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Thyroid Disorders and Autoimmunity among Patients with HIV/AIDS in Northern Nigeria

Abubakar UI[1], Uloko AE[2] and Gezawa ID[2]*

[1]Department of Medicine, Murtala Muhammad Specialist Hospital, Nigeria

[2]Department of Medicine, Aminu Kano Teaching Hospital, Nigeria

Abstract

Background: The association of HIV/AIDS and thyroid disorders has been described. Prevalence, pattern and autoimmune status significantly differ from HIV negative control in several studies. Unfortunately, few studies have determined the prevalence of thyroid disorders and autoimmunity among Nigerians living with HIV/AIDS.

Objective: To determine the prevalence of thyroid disorders and autoimmunity among patients with HIV/AIDS compared with HIV-negative controls.

Materials and Methods: In this cross-sectional, hospital based comparative study, we consecutively recruited 115 patients with HIV/AIDS attending the Aminu Kano Teaching Hospital PEPFAR/HIV clinic and 115 age and gender-matched HIV negative controls from the GOPD respectively. Study duration was 2 months. We used an interviewer-administered questionnaire to record demographic data, relevant history suggestive of thyroid dysfunction, findings on anthropometric and blood pressure measurements, and thyroid examination. Laboratory data evaluated included thyroid function tests, fasting plasma glucose, CD4 cell count, viral load, plasma lipids, and complete blood count.

Results: Of the 115 HIV positive and 115 HIV negative subjects recruited for the study, N(20%) were males, while N(80%) were females in both groups. The mean ± SD age of the subjects and controls was 38.2 ± 9.54 years and 35.9 ± 13.57 years respectively, p=0.138. The prevalence of thyroid dysfunction among the subjects and controls was 32.7% and 34.5% respectively, p=0.775. The predominant form of thyroid disorder identified was primary hypothyroidism, followed by isolated low FT3 among the subjects; while subclinical hypothyroidism followed by primary hypothyroidism is the predominant abnormality among the controls. Thyroid autoimmunity was demonstrated in 14.5% of subjects and 13.6% controls, p=0.846.

Conclusion: The predominant form of thyroid disorder among HIV/AIDS patients was primary hypothyroidism, while subclinical hypothyroidism predominated in non-HIV/AIDS patients. The prevalence of anti-TPO antibodies among HIV infected subjects and HIV-negative controls appear to be quite similar. Based on our findings, routine screening for thyroid disorders in patients with HIV/AIDS may not be recommended.

Keywords: Thyroid disorders; HIV/AIDS; Northern Nigeria

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Correspondence:
Uloko AE, Department of Medicine, Aminu Kano Teaching Hospital, Nigeria, E-mail: andyuloko@yahoo.com

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Introduction

Thyroid function may be altered in 10% to 15% of patients with HIV infection with both hypo- and hyperthyroidism seen, though the predominant abnormality is subclinical hypothyroidism [1]. In the early AIDS epidemic, the diverse endocrine manifestations of HIV infection were more often a consequence of Opportunistic Infections (OIs), neoplasms, or concomitant systemic illness [2]. In advanced HIV disease, infection of the thyroid gland may occur with opportunistic pathogens, including *P. jiroveci*, *Cytomegalovirus* (CMV), *mycobacteria*, *Toxoplasma gondii*, and *Cryptococcus neoformans* while Immune-reconstitution Graves' disease may occur as a late (9 months to 48 months) complication of HAART [2].

The widespread use of potent Antiretroviral Therapy (ART) has led to a decline in the incidence of glandular infiltration by OIs and neoplasms and has generated increased attention toward the metabolic complications of HIV therapy, including insulin resistance, dyslipidemia, and alterations in body fat distribution [3]. In the setting of Highly Active Antiretroviral Therapy (HAART) up to

10% of patients have been noted to have elevated thyroid-stimulating hormone levels, suggesting a manifestation of immune reconstitution [3]. Different classes of antiretroviral drugs can affect thyroid function and produce different patterns of thyroid abnormalities. Similarly, male gender and low level of CD4 count have been identified as risk factors for the development of thyroid dysfunction in HIV infected patients in some studies [3]. This study will establish the prevalence, of thyroid disorders and autoimmunity in patients with HIV/AIDS at Aminu Kano Teaching Hospital Kano, Northwestern. It will also determine whether HIV-infection predisposes Nigerians living with HIV to a higher risk of thyroid function abnormality and whether this category of individuals require routine screening for thyroid dysfunction.

