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Original Article

Fasting Blood Glucose Profile of Children Living with HIV taking First-Line Antiretroviral Treatment in Abidjan, Cote D'Ivoire: A Cross-Sectional Study

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Abstract

Introduction: Approximately 90% of children living with the human immunodeficiency virus are in Sub-Saharan Africa. This study determined the prevalence of dysglycaemia among children living with the human immunodeficiency virus taking first-line antiretroviral treatment. **Material and Methods:** A cross-sectional study was conducted for 6 months among the participants aged from 2 to 15 years in a health center of Abidjan, Cote d'Ivoire, and measured the subjects' fasting blood glucose using the fructokinase method. Definitions of impaired fasting glucose and diabetes mellitus were represented by a fasting blood glucose level between 100 to 125 mg/dl and ≥ 126 mg/dl, respectively. **Results:** Among the 195 children recruited, the mean age was 9±3.6 years with a male: female ratio of 1.19. The mean duration of the antiretroviral treatment was 47 months. Treatment regimens included protease inhibitor-based therapy in 4.1% of cases and two nucleoside reverse transcriptase inhibitors in combination with one non-nucleoside reverse transcriptase inhibitors in the other cases. The mean blood glucose was 75.2 ±10.1 mg/dl. The prevalence of impaired fasting glucose was 2.6% and none had diabetes mellitus. **Conclusion:** Dysglycaemia was seen in 2.6% of the children taking antiretroviral treatment. Monitoring fasting blood glucose levels in children living with the human immunodeficiency virus taking antiretroviral treatment is advocated for prompt diagnosis and early intervention in cases of pre-diabetes in order to prevent progression to diabetes.

Keywords: Dysglycaemia, fasting blood glucose, HIV, children, anti-retroviral treatment

Introduction

The use of highly active antiretroviral therapy (HAART) since 1996 has considerably reduced the mortality and morbidity associated with the human immunodeficiency virus (HIV) infection [1, 2]. Consequently, concerns about morbidity from the long-term complications of the disease, as well as the effects of antiretroviral drugs, understandably have become topical. Various metabolic complications, including glucose dysregulation, have been associated with antiretroviral treatment (ART) [3, 4]. However, the mechanisms involved in the development of these metabolic abnormalities and their interrelationships are not still very clear-cut [3]. Various postulated mechanisms include possible side effects of nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI)[5], and recently, non-nucleoside reverse transcriptase inhibi-

tors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTI)[4, 6, 7] or complications arising from the specific disease process of HIV.[4,8]. About 24.7 million people are living with HIV in Sub-Saharan Africa, and they make up to 71% of the world's population with the infection, although only 12% of the global population lives in the region [9, 10]. Furthermore, the global coverage of antiretroviral therapy reached 46% [43–50%] at the end of 2015, with about 17 million people having access to ART [11]. This number is expected to increase because of the World Health Organization (WHO) management guidelines that recommend commencement of antiretroviral treatment as soon as possible once the diagnosis of HIV is made, especially in children [12].

Given the prospect of the life-long treatment with HAART from childhood, the concern about the development of these metabolic complications is particularly worrisome because of the potentially increased risk of diabetes and cardiovascular disease in early adulthood [1, 13, 14].

There is a paucity of data concerning dysglycaemia in children living with HIV, especially in Sub-Saharan Africa. Such studies are imperative where environmental and other factors that impact these complications (e.g., diet, comorbidities, race, and ethnicity) may differ from those in resource-rich settings. Cote d'Ivoire is one of the West African countries with a relatively high HIV burden (3.7%), where children less than 15 years represent 41.5% of the total population [15]. Therefore, this study aimed to determine fasting blood glucose levels among a pediatric group taking first-line ART and identify possible associated factors.

Material and Methods

The cross-sectional study was carried out at the Cocody Teaching Hospital, Abidjan in Cote d'Ivoire, from July to December 2015. Children aged 2 to 15 years old living with HIV taking first-line ART for more than three months who were being followed-up in the hospital formed the study population after informed consent was obtained. Children were excluded if they were taking hormonal therapy (steroids, testosterone, estrogen, thyroxine, and others), if they had diabetes mellitus or any severe acute illness. Ethical approval was obtained from the National Ethics Committee before the study. Written informed consent was obtained from the parents or caregivers; in addition, childrens' own assent was considered for children who were old enough (from seven years old and above).

