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Full Length Research Paper

The prevalence of diabetes mellitus in human immunodeficiency virus seropositive subject's co-infected with mycobacterium tuberculosis

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Diabetes mellitus (DM), mycobacterium tuberculosis (TB) and human immunodeficiency virus (HIV) are important health issues. A bi-directional association between them has been demonstrated by many researchers. The link of DM and TB/HIV is more prominent in developing countries where TB and HIV are endemic and the burden of diabetes mellitus is increasing. A total of 845 subjects were recruited for this study. Fasting blood sugar was determined by the glucose oxidase method while HIV serology was performed using the National Algorithm. The method adopted for mycobacterium tuberculosis identification was the geneXpart as described by Tenover. The prevalence of DM in HIV seropositive subject co-infected with mycobacterium tuberculosis was 107 (12.6%). Out of the 350 patient that tested positive for HIV, 38 (4.5%) had DM, 11 (1.3%) were of Type-1 origin while 27 (3.2%) were of Type-2 origin. On the other hand, 450 patients were TB positive, 45 (5.3%) had DM, 9 (1.0%) were of Type-1 origin while 36 (4.3%) were of Type-2 origin while that of HIV seropositive subjects co-infected with TB: 24 (2.8%) had DM, 5 (0.5%) were Type-1 origin while 19 (2.2%) were of Type-2 origin. There are highly more female 57 (6.7%) with DM than male 50 (5.9%). Our finding has shown no significant increase in the mean blood glucose concentration of HIV seropositive subjects compared with individuals infected with TB ($P < 0.05$). A significant increase was observed in HIV seropositive subjects co-infected with TB compared with HIV seropositive individuals ($P > 0.05$). The same pattern was observed in HIV seropositive subjects co-infected with TB compared with individual infected with HIV ($P > 0.05$). It is recommended that all patients with HIV and mycobacterium tuberculosis infections should be screened for diabetes mellitus as this would help in effective management of the disease conditions.

Keywords: Diabetics mellitus, TB, HIV, mycobacterium tuberculosis, seropositive.

INTRODUCTION

Diabetes mellitus (DM), human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) and mycobacterium tuberculosis (TB) are associated with immune suppression at different levels (Brown et al., 2010; Houben et al., 2006; Ledergerber et al., 2007; Nnoaham and Clarke, 2008). Human immunodeficiency virus and mycobacterium tuberculosis are chronic communicable diseases which often lead to impaired system in patients (Brown et al., 2010 Houben et al., 2006). Diabetes mellitus on the other hand is a chronic non communicable and metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both (Ronald et al., 2013).

The epidemiology of HIV are well known to be associated with immunological break down of immune system which often expose the individual to communicable disease such as mycobacterium tuberculosis (Nnoaham and Clarke, 2008; Jeon and Murray, 2008). Intriguingly in the recent past, evidences were accumulating on the association between mycobacterium tuberculosis and diabetes mellitus, as well as HIV/AIDS and diabetes mellitus, which gained importance to the communicable and non-communicable disease association (Young et al., 2009) Nevertheless, the HIV-TB link was well recognized since the beginning of HIV epidemic (Ahmed and Hasnain, 2011).

Human immunodeficiency virus is a major risk factor for mycobacterium tuberculosis (Harris and Dye, 2006; Reid et al., 2006; Nijland et al., 2006; Strachan et al., 2005). The risk of developing mycobacterium tuberculosis is estimated to be between 20 to 37 times greater in people living with HIV than among those without HIV infection (Leung et al., 2007; Davies et al., 2006; Restrepo, 2011). In 2009, there were 9.4 million new cases of mycobacterium tuberculosis of which 1.2 (13%) million were among people living with HIV. Of the 1.7 million people who died of mycobacterium tuberculosis, 400,000 (24%) were living with HIV (Leung et al., 2007). It has been observed that HIV seropositve individuals face a 3 - fold risk of developing diabetes mellitus (Nnoaham and Clarke, 2008). A higher association has been found between Type-2 diabetes mellitus and mycobacterium tuberculosis in study populations from central America, Europe, and Asia (Nnoaham and Clarke, 2008). Diabetes mellitus is an important risk factor that is increasing in developing countries (Kumar et al., 2007). Developing countries with exponential economic growth such as India

and China that account for 40% of incidence of TB cases in 2010 are estimated to have 69% increase in people with diabetes mellitus and these are of major concern for the joint burden of disease between diabetes mellitus and mycobacterium tuberculosis (Nnoaham and Clarke, 2008).