Materials and Methods

Study area

The study sites were HIV clinic and general out patients department of Aminu Kano Teaching Hospital, Kano State Nigeria.

Study design

Descriptive cross-sectional hospital-based comparative evaluation of patients with HIV/AIDS and apparently healthy HIV negative controls.

Study population

Subjects: Adult HIV/AIDS patients attending the SS Wali HIV centre of Aminu Kano Teaching Hospital who satisfied the inclusion criteria.

Controls: Apparently healthy HIV-negative individuals who were age and gender matched to the subjects attending the AKTH Kano GOPD for medical checkup.

Study period: The study spanned over six months from January to June 2016 to include data collection, analysis and write-up.

Sampling technique

Subjects who met the inclusion criteria were verified and recruited using systematic random sampling until the estimated sample size was achieved.

Data collection

A total of 230 patients (115 HIV positive and 115 HIV negative) was interviewed. A signed informed consent form was obtained from each study participant before commencement of the study. An interviewer-administered questionnaire in both English and Hausa was deployed to capture relevant sociodemographic and historical details of each study participant. Details of physical examination especially anthropometry, general physical examination, cardiovascular examination and thyroid examination were entered into relevant sections of the questionnaire.

Laboratory analysis

Serum levels of free triiodothyronine, free thyroxine, thyroid stimulating hormones (FT3, FT4, and TSH) and anti-TPO antibody were determined using Electrochemiluminescence assay. Other parameters analyzed were fasting plasma glucose, plasma lipids, CD4 cell count, viral load and complete blood count.

Inclusion criteria

Subjects:

- Patients diagnosed with HIV who were receiving care at the SS Wali AKTH HIV clinic;
- Patients aged 18 to 65 years;
- Patients who gave informed consent.

Controls:

- Apparently healthy HIV negative adults aged 18 to 65 years;
- Not on any drug that can cause thyroid dysfunction e.g. amiodarone;
- Not pregnant
- Those who gave informed consent.

Exclusion criteria

Subjects:

- Age less than 18 years or more than 65 years
- Very ill patients; e.g. those with severely compromised cardio-respiratory disease or those in coma;
- Subjects who decline consent
- Pregnant women
- Patients with ailments that adversely alter body immunity e.g. diabetes mellitus, malignancies, autoimmune disorders, and use of immune-modulating drugs
- In-patients

Controls:

- Age less than 18 years or more than 65 years
- Individuals who decline consent
- Individuals who tested HIV positive
- Pregnant women
- Severely ill patients
- Individuals with ailments that adversely alter body immunity e.g. diabetes mellitus, malignancies, autoimmune disorders, and use of immune-modulating drugs;
- Individuals on drugs that affect thyroid functions e.g. amiodarone

Ethical considerations

- Ethical clearance was obtained from the Research and Ethics Committee of Aminu Kano Teaching Hospital, Kano before the commencement of the study.
- The provision of HELSINKI declaration was respected.

Data analysis

The data generated were collated, checked, and analyzed using a computer based Statistical Package for Social Sciences (SPSS) version 20.0 (Chicago, Illinois, USA). Mean ± SD was used to describe continuous variables, while proportions and percentages were used for categorical variables. Independent student t-test was used for comparison of two means. Chi-squared (χ^2) test or Fisher's exact test as appropriate was used to compare proportions (categorical data). A confidence interval of 95% was used and a p-value of ≤ 0.05 considered significant.

Results

In this study, spanning over six months (January to June, 2016), a total of 115 subjects and 115 controls were recruited. Of these, the number of subjects and controls who completed the study with a complete data set was 110 each for the subjects and controls. Ten subjects (five from each group) dropped out of the study accounting for 4.3% attrition and an overall response rate of 95.7%.