Data collection

Study participants were called the day before the test, and instructed to fast overnight, at least eight hours before the morning of the blood sampling for the study. On the test day, a questionnaire was administered to obtain information on sociodemographic characteristics and other relevant clinical information. Information regarding the CDC clinical stage at HIV diagnosis according to the WHO [16] and recent CD4 count and viral load (less than three months) results were obtained. The immune condition was classified based on the WHO immunological classification system for adults and children [17], as shown in Table 1.

Anthropometric measurements were taken by a trained nurse supervised by the investigator. Weight was measured to the nearest 0.1kg using a portable weighing scale (Medical©) with minimal clothing and no shoes; belt and other accessories were removed, and pockets were emptied. Height was measured to

Table 1: WHO classification system for children and adults [17].

	Age-related CD4 values			
				>5 years
HIV- associated immunodeficiency	**<11 months (% CD4+)**	**11-35 months (% CD4+)**	**36-59 months (% CD4+)**	**(absolute number per mm^3 or % (% CD4+)**
None	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 or <15%

the nearest 0.1 cm using a portable stadiometer (Spirit Height®) with the child standing erect, barefoot, heels together and looking straight ahead. The lower edge of the eye socket was in the same horizontal plane as the external auditory meatus, with the heels and back against the height rule. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m2). Child growth charts from the WHO [18] were used to categorize each subject using the standards deviation ranges:

• Overweight: >+1SD (equivalent to BMI 25 kg/m2 at 19 years)
• Obesity: >+2SD (equivalent to BMI 30 kg/m2 at 19 years)
• Thinness: <-2SD
• Severe thinness: <-3SD

The sexual maturity rating was ascertained by an inspection of breasts/ pubic hair for females and genitalia/pubic hair for males in the presence of a doctor or/and a parent. Puberty was classified using the Tanner stages.[19-21]. The more advanced stage of the two respective pubertal components was used for classification if there was discordance between the examined body sites [21].

From each participant, a sample of 3-5 ml of venous blood was collected under aseptic conditions by a trained nurse in a fluoride oxalate tube for the measurement of fasting blood glucose (FBG). The sample was sent to the laboratory (Pastor Institute of Cote d'Ivoire) for analysis of blood glucose using the fructokinase method. The definitions of impaired fasting glucose (IFG) and diabetes were based on the criteria of the American Diabetes Association (ADA) [22] and the International Society for Pediatric and Adolescent Diabetes (ISPAD) [23]. The normal values of FBG were defined as ≤ 100 mg/dl (5.5mmol/L), while FBG between 100 to 125 mg/dl (5.6–6.9 mmol/L) was classified as impaired fasting glucose (IFG) [ADA, WHO] and FBG ≥126 mg/dl (7.0 mmol/l) defined diabetes. Study participants with abnormalities of the blood glucose values were recalled for further workup.

Data management and analysis

Data were entered using the Access software for Windows and analyzed using Excel for Windows. Numerical values were given for the number of cases (n), mean (standard deviations), proportions, and percentages. P values of less than 0.05 were regarded as significant.

Results

A total of 195 children were recruited while 2 refused consent. The mean age (SD) was 9 (± 3.6) years with a male: female sex ratio of 1.19. The proportion of mothers with no form of education was twice that of fathers (23.6% vs 10.8%).With regards to employment status, majority of the fathers (95.4%) were employed in various capacities with only 4.6 % being unemployed. This was in contrast to few employed mothers, only 28.7%. Table 2 highlights the socio-demographic characteristics and relevant family history of the children in the study.

The stage and characteristics of the disease in association with antiretroviral drug usage are shown in Table 3.

Table 2: Socio-demographic and clinical characteristics of the children.