The association between human immunodeficiency virus infection and Type-2 diabetes mellitus is poorly understood and complicated, the prevalence risk factors of Type-2 diabetes mellitus in HIV infected individuals compared with HIV uninfected persons is conflicting (Goulet et al., 2005; Kilbourne et al., 2001). Few studies have directly compared HIV infected subjects with HIV uninfected, and the results are conflicting (Brown et al., 2005). Other disease state that can increase the risk of developing mycobacterium tuberculosis and Type-2 diabetes mellitus are hodgkin lymphoma, end-stage renal disease, chronic lung disease, malnutrition, alcoholism and drugs (Moller and Hoal, 2010). Low body weight is also associated with risk of mycobacterium tuberculosis. A body mass index (BMI) below 18.5 increases the risk by 2 to 3 times (Restrepo, 2007). An increase in body weight lowers the risk (Restrepo, 2007). People with Type-2 diabetes mellitus are at increased risk of contracting mycobacterium tuberculosis (Nijland et al., 2006). And they have a poorer response to treatment, possibly due to poorer drug absorption in the gastrointestinal mucosa (Strachan et al., 2005). Other clinical conditions that have been associated with active TB include gastrectomy with attendant weight loss and malabsorption, jejunoileal bypass, renal and cardiac transplantation, carcinoma of the head or neck, and other neoplasms (e.g., lung cancer, lymphoma, and leukemia) (Restrepo, 2007).

Overcrowding especially in prisons, poor nutrition may contribute to the strong link observed between mycobacterium tuberculosis and Type-2 diabetes mellitus (Spence et al., 1993; Larouze et al., 2008). Incidence of mycobacterium tuberculosis is greatest among individual with impaired immunity (Houben et al., 2006), though co-infection of human immunodeficiency virus with mycobacterium tuberculosis are increasing daily, we cannot overlook Type-2 diabetes mellitus which have shown a higher prevalence in TB patients compared to HIV. The determination of the prevalence of diabetes mellitus in human immunodeficiency virus subject co infected with mycobacterium tuberculosis may help to X-ray this question by evaluating the prevalence of diabetes

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mellitus in HIV seropositive subjects co-infected with mycobacterium tuberculosis.

MATERIALS AND METHODS

Study population

The research work was carried out in mile four specialist hospital Abakaliki. The hospital is a center of excellence for mycobacterium tuberculosis and human immunodeficiency virus management. Gene (Xpert MTB/RIF) Model GXXVI-16-D was used to analyze the sample for TB patients while spectrophotometer model 6505 was used for fasting glucose analysis. A total of eight hundred and forty five (845) patients were analyzed in this study. The subjects were grouped into three categories: 250 HIV infected patients, 350 individuals infected with mycobacterium tuberculosis and 245 HIV seropositive individuals co-infected with mycobacterium tuberculosis. Most of the HIV seropositive individuals were on ART, HAART and anti-cough, respectively. HIV seropositive individuals, diabetic patients and subjects infected with mycobacterium tuberculosis, and HIV seropositive individual co-infected with mycobacterium tuberculosis were included in this study, while patients below 10 years and those above 80 years were excluded. All patients gave informed consent for study participation. Ethical approval for the study was received from mile four hospital management prior to sample collection and analysis.

Collection of blood samples

About 5 mls of whole blood were collected from each patients and 3 mls were dispensed into a fluoride-oxalate container for glucose estimation, while the remaining 2 mls were used for HIV status screening on the subjects.