Characteristics of the study participants

The two groups were similar with respect to age composition and gender distribution with no statistically significant difference in age (p=0.514) and gender (p=0.867) distribution. The mean ± SD age of subjects and controls was 38.2 ± 9.54 and 35.9 ± 13.57 respectively, with no statistically significant difference in the mean age of the two groups (p=0.138). The predominant age group was 30 years to 39 years with a m:f ratio of 1:4 for both subjects and controls (Table1).

The mean ± SD duration of HIV among the subjects in years was 6.4 ± 4.03, while the mean ± SD duration of ARV use by the subjects in years was 5.7 ± 4.02; 107 (97.3%) subjects were on ARVs with 103 (93.6%) subjects on first line ARVs, while the remaining 4 (3.6%) used second line agents.

Personal history of hypertension, family history of hypertension, family history of diabetes mellitus (all higher in the controls) and mean resting pulse (higher in the subjects) were the only clinical features that demonstrated statistically significant differences between the two groups (Table 2).

Laboratory characteristics of the study participants

Only mean TSH, triglyceride, HDL, hematocrit, white blood cell count and neutrophils showed statistically significant difference between subjects and controls (Table 3).

Prevalence and pattern of thyroid dysfunction among the study participants

The overall prevalence of thyroid dysfunction among the subjects was 32.7% (Male 9.1%, female 23.6%) while among the controls was 34.5% (male 10.9%, female 23.6%) p=0.775. However, there was a statistically significant difference in the prevalence between male (10.9%) and females (23.6%) among the controls (p=0.046) but not among the subjects (p=0.155).

The most prevalent thyroid dysfunction among the subjects was primary hypothyroidism (11.8%, male 4.5% and female 7.3%) followed by isolated low FT3 (9.1%, male 0.9% and female 8.2%), while among the controls, the most common thyroid dysfunction was subclinical hypothyroidism (16.4%, male 4.5% and female 11.8%) followed by primary hypothyroidism (10%, male 4.5% and female 5.5%), p=0.034 (Table 4).

Frequency of anti-TPO antibody among subjects and controls

The prevalence of thyroid autoimmunity (Anti-TPO Ab positive) among subjects and controls was 14.6% (male 5.5% and female 9.1%) and 13.6% (male 4.5% and female 9.1%) respectively, p=0.846. There was no statistically significant difference in the distribution of Anti-TPO Ab among the subjects and controls (p=0.291).

Anti-TPO Ab was most prevalent with primary hypothyroidism and combined low FT3 and FT4 among the subjects (4.5% each); while among controls it was most prevalent with primary hypothyroidism (9%) followed by combined low FT3 and FT4 (3.6%) (Table 5).

Discussion

In the index study, mean values of TSH, FT3 and anti-TPO were found to be lower among the subjects compared with the controls, the difference being more profound for TSH. Collazos et al. [3] also found lower TSH levels among their subjects with HIV compared with controls and also reported that HIV status had no effect on FT3 and FT4. This is in contrast to what was reported by Gagnon et al. [4] in Toronto, Canada where they found higher TSH levels among subjects with HIV compared with controls, but in agreement with this study for lower FT3 among subjects with HIV compared with controls. Palanisamy et al. [5] in India found lower FT4 but higher FT3 and TSH among subjects with HIV compared with controls. In Ibadan, Southwestern Nigeria, Abbiyesuku et al. [6] found higher TSH levels among HIV patients compared with controls, but as in the index study they reported lower FT3 levels among their HIV infected patients compared with controls. The lower FT3 found among the cases compared with controls in many of these studies including this study, may be explained by higher incidence of non-thyroidal illness (low T3 syndrome) in the setting of HIV infection and it could also be as a result of additive effect of HIV infection itself and various components of HAART on thyroid function.

Studies on the prevalence of thyroid abnormalities among blacks suggest that they tend to have lower prevalence of thyroid dysfunction [7,8]. The prevalence of thyroid dysfunction among the subjects in this study was 32.7%, while among the controls the prevalence was 34.5%. This is similar to the report by Shujing et al. [9] in Guangzhou, China where they found a prevalence of 33% among their subjects. In the latter study, similar laboratory technique was used and the mean duration of HIV infection and ARVs use by their subjects was comparable to that of the subjects in this study.