Characteristics of children Socio-demographic		Frequency (N=195)	Percent (%)
Sex	Male	106	54.4
	Female	89	45.6
Residence	Cocody	69	35.4
	Other towns of Abidjan	101	51.8
	Outside of Abidjan	25	12.8
Educational level	Not attended school	15	7.7
	Nursery	14	7.2
	Primary	123	63.1
	Secondary	43	22.1

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Orphaned	At least one parent	50	25.6
	Both father and mother	12	6.2
	Not orphaned	133	68.2
Familial medical past history			
Diabetes	Familial history	24	12.3
	No history	168	86.2
	Unknown	3	1.5
Hypertension	Familial history	32	16.4
	No history	160	82.1
	Unknown	3	1.5
Obesity	Familial history	13	6.7
	No history	179	91.8
	Unknown	3	1.5
HIV status of the mother	Positive	145	74.4
	Negative	2	1.0
	Unknown	48	24.3
HIV status of the father	Positive	42	21.5
	Negative	57	29.2
	Unknown	96	49.2
HIV status of the siblings	Positive	24	12.3
	Negative	165	84.6
	Unknown	6	3.1
Clinical data			
Physical activity	No exercise	81	41.5
	Engaged in exercise	114	58.5
CDC stage	N	15	7.7
	A	34	17.4
	B	68	34.9
	C	78	40.0
Nutritional status	Obese	1	0.5
	Normal	157	80.5
	Thinness	28	14.4
	Severe thinness	9	4.6
Pubertal stage	I	137	70.3
	II	29	14.9
	III	25	12.8
	IV	4	2.1

A sizeable number of the children (72.8%) showed no immune deficiency, and slightly higher than half of them had an undetectable viral load. The median duration of the antiretroviral treatment was 47 months (ranging from 3 to 157 months). Almost all (96.9%) the children were taking cotrimoxazole prophylaxis for opportunistic infections. The mode of acquisition of the HIV infection was by vertical transmission in 74 children (37.9%), by blood transfusion in one child (0.5%) while the route of transmission could not

Table 3: HIV infection and Antiretroviral Therapy (ART).

HIV and ART information		Frequency	Percent (%)
Type of HIV	HIV 1	194	99.5
	HIV1+2	1	0.5
Immune status	Severe deficiency	32	16.4
	Moderate deficiency	21	10.8
	No deficiency	142	72.8
Viral load (copies)	Undetectable	115	59.0
	[0-500]	30	15.4
	[500-1000]	4	2.1
	Greater than 1000	46	23.6
Duration of ART (months)	[3-22]	46	23.6
	[23-46]	50	25.6
	[47-71]	50	25.6
	[72-157]	49	25.1
ART Regimen	2 INRT+1 INNRT	187	95.9
	2 INRT+ 1 PI	8	4.1

Table 4: The ARV regimen used for the children.

ARV Regimen	Frequency (N)	Percent (%)
ABC+3TC+EFV	6	3.1
ABC+3TC+LOPI-RITO	1	0.5
ABC+3TC+NVP	7	3.6
ABC+DDI+LOPI/RITO	1	0.5
AZT+3TC+EFV	**89**	**45.6**
AZT+3TC+LOPI-RITO	6	3.1
AZT+3TC+NVP	**70**	**35.9**
D4T+3TC+EFV	6	3.1
D4T+3TC+NVP	8	4.1
TDF+3TC+EFV	1	0.5
Total	**195**	**100**

be determined in 120 children (61.5%).

The initial ART commenced at diagnosis remained unchanged in 85.6% of the children. In the few instances of a change in the drug regimen, the reasons were drug allergy or situations when drugs like Didanosine (DDI) and Stavudine (D4T) were withdrawn from conventional ART regimens.

Table 4 shows the details of the specific drug combination used for the children. The most typical regimen used for the study participants was zidovudine (AZT) + lamivudine (3TC) with efavirenz (EFV) followed by AZT+3TC with nevirapine (NVP). A protease inhibitor-based regimen was used in only 4.1% of the children, lopinavir boosted by ritonavir being exclusively used in such instances.

With regards to blood glucose (BG) levels, the mean BG was 75.2±10.1 mg/dl. Only five children (2.6%) had impaired fasting glucose. None had diabetes

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mellitus. Given the small numbers of children with glucose abnormalities, pertinent analysis to identify associated factors was not possible. However, the characteristics of the five children (three females and two males) with glucose abnormalities are displayed in Table 5. Notably, their ages were in the pubertal range (8.3 to 14.3 years), and three were already in puberty. The lowest viral load for this group ranged from at least 1000 to 56000 copies. The duration of ART ranged from 25 months to 107 months. Only one patient had a family history of diabetes, while none had a family history of hypertension.

