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GLUCOSE DISTRIBUTION OF HIV PATIENTS CO-INFECTED WITH MYCOBACTERIUM TUBERCULOSIS

Anwara Ogbonnaya*, Humphrey Osadolor Benedo, Edeogu Chucks Oswald, Akinpelu Moronkeji, Patrick Manafa Onochie

University of Benin, Benin City, Nigeria.
Ebonyi State University, Abakaliki, Nigeria.
University of Medical Sciences, Ondo, Nigeria.
Nnamdi Azikiwe University, Awka, Nigeria.

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***Corresponding Author**
Anwara Ogbonnaya

ABSTRACT

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia resulting in defective insulin secretion, insulin action or both. This study was designed to access the serum glucose levels of patients infected with Human Immunodeficiency Virus, patients infected with *Mycobacterium tuberculosis* and HIV patents co-infected with *Mycobacterium tuberculosis.* A total of 400 subjects consisting of 150 HIV seropositive subjects, 150 individuals infected with *M. tuberculosis* and 100 HIV individuals co-infected with *M. tuberculosis*, were enrolled for this study. HIV diagnosis was performed using the National Algorithm utilizing Determine, Uni-Gold and Stat-Pak rapid test kits. The method adopted for *Mycobacterium tuberculosis* identification was the gene-Xpert procedure. Fasting blood glucose was assayed using glucose oxidase method. A significant difference was observed in age and gender of HIV, TB and HIV positive subjects co-infected with TB ($P < 0.001$ and $P < 0.002$ respectively). HIV/TB infected subjects had the highest hyperglycemic index (37.0 %) while group infected with *Mycobacterium tuberculosis* had (28.0%). The HIV infected group had (22.7%). HIV subject co-infected with TB were found to be twice more likely to be hyperglycemic than the HIV counterparts. This study further revealed that adults within the age range of 30-69 had a higher percentage of HIV infection, TB and HIV co-infection with TB. It is therefore recommended that all patients with HIV, TB and HIV/TB co-infection should be screened for Diabetes Mellitus, the use of specific and predictive methods should be encouraged for Glucose examination in TB/HIV co-infected subjects.

KEYWORDS: *Mycobacterium tuberculosis* and HIV.

INTRODUCTION

Diabetes mellitus (Dm), is a chronic and metabolic disorder characterized by hyperglycemia resulting from defective insulin secretion, action or both. It occurs as a result of deficient insulin production by the pancreas or inability of the body to effectively utilize insulin being produced by the pancreas (Johan *et al*., 2017). The connection between Diabetes mellitus and immunodeficiency has been reported (Ogbonnaya *et al*., 2015). Diabetes mellitus presents extensive damages resulting in microvascular complication affecting organs such as the kidneys, eyes, lungs and the nerve cells (Joshua and Mark, 2016; Aastha *et al*., 2016). Adults over 45 years of age are mostly affected, however, obese and sedentary life style often result to increased chance of developing Dm. People of African, Hispanic, and Native American descent or immediate family member afflicted with Dm have an increased chance of developing Dm. Native Americans are mostly affected and women are more often diagnosed with the disease (Carson *et al*., 2015). Diabetes mellitus and *Mycobacterium Tuberculosis* (TB) were strongly linked in study populations from Central America, Asia and Europe (Marcin *et al*., 2014). Forty percent incident of TB cases was reported in India and in China, an estimated rise of 69% in subjects with Diabetes mellitus was a major concern to the joint burden of disease control between Dm and *Mycobacterium tuberculosis* (Anil *et al*., 2017). Also a two to three times risk of *Mycobacterium tuberculosis* infection in diabetes mellitus patients was reported by a cohort study by Remi *et al*., (2017) showed that diabetes mellitus patients have an approximately 3-fold risk of developing active TB than people without diabetes. Solomon *et al*., (2016) also reported the increased prevalence of diabetes mellitus in Human Immunodeficency Virus (HIV) infected individuals as a result of impaired immunity observed in HIV patients. Studies from India, Asia and Africa, have shown a significant increase of diabetes mellitus in HIV infection in every population studied (Shih *et al*., 2018; Alejandro *et al*., 2016). In Indonesia, diabetes mellitus is strongly associated with *M. tuberculosis* with a prevalence of 13.2% (Chunlan *et al*., 2017). TB and DM are interrelated with each other on a number of different demographic levels. such as gender, age, education, locality, family history, marital status and socio-economic status, This study is aimed at understanding the fasting glucose condition in HIV infected subject co-infected with *Mycobacterium tuberculosis*.