Table 1: Comparison of subjects and controls by age and gender.

AGE (Years)	GENDER					
	Subjects			Controls		
	Male n (%)	Female n (%)	Total n (%)	Male n (%)	Female n (%)	Total n (%)
<20	2 (1.8)	5 (4.5)	7 (6.4)	3 (2.7)	6 (5.5)	9 (8.2)
20-29	3 (2.7)	17 (15.5)	20 (18.2)	6 (5.5)	21 (19.1)	27 (24.5)
30-39	7 (6.4)	29 (26.4)	36 (32.7)	4 (3.6)	25 (22.7)	29 (26.4)
40-49	3 (2.7)	24 (21.8)	27 (24.5)	7 (6.4)	12 (10.9)	19 (17.3)
50-59	3 (2.7)	8 (7.3)	11 (10.0)	3 (2.7)	12 (10.9)	15 (13.6)
≥ 60	4 (3.6)	5 (4.5)	9 (8.2)	0 (0.0)	11 (10.0)	11 (10.1)
Total	22 (20.0)	88 (80.0)	110 (100.0)	23 (20.9)	87 (79.1)	110 (100.0)

Table 2: Comparison of clinical characteristics between subjects and controls participants.

Clinical characteristics	Subjects	Controls	p-value
Age ± SD (yrs)	38.2 ± 11.75	37.6 ± 13.12	0.086
Discriminating features of thyroid hyper function n (%)	22 (20)	19 (17.3)	0.603
Discriminating features of thyroid hypo function n (%)	4 (3.6)	3 (2.7)	>0.999
Personal history of hypertension n (%)	15 (13.6)	31 (28.2%)	0.008*
Family history of hypertension n (%)	37 (33.6)	58 (52.7)	0.008*
Family history of thyroid disease n (%)	4 (3.6)	6 (5.4)	0.517
Family history of diabetes mellitus n (%)	15 (13.6)	28 (25.5)	0.027*
History of cigarette smoking n (%)	16 (14.5)	10(9.1)	0.21
History of alcohol consumption n (%)	9 (8.2)	3 (2.7)	0.075
Goitre n (%)	0 (0.0)	0 (0.0)	-
Opportunistic infection n (%)	0 (0.0)	0 (0.0)	-
Height ± SD (m)	1.64 ± 0.09	1.65 ± 0.10	0.273
Weight ± SD (kg)	67.1 ± 15.97	67.0 ± 12.42	0.968
BMI ± SD (kg/m^2)	24.8 ± 5.16	24.7 ± 4.99	0.886
Waist circumference ± SD (cm)	88.5 ± 11.85	86.7 ± 14.66	0.32
Resting pulse ± SD (beats/min)	87.1 ± 14.64	78.6 ± 13.60	<0.001*
Systolic blood pressure ± SD (mmHg)	126.2 ± 19.11	129.5 ± 19.34	0.208
Diastolic blood pressure ± SD (mmHg)	82.5 ± 11.84	81.9 ± 13.38	0.709

*Statistically Significant; BMI: Body Mass Index; Discriminating features of hyperthyroidism, weight loss, anxiety, heat intolerance, excessive sweating, hyperdefecation, irritability, wasting, warm and sweaty palm, irregular menses; Discriminating features of hypothyroidism, slow activity, weight gain getting tired easily, cold intolerance, depressed mood, body swelling; SD: Standard Deviation

Table 3: Comparison of laboratory characteristics between subjects and controls.

