Obesity when the BMI is equal to or greater than 30 kg/m^2.

2.6. Statistical Analysis

The mean values accompanied by the standard deviation were produced using the XLSTAT 2022.1.2 software. The statistical analysis of the results was carried out using the analysis of variances (ANOVA) and the t-student comparison test. For both tests, significance level was set at $p < 0.05$.

2.7. Ethical Considerations

This study was authorized by the National Ethics Committee for Life Sciences and Health (N/Ref: 127-18/MSHP/CNESVS-km). This research was done per the Declaration of Helsinki (2013) and the laws in force in Côte d'Ivoire. The study participants gave informed consent, with all provisions to preserve confidentiality and anonymity. Before any sampling, oral and written consent from witnesses was also obtained.

3. Results

3.1. Anthropometric Characteristics and Glycated Hemoglobin Status (HbA1c) in the Study Population

Among the 60 type 2 diabetic patients recruited, there were more women (43; 72%) than men (17; 28%) (*i.e.*, a sex ratio [M/F] of 0.39 (Table 1). Their average glycated hemoglobin values were 10.19% and 10.03%, respectively.

These patients presented a mean age of 54 ± 9.38 years and a mean HbA1c value of 10.1% ± 1.6% (Table 1). In addition, the 51 - 70 age group was the most affected by this disease, with a proportion of 77% (46/60) and an average value of HbA1c of 9.8% ± 1.1%. On the other hand, 23% of the patients (14/60) were 30 - 50 years old, with an average HbA1c value of 10.16% ± 0.74% (Figure 1).

Then the participants' BMI results in a 30.25 ± 5 kg/m^2 value with a mean weight of 84 ± 15.4 kg (Table 1). Fifty-seven percent (57%; 34/60) of patients showed mean BMI values greater than 30 and HbA1c of 10.57% ± 2.34% than the 33% (20/60) of patients with mean BMI values between 25 - 29.99 and 9.55 ± 2.26 HbA1c. Only 10% (6/60) of the patients had a normal average BMI value between 18 - 24.99 with an average HbA1c of 10.08% ± 2.05%.

3.2. Profile of Glycated Hemoglobin (HbA1c) According to the Duration of Diabetes and Antidiabetic Treatment in the Study Population

More than half of the patients (34/60; 57%) had diabetes less than or equal to 5

years, with an average HbA1c of 10.47% ± 2.4%. Sixteen (27%) patients had diabetes between 6 and 10 years, with an average HbA1c of 9.73% ± 1.26%, and 10/60 (16%) had diabetes for more than 10 years, with an average HbA1c of 10.57% ± 1.6% (Table 2).

Table 1. General characteristics of the study population.

Characteristics	Values
Number of patients	60
Men	17 (28%)
Women	43 (72%)
Sex ratio	0.39
Mean age (years)	54 ± 9.38
Average weight	84 ± 15.4
Average BMI (kg/m^2)	30.25 ± 5
Mean blood glucose (g/L)	2.3 ± 0.48
Mean HbA1c (%)	10.1 ± 1.6%.
Mean HbA1c at the commencement of treatment	11 ± 2.4 (%)
Average duration of diabetes (years)	11.8 ± 5.8
Average duration of oral treatment (years)	6.4 ± 2.7
Average commencement of insulin treatment (years)	5.3 ± 3.1
Mean insulin dose (IU/kg/d)	0.9 ± 0.21

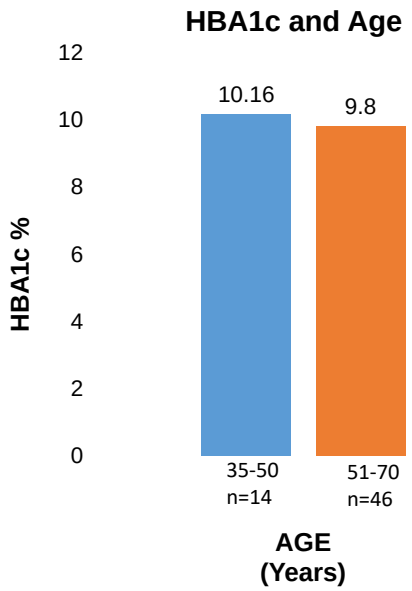

Figure 1. Distribution of the population according to HbA1c and age.

Table 2. Distribution of patients according to HbA1c, duration of diabetes, and insulin therapy.

	Mean HbA1c (%)	Number of patients	p-value
Duration of Diabetes (years)			
0 - 5	10.47 ± 2.4	34 (56%)	p = 0.1
5 - 10	9.73 ± 1.26	16 (27%)	
>10	10.57 ± 1.6	10 (17%)	
Duration of insulin therapy (years)			
0 - 5	9.63 ± 1.06	36 (60%)	p = 0.11
5 - 10	11.12 ± 1.96	22 (37%)	
>10	10.47 ± 1.54	2 (3%)	

3.3. Influence of Antidiabetic Treatment on Glycated Hemoglobin (HbA1c) in the Study Population

The mean duration of treatment with oral antidiabetics was 6.4 ± 2.7 years (Table 1). When insulin treatment commenced, the mean value of glycated hemoglobin was 11% ± 2.4%. The mean HbA1c values of patients on insulin for more than 5 years were higher (11.12% ± 1.96%; 10.47% ± 1.54%) than those on insulin therapy for 5 years (9.63% ± 1.06%) (Table 3). Depending on the insulin regimen, 92% of the patients were on a "premix" insulin regimen versus 8% on Basal Bolus insulin with no difference in the mean HbA1c value (Table 3). Mean HbA1c values for patients were higher (10.67% ± 2.44%) at an insulin dose of 1 - 1.49 IU/Kg/d (Table 3).