MATERIALS AND METHODS

STUDY AREA

This study was carried out at Federal Teaching Hospital (FETHI), Ido Ekiti. Nigeria. It is a Tertiary institution for treatment and training and it services an estimated population of 107,000.

The geographical area boarding the northern part has an estimated area of 6353km and an estimated population of 2,737,186. The institution since 2006 has been a referral hospital for HIV/AIDS diagnosis and treatment and also offers free treatment and management of patients infected with *M. tuberculosis*. The hospital serves as reference Centre for HIV cases in the state and also service neighboring states such as Osun, Kogi, and Kwara states respectively.

STUDY DESIGN

A total of four hundred (400) subjects were recruited and their samples analyzed in this study. These subjects were grouped into three categories; 150 HIV seropositive subjects, 150 individuals infected with *M. tuberculosis* and 100 HIV individuals co-infected with *M. tuberculosis*. all the subjects that participated in this research were on Antiretroviral therapy (ART), Highly active antiretroviral therapy (HAART), and anti-TB Drugs.

SAMPLE COLLECTION

Five milliliters (5mls) of whole blood were collected from each subject and was dispensed into a fluoride-oxalate container for glucose estimation, the plasma obtained after glucose analysis was used in screening for HIV using the Determine, Uni- Gold and Stak-pak kits respectively.

Sputum Sample Collection Procedures

Sputum samples were collected from the individual subjects early in the morning before mouth brushing. Sputum samples were obtained from patients by coughing. Patients were instructed to take deep breaths then cough to expel sputum from the lungs; a process which was repeated till the desired amount of specimen required for the procedure was obtained. Specimen obtained was collected into pre labeled sterile screw cap containers to prevent leakages. Specimens were transported to the laboratory as soon as possible after collection.

Estimation of glucose

Glucose concentrations was determined according to the glucose oxidase method as described by Kumar and Gill, (2018).

Identification of *Mycobacterium tuberculosis* (MTB) Genexpert techniques as described by Somily *et al*., (2016).

Determination of HIV Seropositivity

The method used in this study was the National Algorithm for HIV screening utilization Determine, Uni-Gold and Stak Pak kits (Ogbonnaya *et al*., 2015).

STATISTICAL ANALYSIS

Data collected were subjected to SPSS Version 24.0 (IBM, 2016) statistical analysis using the chi-square and students't-test. Data was significant when $P \leq 0.05$.

RESULTS

Table 1.0: Age and gender distributions of Human immunodeficiency virus-seropositive subjects, *M. Tuberculosis* positives, and HIV Subjects Co-infected with *M. Tuberculosis*.

Age group (in years)	HIV (%) N = 150	TB (%) N = 150	HIV/TB (%) N = 100
10 – 19	11 (7.3)	2 (1.3)	0 (0.0)
20 – 29	13 (8.7)	23 (15.3)	2 (2.0)
30 – 39	33 (22.0)	44 (29.3)	38 (38.0)
40 – 49	56 (37.3)	36 (24.0)	40 (40.0)
50 – 59	29 (19.3)	22 (14.7)	20 (20.0)
60 – 69	8 (5.3)	23 (15.3)	0 (0.0)
	Chi square = 56.747, p value ***<0.001***		
Gender			
Male	59 (39.3)	87 (58.0)	57 (57.0)
Female	91 (60.7)	63 (42.0)	43 (43.0)
	Chi square = 12.539, p = ***0.002***		

Table 1.0. Shows a statistically significant difference between age and gender of HIV, TB and HIV/TB subjects in the three study categories ($P < 0.001$ and $P < 0.002$ respectively). Furthermore, higher percentage of male subjects were infected with TB and HIV/TB (58.0%), (57.0%) than Female subjects which had (42.0% and 43.0%). Also higher percentage of females were infected with HIV (60.7%) than Male (39.3%) subjects. The

preponderance of the subjects infected with HIV, TB, and HIV/TB fell within 30 to 49 years age bracket.

Table 2.0: Blood glucose condition of Human immunodeficiency virus-seropositive Subjects, *M. tuberculosis* positives, and HIV Subjects Co-infected with *M. tuberculosis.*

Glucose condition	**HIV (%) N = 150**	**TB (%) N = 150**	**HIV/TB (%) N = 100**
Hyperglycemia (≥7.0 Mmo/l)	34 (22.7)	42 (28.0)	37 (37.0)
Normal Glucose (3.6 –6.9 Mmo/l)	114 (76.0)	95 (63.3)	60 (60.0)
Hypoglycemia (<3.6 Mmo/l)	2 (1.3)	13 (8.7)	3 (3.0)
	Chi square = 16.830,		*p =* ***0.002***
Mean ± SD	6.18 ± 1.83	7.80 ± 1.83	8.06 ± 2.01
	F = 40.141,		*p <****0.001***