Sputum sample collection procedures

Three consecutive sputum samples (spot, early morning, spot) were collected from the patients in sterile wide capped containers before eating or drinking. The subjects were asked to breathe in and out deeply 2 to 4 times, to give a series of low deep coughs to raise sputum from the lungs and deposit material into the container. The containers were covered with a screw cap cover to prevent leakage, and then labeled with date and time of collection. The sputum specimens were collected from subjects for three day each morning with three containers, respectively. The demographic information of each of the patients was obtained with a well structured questionnaire and corresponding medical records. The result of HIV status of such patient and confirmation were extracted from the patient's medical records obtained from mile four hospital referral HIV and TB Laboratory center.

Estimation of glucose

Glucose concentrations were determined according to the glucose oxidase method as described by Carl et al. (2008).

Identification of acid fast baccili (AFB)

This was performed using the geneXpert techniques as described by Tenover and Baron, (2012). This procedure is essentially a PCR technique.

Determination of HIV seropositivity

The method adopted in this study is the National Algorithm for HIV screening utilization determine, Stak Pak and Uni-Gold kits (WHO, 2008).

Statistical analysis

Data collected were subjected to statistical analysis using the chi square and students'-test. Values were deemed significant if P < 0.05.

RESULTS

Between May 2013 and January 2015, a fasting glucose concentrations of 845 patients infected with human immunodeficiency virus infection, mycobacterium tuberculosis positive patients and those suffering from HIV co-infection with TB comprising of 350 seropositve HIV subject, 450 TB positive patients and 245 HIV subjects co-infected with mycobacterium tuberculosis were analyzed. The age distributions are shown in Table 1. Data collected and analyzed shows that HIV seropositive patients within the age bracket of 31 to 40 years has the highest HIV occurrence with 86 (10.2%). Mycobacterium tuberculosis occurred more within the age group of 31 to 40 years with 111 (13.1%). While patients with HIV co-infected with TB appeared high within the age group of 41 to 50 with 88 (10.4%). Table 2 presents the gender distribution of Type-1 and Type-2 DM in HIV seropositive patient, TB positive patients and HIV subject's co-infected with TB. Out of the 350 patient that tested positive for HIV, 38 (4.5%) had DM, 11 (1.3%) were of Type-1 origin while 27 (3.2%) were of Type-2 origin. On the other hand, 450 patients that tested TB positive 45 (5.3%) had DM, 9 (1.0%) were of Type-1 origin while 36 (4.3%) were of Type-2 origin while that of HIV seropositive subjects co-infected with TB 24 (2.8%) had DM, 5 (0.5%) were Type-1 origin while 19 (2.2%) were of Type-2 origin. There are highly more female 57 (6.7%) with DM than male 50 (5.9%).

Analysis of clinical data generated from the clinical record of the patients as presented in Table 3 shows that 20 (2.4%) of the HIV seropositve patients with DM are on ART while 18 (2.1%) are not taking ART. 24 (2.8%) are on HAART and 14 (1.7%) not on HAART. Among the 45 TB cases with DM, 32 (3.8%) are on anti - cough while 13 (1.5%) are not on anti - cough drugs. While that of HIV seropositive patients co-infected with TB shows that 20 (2.4%) are on anti - cough, 4 (0.5%) are not on anti - cough. 15 (1.7%) and 14 (1.7%) are on ART and HAART, respectively. While 9 (1.1%) and 10 (1.1%) are not taking

Table 1. Age distribution of HIV seropositve patients, mycobacterium tuberculosis positive patients and HIV seropositive patients co-infected with mycobacterium tuberculosis.