All had a normal BMI. Concerning the ART regimen, all the children with glucose disorders were taking a regimen containing two nucleoside reverse transcriptase inhibitors (especially zidovudine and lamivudine), and one was taking a non-nucleoside reverse inhibitor (nevirapine or efavirenz), as shown in the table.

Discussion

Impaired fasting glucose was seen in 2.6% of the study participants. A Latin-American study by Hazra et al. [24] showed a lower prevalence of 0.4%, while no case of IFG was documented in a Thai study by Lee et al. [25]. Conversely, a Spanish study by Dapena et al. [1] reported a higher prevalence of 7%. The reasons for the differences may be related to some peculiarities of the various study populations, such as the mean age, diet, and genetic susceptibility. With regards to the two studies [24,25] with lower prevalence, possible factors could have been the lower mean age of 7.5 years [24] and 8 years [25], respectively, in comparison to the mean age of 9 years in the pressent study as well as the higher cut-off BG level of less than 110 mg/dl for IFG compared to the level of 100 mg/dl used in this study. In the Spanish study [1] with a higher prevalence, the older age group constituted the majority of their participants

Table 5: Characteristics of children with impaired fasting glucose.

Parameters	Patient A	Patient B	Patient C	Patient D	Patient E
Age (months)	100	134	172	158	117
Sex	F	M	F	F	M
ART Duration (months)	94	25	107	69	47
ARV regimen	AZT+3TC+NVP	AZT+3TC+NVP	AZT+3TC+EFV	AZT+3TC+EFV	AZT+3TC+EFV
CD4 rate	938	312	557	786	533
Viral load	1000	4770	1000	56000	1000
Familial Hx of diabetes	No	No	Yes	No	No
Familial Hx of High BP	No	No	No	No	No
Exercise	Yes	Yes	Yes	No	Yes
Snacks	Yes	Yes	Yes	No	Yes
BMI (kg/m2)	14.6 (normal)	17.58 (normal)	15.76 (normal)	19.31 (normal)	16.31 (normal)

with a median age of 13 years, which may be related to the relatively higher prevalence of IFG compared with other studies [24,25], including the present study.

The mechanism of impaired glucose tolerance in HIV is not completely elucidated, but it is known that during any infectious process, the release of cytokines may affect glucose metabolism [8]. In HIV infection, there is an increased release of TNF-α, IL-6, and IL-8 by both infected T cells and adipose tissues. Also, these inflammatory cytokines can induce insulin resistance with consequent dysglycaemia [8, 26].

The implication of impaired fasting blood glucose in these children is that prediabetes (PreDM) not only predicts the future development of DM, with 4–20% of pre-DM progressing to DM annually in the general population if no interventions are made, but it is also an independent risk factor for cardiovascular diseases (CVD) [8, 27].

A described associated factor of IFG in children living with HIV is pubertal onset. The small numbers of children with IFG did not enable multiple regressions, but it is noteworthy that the affected five children were in the pubertal age range, with three already in puberty. In a large cohort of 451 HIV-infected children, Geffner et al. documented advanced pubertal staging among the significant risk factors in a cohort with insulin resistance [28]. The authors suggested that their findings may mimic the usual physiological decrease in insulin sensitivity associated with the adolescent period, partly related to the rise in the growth hormone, which is one of the counter-regulatory hormones to insulin [28, 29]. However, it should also be noted that pre-pubertal children may also be at risk of dysglycaemia. In a multisite US-based prospective, 48-week observational study of HIV-infected, pre-pubertal children, Chantry et al. [3] documented an increase in the prevalence of abnormal glucose tolerance as defined by a HOMA-IR > 3.16 from 1% at the entry to 8% at 48 weeks. Despite the non-statistically significant change in the number of children with frankly abnormal values, the authors suggested that the development of glucose intolerance even in pre-pubertal children warrants caution and further studies.