Table 3.0: Diabetic condition counts of Human immunodeficiency virus-seropositive Subjects, *M. Tuberculosis* positives, and HIV Subjects Co-infected with *M. Tuberculosis.*

Variable	**Hyperglycemia**				
	Yes (%)	**No (%)**	**OR (95% CI)**	**X^2**	**p – value**
HIV	34 (22.7)	116 (77.3)	1.00	6.090	**0.048**
TB	42 (28.0)	108 (72.0)	1.33 (0.76 – 2.31)		
TB/HIV	37 (37.0)	63 (63.0)	**2.00 (1.11 – 3.64)**		

Table 4.0: Tukey Post Hoc HSD Test for the Mean Blood Glucose concentrations of Human immunodeficiency virus-seropositive Subjects, *M. tuberculosis* positives, and HIV Subjects Co-infected with *M. tuberculosis*.

(I)	**(J)**	**/(I – J)/**	**P-value**
HIV	TB	1.62	**0.005**
HIV	HIV/TB	0.88	**0.024**
TB	HIV/TB	0.26	0.603

In Table 2.0, the blood glucose condition of Human immunodeficiency virus, *M. tuberculosis*, and HIV/TB groups were compared to ascertain the degree of (hyperglycemia, hypoglycemia, and the normal glucose levels) existing in the three-study category. Higher percentage of Hyperglycemia were observed in HIV/TB category (37.0%). *Mycobacterium tuberculosis* group had (28.0%) while HIV infected group had (22.7%). The difference means blood glucose levels of HIV, TB, and HIV/TB groups were also compared with ANOVA and result recorded indicated a higher statistical significance decrease ($P < 0.002$). HIV/TB subjects had the highest mean blood glucose level of (8.06 ± 2.01) {(Mean ± SD) (mmol/l)}

followed by the TB and HIV subjects (7.80 ± 1.83 and 6.18 ± 1.83 respectively) {(Mean ± SD) (mmol/l)}.

Table 3.0 display the diabetic condition counts of the three study categories studied, result observed showed stronger significant diabetic relationship between HIV, TB and HIV/TB category ($P < 0.048$). TB/HIV co-infected subjects were outright found to be twice more likely to be hyperglycemic than the HIV counterparts [(2.00 (95% CI of 1.11 – 3.64)] as a follow-up to Table 3.0; Table 4.0 displays the multiple comparison tests to ascertain which of the groups was responsible for higher significant relationship noticed in the mean blood glucose concentrations of the three study categories. Results recorded showed that HIV and TB group, and HIV and HIV/TB subgroups contributed higher to the significant differences ($P < 0.005$ and $P < 0.024$ respectively) observed than the TB and HIV/TB group which was not significant ($P > 0.603$).

DISCUSSION

Our study explores the blood glucose condition of HIV; TB and HIV/TB affected subjects and to ascertain the degree of organ damage that exist in the three-study category. Result recorded in this study showed a significant difference in HIV and HIV/TB in adults above sixty years of age. Higher percentage of female subjects were infected with HIV (60.7%) than Male (39.3%) subjects. This finding is in tandem with the earlier studies by Ogunmola *et al*., (2015) and Tadele *et al*., (2018) who recorded significant variations in gender disparity of HIV and HIV/TB infection. The gender disparity in this study is consistent with patterns observed in previous studies (UNAIDS, 2018). This disparity could be attributed to women having older sexual partners who have had greater exposure to the risk of HIV infection or as a result of biological differences between them (Medina-Perucha *et al*., 2018). Our study revealed that higher percentage of male subjects were infected with TB (58.0%) and HIV/TB (57.0%) than female subjects which had (42.0% and 43.0%). Our study is also in consonant with the work of (Rao, 2016) who recorded higher prevalence of TB in male subjects 308 (69%) than 138 (31%) in females. With regard to the gender structure, a predominant increase in TB/HIV patients have been reported in male subjects than female with a positive difference of 88.8%, compare to 69% for females (Kurti *et al*., 2014; Matilda *et al*., 2017). Eighty-eight (88%) of TB and HIV patients were males. Men have a higher prevalence of TB and, in many settings, remain infectious in the community for a longer period of time than women. Men generate greater number of secondary infections than women which can result