Age group (years)	HIV positive (%)	TB positive (%)	HIV co - TB positive (%)	Total
11 - 20	11 (1.3)	9 (1.1)	5 (0.5)	25 (3.0)
21 - 30	40 (4.7)	75 (8.9)	37 (4.4)	152 (17.9)
31 - 40	86 (10.2)	111 (13.1)	74 (8.8)	271 (32.1)
41 - 50	62 (7.3)	102 (12.0)	88 (10.4)	252 (29.8)
51 - 60	31 (3.7)	37 (4.4)	30 (3.6)	98 (11.6)
>60	20 (2.4)	16 (1.9)	11 (1.3)	47 (5.6)
Total	250 (29.6)	350 (41.4)	245 (29.0)	845 (100)

Legend: the incidence of human immunodeficiency virus, TB and HIV seroposive patients co-infected with TB were higher within the age group of 21 to 50 years.

Table 2. Gender distributions of Type-1 and Type-2 diabetes mellitus in HIV seropositive patients, mycobacterium tuberculosis positive patients and HIV seropositive subjects co infected with mycobacterium tuberculosis.

Disease	N	Type-1 DM (%)	Type-2 DM (%)	Male (%)	Female (%)	Total with DM (%)	Glucose concentration {(Mean U/L ± SD) (Mmol/L)}
HIV +ve	250	11 (1.3)	27 (3.2)	15(1.7)	23 (2.7)	38 (4.5)	8.24 ± 0.96
TB +ve	350	9 (1.0)	36 (4.3)	25 (3.0)	20 (2.4)	45 (5.3)	8.54 ± 1.38
HIV co TB +ve	245	5 (0.6)	19 (2.2)	10 (1.2)	14 (1.4)	24 (2.8)	8.89 ± 1.18
Total	845	25 (2.9)	82(9.7)	50 (5.6)	57 (6.7)	107 (12.6)	-

Legend: The incidence of diabetes mellitus were higher in female than their male counterpart.

any ART and HAART, respectively. The mean CD4 counts of patients with HIV seropositive were higher than HIV seropositive counterpart co-infected with mycobacterium tuberculosis were 456.3 and 335.8, respectively.

Table 4 shows the comparison of glucose concentrations of HIV seropositive patients with mycobacterium tuberculosis positive patients, Our finding has shown no significant increase in the mean blood glucose concentration of HIV seropositive subjects compared with individuals infected with TB (P < 0.05). The minimum and maximum blood glucose concentration for HIV positives were 7.30 and 10.6 Mmol/L, respectively while that of TB positive counterpart where 7.50 and 13.50, respectively. On the other hand, a significant increase was observed in the mean blood glucose concentration of HIV seropositive subjects co-infected with TB compared with HIV seropositive individuals (P > 0.05). The minimum and maximum blood glucose concentration for HIV positive were 7.30 and 10.60 Mmol/L, while that of HIV seropositive subjects co-infected with TB were 7.50 and 11.40, respectively. The same pattern was observed in HIV seropositive subjects co-infected with TB compared with individual infected with TB (P > 0.05). With minimum and maximum blood glucose concentration of 7.50 and 13.50 Mmol/L for

TB positive patients alone and 7.50 and 11.40 for HIV seropositive subject's co-infected with TB.

DISCUSSION

In the recent decades, the number of human immunodeficiency virus and mycobacterium tuberculosis infections and those with HIV co-infected with mycobacterium tuberculosis has increased in several folds especially in sub-African countries, The growing association between HIV and TB is globally recognized (Ahmed et al., 2007; Thuy et al., 2007; Nsubuga et al., 2002). Similar reports are found in Nigeria (Okogun et al., 2002; Umeh et al., 2007; Nwobu et al., 2004). In this work, Table 1 shows the age group with highest rate of HIV and TB are within the age group of 21 to 50 years and this is in contrast with the studies of (Taura et al., 2008; in Kano, Umeh et al., 2007; Nasarawa and Nwachukwu et al., 2009) in Abia all in Nigeria.

A possible mechanism of the association of diabetes mellitus and mycobacterium tuberculosis is the depression of the immune response from protective immune mechanism, which in turn facilitates the progression of latently infected mycobacterium tuberculosis to active TB (Sulaiman et al., 2011; Blanca

Table 3. Clinical profile/data of diabetes mellitus in HIV seropositive patients, mycobacterium tuberculosis positive patients and HIV seropositive subject's co-infected with mycobacterium tuberculosis.