Laboratory characteristics	Subjects (Mean ± SD)	Controls (Mean ± SD)	p-value
TFT			
FT3 (pmol/l)	1.2 ± 1.27	1.6 ± 1.37	0.946
FT4 (pmol/l)	3.0 ± 3.49	2.9 ± 2.94	0.202
TSH (miu/l)	2.6 ± 1.88	3.5 ± 2.81	0.006*
anti-TPO Abs (iu/ml)	1.2 ± 16.1	1.6 ± 17.1	0.183
CD4 Count(cells/ml)	503.1 ± 290.56	-	-
viral load (cells/ml)	27381.7 ± 7461.13	-	-
FPG (mmol/l)	4.7 ± 0.63	4.8 ± 0.69	0.449
FPL			
TC (mmol/l)	4.9 ± 1.03	4.9 ± 1.19	0.935
HDL (mmol/l)	1.2 ± 0.41	1.6 ± 0.43	<0.001*
LDL (mmol/l)	3 ± 1.01	2.9 ± 0.98	0.451
TG (mmol/l)	1.2 ± 0.54	1.6 ± 0.61	<0.001*
CBC			
Haematocrits (%)	34.6 ± 4.08	38.3 ± 4.49	<0.001*
Total WBC (cells/nl)	5.1 ± 3.82	6.0 ± 1.72	0.024*
Neutrophils (%)	46.9 ± 10.61	56.5 ± 7.89	<0.001*
Lymphocytes (%)	42.4 ± 9.39	40.3 ± 6.83	1.922
MCV (fl)	77.9 ± 8.54	76.8 ± 6.98	0.334

CBC: Complete Blood Count; FPG: Fasting Plasma Glucose; FPL: Fasting Plasma Lipids; FT3: Free Triiodothyronine; FT4: Free Thyroxine; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; MCV: Mean Corpuscular Volume; T.ch: Total cholesterol; TFT: Thyroid Function Test; TG: Triglyceride; TSH: Thyroid Stimulating Hormone; WBC: White Blood Cells; *Statistically Significant

The prevalence of thyroid dysfunction among subjects in this study is lower than reported from many studies across the world [4,9-11]. Many of those studies however, had subjects with longer duration of HIV but shorter duration of ARVs use than the subjects in this study. One of these studies by Amadi et al. [11], who reported prevalence of 100% (all overt hypothyroidism), was carried out in Jos, North-central Nigeria which is a mountainous iodine-deficient region of the country. These variations in geographical location and exposure of

Table 4: Comparison of prevalence and pattern of thyroid dysfunction between subjects and controls.

Pattern	Subject n (%)			Controls n (%)			
	Male	Female	Total	Male	Female	Total	p-value
Subclinical hypothyroidism	2 (1.8)	4 (3.7)	6 (5.5)	5 (4.6)	13 (11.8)	18(16.4)	0.009*
Isolated low FT3	1 (0.9)	9 (8.2)	10 (9.1)	2 (1.8)	1 (0.9)	3 (2.7)	0.045*
Isolated low FT3 & FT4	2 (1.8)	5 (4.6)	7 (6.4)	0(0.0)	5 (4.5)	5 (4.5)	0.553
Primary hypothyroidism	5 (4.5)	8 (7.3)	13 (11.8)	5(4.5)	6 (5.5)	11 (10)	0.665
Subclinical hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.9)	>0.999
Isolated high FT3	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	>0.999
Total	10 (9.1)	26 (23.6)	36 (32.7)	12 (10.9)	26 (23.6)	38 (34.5)	0.775

FT3: Free Triiodothyronine; FT4: Free Thyroxine; *Statistically Significant

Table 5: Comparison of frequency of anti-TPO antibody between subjects and controls.

Anti-TPO Ab Positivity							
Pattern of thyroid function	Subject n (%)			Controls n (%)			
	Yes	No	Total	Yes	No	Total	p-value
Normal	3 (2.7)	71 (64.6)	74 (67.3)	0 (0.0)	72 (65.5)	72(65.5)	0.247
Subclinical hypothyroidism	2 (1.8)	4 (3.6)	6 (5.5)	1 (0.9)	17 (15.5)	18(16.4)	>0.999
Isolated low FT3	1 (0.9)	9 (8.2)	10 (9.1)	0 (0.0)	3 (2.7)	3 (2.7)	>0.999
Combined low FT3 & FT4	5(4.5)	2 (1.8)	7 (6.3)	4(3.6)	1 (0.9)	5 (4.5)	>0.999
Primary hypothyroidism	5 (4.5)	8 (2.3)	13 (11.8)	10(9.0)	1(0.9)	11 (9.9)	0.181
Total	16 (14.5)	94 (85.5)	110 (100.0)	15 (13.6)	95 (86.4)	110 (100.0)	0.846

FT3: Free Triiodothyronine; FT4: Free Thyroxine

the study population to varying degrees of iodine deficiency may be the reason behind the reported higher prevalence rates from these studies. On the other hand, studies that reported lower prevalence rates of thyroid dysfunction among their subjects have shorter mean duration of HIV and lower levels of CD4 count than the subjects in the index study [12].