Increased BMI is one of the proven traditional risk factors for dysglycaemia in the general population, including people living with HIV(PLHIV)[30]. Nevertheless, there seems to exist a clear subset of PLHIV, especially in people from sub-Saharan Africa who develop IFG and DM in the absence of high BMI [4], as noted in this study in which all children with IFG had normal BMI. Some studies (albeit in adult series) from South Africa [31], Rwanda [32], Tanzania [33], and Ethiopian migrants [34] in Israel have demonstrated situations of increased rates of IFG and DM not correlating with central obesity or reduced BMI [4]. The etiology and the underlying bioenergetics pathway changes of this non-obese DM phenotype are not completely elucidated yet. However, postulated pathophysiologic features that may contribute to the development of glucose intolerance in the absence of more widely recognized risk factors, such as obesity or advanced age, refer to elevated levels of inflammatory cytokines. This is thought to be related to the impairment of the mucosal defense, chronic gastrointestinal enteropathy, and opportunistic infections [4, 35-37]. Therefore, clinicians caring for children living with HIV need to watch out for dysglycaemia in these children, even in the absence of increased BMI.

Some families of ART have been implicated in the derangement of glucose metabolism [6, 7, 33]. These include NRTIs such as zidovudine and stavudine [4, 7] and NNRTIs such as efavirenz [6, 7]. This is of concern, seeing that the children with IFG in the present study were on a regimen that included these drugs. NRTIs are implicated in mitochondrial toxicity by inhibiting DNA polymerase γ [38]. The stress of the endoplasmic reticulum, generation of reactive oxygen species, altered lipid metabolism, changes in adipocytokine secretion, and inhibition of insulin signaling associated with these changes eventually result in a disruption in optimal glucose metabolism and subsequent deranged blood glucose levels [39].

The association of efavirenz with dysglycemia is critical because first-line ART regimens in the developing world include non-nucleoside reverse transcriptase inhibitors, and efavirenz is selected more often because of its perceived lower toxicity than nevirapine [6].

Another factor that may be related to dysglycaemia is the viral load, which correlates with the inflammatory processes. High and fluctuating viral load levels in HIV infection induce a chronic inflammatory state, leading to a decrease in adiponectin levels and an increase in insulin resistance [5]. The lowest viral load noted in the participants in the current study was 1000 copies.

Another important point worthy of mention is that the low literacy rates in association with high unemployment rates of mothers observed in the present

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study have implications on the health of the children. It has been documented that there is a strong connection between the well-being of children and the educational level of their mothers [40]. Mothers who are educated are more likely to be empowered socially and economically, which will positively impact their children's health. Relevant stakeholders and policymakers need to scale up the education and empowerment of mothers in the community.

A limitation of the study was the inability to determine insulin resistance in the study participants due to the high costs, even though we desired to because some studies which did not document any incidence of IFG in children living with HIV on ART noted significant levels (6.5%) of insulin resistance[25] and those that documented lower rates of IFG than our study, recorded a high prevalence rate of 6.8% [24]. The gold standard method for the determination of insulin sensitivity and pancreatic β-cell function is the hyperinsulinemic-euglycemic clamp and hyperglycemic clamp, respectively [25, 41, 42]. However, it is an invasive and resource-intensive method that is not very feasible clinically on a large scale. Therefore, many studies use fasting insulin or c-peptide to glucose ratio or surrogate estimates such as homeostasis model assessment for insulin resistance (HOMA-IR) since these have been shown to correlate with the clamp procedures [43, 44]. Additionally, the findings from this study may not be generalizable to other populations of children living with HIV. Nevertheless, the present study remains relevant in resource-constrained settings, where measurement of fasting insulin levels may not be easily available and affordable. Regular monitoring of blood glucose levels, which is largely affordable, can detect early cases of prediabetes and/or diabetes as defined by the International Society for Pediatric and Adolescent Diabetes (ISPAD) and International Diabetes Federation (IDF) [22, 23].

Conclusion

Dysglycaemia (IFG) was seen in 2.6% of the children taking ART. None had frank diabetes mellitus. The age of the affected children was in the pubertal ranges, with three of them already in puberty. All children had normal BMI, and one patient had a family history of DM with no family history of hypertension. Monitoring FBG in children living with HIV taking antiretroviral treatment is advocated for prompt diagnosis of prediabetes to enable early intervention to prevent diabetes progression with its attendant increase in disease burden, morbidity, and mortality in these children. en, morbidity, and mortality in these children.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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