Disease	N	No. with DM	Anti cough	No. - anti cough	ART	No. ART	HAART	No. HAART	CD4 Count {(Mean U/L ± SD) (Cells/μL)}
HIV +ve	250	38 (4.5)	-	-	20 (2.4)	18 (2.1)	24 (2.8)	14 (1.7)	456.3 ± 2739.1
TB +ve	350	45 (5.3)	32 (3.8)	13 (1.5)	-	-	-	-	-
HIV co TB +ve	245	24 (2.8)	20 (2.4)	4 (0.5)	15 (1.7)	9 (1.1)	14 (1.7)	10 (1.1)	335.8 ± 1576.3
Total	845	107 (12.6)	52 (6.2)	17 (2.0)	35 (4.1)	27 (3.2)	38 (4.5)	24 (2.8)	-

Legend: the prevalence of DM in HIV seropositve subject co infected with TB were 107 (12.6). The Mean CD4 count of patients with human immunodeficiency virus were increased than patients with HIV.

Table 4. Comparison of glucose concentrations of HIV seropositive patients, mycobacterium tuberculosis positive patients and HIV seropositive subjects co-infected with mycobacterium tuberculosis.

Disease	N	No. with DM	Minimum glucose con (Mmol/L)	Max glucose con (Mmol/L)	Glucose concentration {(Mean U/L ± SD) (Mmol/L)}	P-Value
HIV +ve	250	38	7.30	10.60	8.24 ± 0.96	0.021
TB +ve	350	45	7.50	13.50	8.54 ± 1.38	-
HIV +ve	250	38	7.30	10.60	8.24 ± 0.96	0.750
HIV and TB	245	24	7.50	11.40	8.89 ± 1.18	-
TB +ve	250	45	7.50	13.50	8.54 ± 1.38	0.790
HIV and TB	245	24	7.50	11.40	8.89 ± 1.18	-

Legend 1: No significant increase was observed in the mean blood glucose concentration of HIV seropositive subject compared with individual infected with TB (P<0.05). But there was a significant increase in the mean blood glucose concentration of HIV seropositive subjects co infected with TB compared with HIV seropositive subjects (P>0.05). The same pattern was seen in HIV seropositive subjects co infected with TB compared with individual infected with TB (P>0.05).

et al., 2011). Fehmida et al. (2004) had reported that subjects with human immunodeficiency viral infection have a high prevalence of diabetes mellitus due to impaired immunity seen in HIV subjects. Various reports from Africa, Asia and India showed a significant increase of diabetes mellitus in human immunodeficiency virus infection in every 100, 000 population studied (Grens et al., 2008; Gale et al., 2010; Cooke et al., 2014). In this study, the prevalence of DM in HIV seropositive subjects co-infected with mycobbacterium tuberculosis was 107 (12.6%).

The gender distribution of Type-1 and Type-2 DM in HIV seropositive patients, TB positive patients and HIV subject's co-infected with TB shows that, out of the 350 patient that tested positive for HIV, 38 (4.5%) had DM, 11 (1.3%) were of Type-1 origin while 27 (3.2%) were of Type-2 origin. On the other hand 450 patients that tested TB positive 45 (5.3%) had DM, 9 (1.0%) were of Type-1 origin while 36 (4.3%) patients were of Type-2 origin while that of HIV seropositive subjects co-infected with TB 24 (2.8%) had DM, 5 (0.5%) where Type-1 origin while 19 (2.2%) were

of Type-2 origin. There are highly more female 57 (6.7%) with DM than male 50 (5.9%). And this work is in contrast with the work of (Onubogu et al., 2010). The difference in the infection rate in females could be as a result of biological factors such as higher susceptibility to infection due to low immunity seen in women (Onubogu et al., 2010). Analysis of clinical data generated from Table 3 shows that 20 (2.4%) of the HIV seropositve patients with DM are on ART while 18 (2.1%) not on ART. Among the 45 TB cases with DM, 32 (3.8%) are on anti - cough while 13 (1.5%) where not on anti - cough drugs].