from difference in social mixing patterns, in both high and low-middle income countries. Despite spending less time at home, men remain at higher risk of acquiring tuberculosis than women from a household contact (Anthony *et al.*, 2018). Addressing men's burden of disease and disadvantage in TB care is therefore an issue not only for men's health but for broader TB prevention and care. Also Higher percentage of Hyperglycemia were observed in HIV/TB category (37.0%). *Mycobacterium tuberculosis* group were (28.0%) while HIV infected group had (22.7%). Hyperglycemia had been reported in *Mycobacterium tuberculosis* subjects, but the long-term and short-term complication has not been elucidated. Certain characteristics were associated with different blood glucose levels recorded in this study. Although there were higher number of patients with HIV-associated TB, the diagnosis of HIV was a strong risk factor as shown in this research. Both HIV and TB can damage the immune system and this might result in poor glycemic result in patients (Nang *et al*., 2019). Because of that, we interpret this finding with caution because a proportion of hyperglycemic subjects did not have pre-TB glucose measurements and might represent undiagnosed diabetes. Furthermore, we were unable to perform an adjusted analysis that would take into consideration other confounders such as duration of HAART use, HAART scheme, and BMI. In another study, conducted in Tehran, Iran, investigators found no associations between glucose status and treatment outcomes (Tabarsi *et al*., 2014). We hypothesized that differences in the relationship between hyperglycemia and TB treatment outcomes might be due to a number of reasons such as higher probability to detect adverse TB outcomes, larger sample size means and other modifiers of effects such as HIV, malnutrition, drug abuse and age), and the cut-off used to define hyperglycemia in each study.

The diabetic condition counts of the three study categories presented in this work showed stronger significant diabetic increase between HIV, TB and HIV/TB category ($P < 0.048$). TB/HIV co-infected subjects were outright found to be twice more likely to be hyperglycemic than the HIV counterparts [(2.00 (95% CI of 1.11 – 3.64)]. Natacha *et al*., (2018) reported that the odds ratio of contracting HIV among DM patients with TB were nearly 10 times higher (OR 9.7; 95% CI 3.05–31.00). Data available till now proves that DM-TB patients are of older age than those who do not suffer from DM; the reason may be because DM type 2 persists more in old age people (Rahul *et al*., 2016). People with DM have a significant higher risk of developing active TB which is 2-3 times higher than those without diabetes (Kapur *et al*., 2013). DM patients with TB are also reported to have worse treatment outcomes compared with patients without DM, with delays in sputum culture

conversion, an increased risk of failure or death during anti-TB treatment and an increased risk of recurrent disease after successful completion of anti-TB treatment (Wang *et al*., 2016). The Prevalence of active TB in DM patients was much higher than the national estimate in the general population, demonstrating that screening approaches targeting DM patients are potentially more efficient than screening the general population. This is particularly so in DM patients with HIV-infections who are at an even greater risk of TB. As a follow-up to this findings, the multiple comparison tests was used to ascertain which of the group is causing stronger significant diabetic increase noticed in the mean blood glucose concentrations of the three study categories and result showed that HIV and TB group, HIV and HIV/TB group contributed higher to the hyperglycemia noticed in the three study categories ($P < 0.005$ and $P < 0.024$) than the TB and HIV/TB group which did not show any significant change ($P > 0.603$). A study from Nepal, a neighboring country of India, has shown significantly higher proportion of DM in pulmonary TB patients compared to extra-pulmonary TB patients. Magna *et al*., (2016) in a newly diagnosed tuberculosis patients observed increased risk of TB in DM patients regardless of the variation of results or the rate of positive smears at the time of diagnosis of DM. In this study we noted a significant association between diabetes and TB, this findings is in agreement with the majority of the published literature from other settings. The coexistence of a high prevalence of HIV, TB and diabetes has significant implications for optimal control of each condition, highlighting the importance of targeting TB control interventions, such as intensified TB screening for diabetes and diabetes/HIV-patients. In addition, given that the association between ages of TB subjects and diabetes was significantly decreased in all the three studied categories, and that the study was powered to detect the proportion of their glucose condition, this study was not able to include HIV and TB uninfected individuals. The reason for the optimum raise in the mean blood glucose of *Mycobacterium tuberculosis* subjects and in HIV subjects co-infected with *Mycobacterium tuberculosis* could be as a result of drugs and disease. the metabolism driving drugs interactions of subjects with TB up to six months often result to multidrug resistance to *Mycobacterium tuberculosis* (MDR-TB) and this has created major threats to global public health (Raviglione *et al.*, 2016), the advent of MDR-TB has been linked to the failure of treatment over a long period of time. failure to complete a full dose of treatment leading to the development of drug resistance and relapse, which requires up to 2 years to treat (Catherine *et al.*, 2017). The major benefits of HAART include suppression of viral load, improvement in $CD4^+$ count, decrease in opportunistic infections and length of hospital stay, and reduction in mortality (Brooks, 2014; Yin *et al*., 2014). HAART however, has also led to

an increase in metabolic dysfunction, including insulin resistance, diabetes dyslipidemia and lipodystrophy (Cunha *et al*., 2015). A recent analysis has found that diabetes is four-fold more common is HIV-infected men exposed to highly active anti retroviral therapy (HAART) than in HIV seronegative men (Avari and Devendra, 2017). HAART is based on the use of a class of drugs known as protease inhibitors (PIs), which have been used extensively as antiretroviral agents. The various PIs used include atazanavir, darunavir, saquinavir and ritonavir.