4. Discussion

In this study, most type 2 diabetics were female (72%). These results are similar to those of the work of Aouiche and Boudiba, who obtained a female predominance of 60% [9]. This could be explained by the fact that women are more sedentary in our society [10].

The mean age of the study population of 54 ± 9 years is comparable to Naceur's findings whose mean age was 54 years [11]. The average duration of diabetes of approximately 12 years and an average duration of insulin treatment initiation of 5.4 ± 3.1 years indicate that the patients required insulin after approximately 7 years of disease progression. These results are consistent with LaSalle and Berria, who estimated that 50% of patients begin insulin therapy within 5 years after failing to achieve or maintain glycemic control despite taking several oral antidiabetics [12]. The average HbA1c at the start of insulin therapy was 11.4%, unlike Home et al., who found an average HBA1c of 9.5% [13]. This difference shows that the start of insulin treatment occurred late in this present cohort. In this study, the average duration of initiation of insulin treatment of 5 years is a sufficiently long period to judge the effectiveness of insulin treatment

Table 3. Distribution of patients according to insulin regimen, insulin doses, and HbA1c.

	Mean HbA1c (%)	Number of patients	p-value
Insulin regimen			
Prémix + Metformin	10.12	55 (92%)	p = 0.1
Basal Bolus + Metformin	10.58	5 (8%)	
Insulin doses (UI/kg/j)			
0.5 - 0.99	9.73 ± 3.26	32 (53.3%)	p = 0.1
1 - 1.49	10.67 ± 2.44	27 (45 %)	
1.5	8.4	1 (1.7%)	

on glycemic control. This duration agrees with the Cardiovascular risk evaluation in people with type 2 diabetes on insulin therapy (CREDIT) study in which the treatment initiation lasted 4 years to assess glycemic control and help in treatment planning [13].

In this present study, the average glycated hemoglobin of 10.1% ± 1.66% is close to that of 11.2% ± 1.6% found in the work of Grira [14]. This value reflects a profound blood sugar imbalance in both men and women. Indeed, the measurement of glycated hemoglobin makes it possible to assess the level of glycemic balance in type 2 diabetics under treatment. The normal glycemic balance of type 2 diabetic patient under treatment is defined by values lower than or equal to 7% [15]. The glycemic imbalance without significant difference between the two genders was also found in Lofti [16].

This study shows that most type 2 diabetes patients have obesity (BMI of 30.25 ± 5) associated with a glycemic imbalance present in all BMI levels (p = 0.1). These results differ from those of Mimita, who observed that the higher the glycated hemoglobin, the higher the BMI [17].

In this study, the glycemic imbalance was present regardless of the duration of diabetes. Indeed, regardless of the development stage of diabetes, the patients had an HbA1c level of around 10%, well above the reference value. Type 2 diabetes worsens over time with progressive depletion of insulin secretion [18]. This observation is different from that of Faraoun's work, which showed that the longer the duration of diabetes, the more there is a loss of glycemic control reflected in the elevation of HbA1c [18].

The duration of insulin treatment initiation is longer (5 years) in the present study than that of the study by Aouich and Boudib, which was 3 years [11]. Despite 5 years of insulin therapy, the study's participants' glycemic imbalance persists. In fact, the duration of insulin therapy initiation makes it possible to generally assess the progress of insulin treatment in type 2 diabetics and its impact on glycemia. It also leads to assessing the time taken by the patient to achieve glycemic control [13].

Two treatment regimens were used—a two-injection regimen with premixed insulin and a 4-injection regimen known as a "basal bolus." The "premix" regi-

men (91%), which was the most prescribed, is different from that of Grira's work which found a predominance of the "basal bolus" regimen (64%) [14]. This difference is due to the refusal of multiple injections by patients with very low adherence to insulin treatment.

In the present study, the HbA1C levels observed during the two regimens did not vary (10.12% for the premixed insulin; 10.58% for the basal bolus regimen). These results differ from those of Aouiche and Boudib [11] (8.7% ± 0.51% for premix insulin; 6.81% ± 0.69% for the basal-bolus regimen). This difference is explained by the fact that the "basal bolus" regimen, the most physiological insulin regimen, lowers blood sugar better than the premix regimen [18]. In fact, insulin therapy regimens make it possible to assess the performance of different insulin types according to patient profiles and their effect on glycemia [13].

The mean daily insulin dose is 0.9 ± 0.21 IU/kg/d higher than the 0.5 ± IU/Kg/d and 0.66 IU/Kg/d observed by Home and Grira, respectively [13] [14]. Despite the 0.9 IU/Kg/d dose at the start of insulin, almost 46% of the patients had proven exogenous insulin resistance, and there was no significant drop in HbA1c ($p = 0.1$), unlike in Grira's work, which revealed a drop in HbA1c from 11.2% at the start to 8.7% at the end of the study.

5. Conclusions

This study showed that a subpopulation of type 2 diabetic patients, resistant to oral antidiabetic treatment, had poor glycemic control despite insulin treatment starting at least 5 years after disease onset. The very high levels of glycated hemoglobin, regardless of age, sex, duration of treatment, duration of insulin treatment, insulin regimen and dose, explain this profound imbalance. All this suggests an insulin resistance that escapes the usual therapies and is of still unknown etiology in this subgroup of type 2 diabetic patients.

In perspective, studying the insulin gene and its receptor will make it possible to search for molecular abnormality or mutations for a better understanding of this complex pathology.

Ethical Statement

The study was authorized for implementation by the national ethics committee for life and health sciences (CNESVS) assigned number (N/Ref: 127-18/MSHP/CNESVS-km). Informed Consent has been obtained from the individuals for the use of blood samples for the research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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