HIV seropositive patients co-infected with TB shows that 20 (2.4%) where on anti - cough while 4 (0.5%) not on anti - cough. 15 (1.7%) and 14 (1.7%) are on ART and HAART, respectively while 9 (1.1%) and 10 (1.1%) are not taking any ART and HAART, respectively. The effect of these drugs could be the major reason for the increase in prevalence rate of DM in HIV and those co-infected with TB. More so, a substantial decrease in the mean CD4 count was recorded among the group with HIV co-infected with TB, where a decreased CD4 count was lower than their counterpart with HIV 335.8 ± 1576.3 and 456.3 ± 2739.1 cell/μl, respectively. The sharp decrease recorded among this group in their CD4 count, could also be as a result of the afore mentioned drugs given to this group where majority of HIV seropositive subject. Co-infected with TB are subjected to ART, HAART and at the same time anti - cough. Brown et al. 2005 had directly compared the HIV uninfected individuals and 7% of the HIV infected subjects not taking CART had prevalent diabetes at baseline, compared with 14% of subjects who were on CART. Some protease inhibitors (PIs) and reverse transcriptase nucleoside inhibitors (NRTIs) which are normal baseline drugs for HIV and TB infection confer added risk of Type 2 diabetes mellitus, and these medications may exacerbate the underlying diabetes mellitus in HIV subjects co-infected with TB (Rinin et al., 2012). Despite mild toxicity and adverse effects, human immunodeficiency virus (HIV) protease inhibitors (PIs), used in combination with reverse transcriptase nucleoside inhibitors (NRTIs), have turned AIDS into a chronic inflammatory disease (Rinin et al., 2012).

Finally, the blood glucose concentrations of the three groups were compared. In the first comparison, Data generated showed no significant difference among the patients infected with HIV virus and TB positive patients $P \leq 0.05$. The minimum and maximum blood glucose concentration of HIV positives were 7.30 and 10.6 Mmol/L, respectively while that of TB positive counterpart where 7.50 and 13.50Mmol/L, respectively. Interestingly, a significant difference was recorded in the blood glucose concentration of patients infected with HIV and HIV subjects co-infected with TB $P \geq 0.05$. The same pattern was observed when the blood glucoses concentration of patients with TB positives and HIV seropositive patients co-infected with TB was compared $P \geq 0.05$. The minimum and maximum glucose concentration for HIV seropositive subjects co-infected with TB where 7.50 and 11.40 Mmol/L, respectively. Diabetes mellitus, a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both, has been linked with depressed immunity (Metzger, 2007; Ledergerber et al., 2007). The condition relatively present a long-term microvascular complication affecting the eyes, kidneys, the nerves cells and the lungs (Ledergerber et al., 2007), leading to risk of HIV and mycobacterium tuberculosis infections (Jeon and Murray, 2008; Butt et al., 2009). It has been reported that patient with mycobacterium tuberculosis taking anti - cough drugs duely develop multi-drug resistant to TB (MDR-TB) which might lead to impaired absorption of anti - TB drugs in the gastrointestinal mucosa especially in DM patients, this MDR-TB often result to sub-lethal dose achievement at the tissues levels where the bacteria exist and facilitate the development of drug resistance (Fisher-Hoch et al., 2008; Subhash et al., 2003).

CONCLUSION

The interaction of diffenents drugs methabolic activities on DM patients, HIV and TB counterpart could contribute to long-term macrovascular complications affecting the immune system in these patients. It is recommended that all patients with human immunodeficiency virus and mycobacterium tuberculosis infections should be screened for diabetes mellitus at the time of diagnosis and at the initiation of highly active antiretroviral therapy ART and (HAART), and three to six months thereafter. It is highly recommended to place this patient early in DM special diet so as to maintain their sugar levels at base line, further research efforts in the interactions between diabetes mellitus, human immunodeficiency virus and mycobacterium tuberculosis interplay should also be encouraged.

Conflicts of interest

Authors have none to declare.

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