PIs have been shown to increase insulin resistance and reduce insulin secretion, by interfering with GLUT-4 mediated glucose transport (Xu *et al*., 2018). Risk factors for development of diabetes with PI therapy include positive family history of diabetes, weight gain, lipodystrophy, old age and hepatitis C infection (Syed *et al*., 2018). PIs interfere with cellular retinoic acid-binding protein type 1 (CRABP 1) that interacts with peroxisomal proliferator-activated receptor (PPAR) γ. Inhibition of PPAR-γ promotes adipocyte inflammation, release of free fatty acids and insulin resistance (Francisco, *et al*., 2013).

Resistance to the first line of TB drugs such as Isoniazid (INH) is most often as a result of mutations in *KatG*, which encode a catalase-peroxidase in the activator of INH (Jessica *et al*., 2015), but other genes have also been associated with INH resistance in TB (Vilcheze *et al*., 2014). In particular, gene involved in the biosynthesis of Mycothiol, the main reducing thiol in Mycobacteria and a storage molecule for cysteine have also been implicated to be resistance to INH and the second line drugs ethionamide (ETH) in mycobacteria (Catherine *et al*., 2017). In a recent mechanism by which mutations in the *MshA*-encoded glycosyltransferase, the first step in mycothiol biosynthesis, leading to a defect in mycothiol production and INH or ETH resistance had been demonstrated in *M. tuberculosis* and there was mutant's accumulation of cysteine leading to drug resistance (Tan *et al*., 2017). As a follow-up on this study the odds ratios of the diabetic condition counts of the three categories was analyzed using HIV as an indicated, 1.00 was taken as a reference odd point. A 1.33 odds ratio was recorded for TB subjects with a 95% confidence interval ranging from (0.76 - 2.31) and an odds ratio of 2.00 with a 95% confidence interval ranging from (1.11 - 3.64) recorded for HIV/TB subject. This result depicts a higher significant increase in diabetic condition of TB and HIV/TB categories ($P < 0.048$). TB/HIV co-infected subjects were outright found to be twice more likely to be hyperglycemic than their HIV counterparts [(2.00 (95% CI of 1.11 – 3.64)]. The International Diabetes Federation (IDF) in 2015 revealed that

8.8% of the world's population had diabetes mellitus and with 69.2 million people with DM, India ranked second in the world (Ogurtsova *et al*., 2017). The multiple comparison tests of the mean blood glucose concentrations of HIV, TB and HIV/TB subjects, recorded in this study were significant decreased ($P < 0.005$ and $P < 0.024$ respectively). But the significant rise of Hyperglycemia recorded in TB and HIV/TB infected subject could be as a result of the incidence of multi-drug resistant TB (MDR TB) which had been previously reported to be high among diabetes mellitus patients (Balewgizie *et al*., 2018). In a large des riptive survey of *Mycobacterium tuberculosis*-infected patients in Southern Ethiopia, less than fifth of them was HIV infected related to other reports from the region (UNAIDS, 2018).

CONCLUSION

This study establishes high prevalence coexistence of HIV, TB and HIV/TB in diabetes patients, It is imperative that subjects in this status should be targeted for optimal control of each condition, highlighting the importance of targeting TB control interventions, such as intensified TB screening for diabetes and diabetes/HIV-patients of various age groups of different disease state. Since HIV patients within the age range of 30-69 had a higher percentage of TB and HIV co-infection with TB, developing of programmers targeting this age groups should be paramount. Furthermore, application of methods with high productivity, sensitivity and specificity will further help in prompt medical treatment and Laboratory monitoring of such individuals.

RECOMMENDATION

Suggestion based on the findings in this study tilts toward screening of HIV and TB infected patients for diabetes mellitus at the time of diagnosis and at the initiation of introduction of anti-tuberculosis drugs. Furthermore, the use of Gene-Xpert machine should be encouraged in all centre's because of its advantage over conventional microscopic methods. In addition, research efforts should be made toward discovery of glycemic agents that targets the multi-complex glucose transport mechanism in HIV and TB.

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