The most common pattern of thyroid dysfunction among subjects in this study was primary hypothyroidism, followed by isolated low FT3, combined low FT3 & FT4, subclinical hypothyroidism and isolated high FT3 in that order. Among the controls, the most common thyroid dysfunction was subclinical hypothyroidism, followed by primary hypothyroidism, combined low FT3 & FT4, isolated low FT3 and subclinical hyperthyroidism in that order. Similar findings were reported by Ketsamathi et al. [13] in Bangkok. Several studies have also found primary hypothyroidism as the most frequent thyroid abnormality among their study population [9,11,14,15]. However, Gagnon et al. [2] in Toronto, Canada and Guilherme et al. [10] in Rio de Janeiro, Brazil, reported subclinical hypothyroidism as the most common pattern of thyroid dysfunction among their subjects. The longer duration of HIV infection among subjects in those studies and the fact that many of the patients were not on ARVs may explain the difference. Some studies have reported an association between ARV use, low levels of CD4 count and overt hypothyroidism [10,16]. The isolated low FT3, and isolated combined low FT and FT4 found in this study, were also reported by Rasoolinejad et al. [17] in Tehran, Iran and Abbiyesuku et al. [6] in Ibadan, Nigeria, as the most common thyroid dysfunction among their subjects. Both abnormalities could be due to sick euthyroid syndrome in the setting of advanced HIV infection. They could also be due to clinical or subclinical opportunistic infection. We found no statistically significant difference in the prevalence of thyroid autoimmunity between the subjects and controls in this study. Anti-TPO Ab was most prevalent with primary hypothyroidism and isolated low FT3 and FT4 among the subjects (4.5% each), while among controls the antibodies were most prevalent among those with primary hypothyroidism (9%), followed by isolated low FT3 and FT4 (3.6%).

The prevalence of thyroid autoimmunity found in this study is higher than reported from many other studies across the world [10,12,16,18,19]. Nelson et al. [15] in England reported a prevalence of 1.1% and Ketsamathi et al. [12] in Bangkok, reported 6.5%. Nelson found that thyroid anti-bodies were present in 40% of those with hypothyroidism and 56.7% of patients with hyperthyroidism. Our subjects had longer duration of HIV and ARVs use and higher CD4 count. This may suggest greater immune restoration with longer duration of ARV use and explain the higher prevalence of autoimmunity among our patients.

Conclusion

The prevalence of thyroid dysfunction is lower among HIV-positive subjects than among the controls in this study. Although the prevalence of thyroid autoimmunity (Anti-TPO antibody positive) was higher among HIV-positive subjects than among controls, the difference was not statistically significant. We however, found statistically significant difference in the pattern of thyroid dysfunction between HIV positive patients and HIV-negative controls, with primary hypothyroidism being the predominant pattern among HIV positive patients, followed by isolated low FT3, while subclinical hypothyroidism and primary hypothyroidism respectively, and predominated among the HIV negative controls. Anti-TPO Ab was most prevalent with primary hypothyroidism and isolated low FT3 and FT4 among the subjects while among controls was most prevalent with primary hypothyroidism followed by isolated low FT3 and FT4. While our finding of similar prevalence rate of thyroid dysfunction and autoimmunity among subjects and controls in this

study may not support routine screening for thyroid disorders, the high prevalence of thyroid autoimmunity in HIV positive patients may portend future development of symptomatic thyroid disease. We therefore recommend a larger prospective study to identify the risk factors for progression to overt thyroid disease in euthyroid HIV infected subjects with thyroid autoimmunity.

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