Comparative Diagnosis of Latent Tuberculosis Infection amongst HIV and Diabetic Patients Attending Tertiary Hospitals in Anambra State

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Authors’ contributions

This work was carried out in collaboration among all authors. Author UKC designed the study. Author EPC performed the statistical analysis and wrote the protocol. Authors ONMA, UCU and UCN wrote the first draft of the manuscript. Authors UCN and IMO managed the analyses of the study. All authors read and approved the final manuscript.

ABSTRACT

Aims: The aim of this research work was to survey the epidemiology and diagnosis of Latent Tuberculosis Infection (LTBI) amongst HIV and Diabetic patients in Anambra state of Nigeria using Tuberculin Skin Test (TST) and Interferon Gamma Release Assay (IGRA).

Study Design: This was a multicenter study covering three tertiary hospitals in Anambra State involving 480 adult HIV positive and Diabetic patients with 240 normal participants as control.

Place and Duration of Study: This study conducted from February 2016 to April 2018 involved the general hospitals chosen from the three senatorial zones in the state.

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Methodology: IGRA using T spot TB as well as TST were done for all the participants. HIV screening, CD4 count and Fasting Blood Sugar were also done accordingly.

Results: Overall prevalence of Latent Tuberculosis Infection (LTBI) was 24.4% and 22.5% for IGRA and TST respectively, of the two health groups, HIV group had 35% and 20% for IGRA and TST respectively in their overall prevalence, this was significant (P<.05) compared with the controls which had 2.5% and 4% respectively to IGRA and TST. The diabetics group on the other hand had 13.8% and 25% for IGRA and TST respectively, this also was significant (P<.05) in comparison to its control group with 1.6% each for both IGRA and TST. Out of the 480 patients, 74(15.4%) of them had concordant result, this was 63.2% of the total positive value in the two groups worked on while 43(8.95%) and 34(7%) patients constituted the discordant figures for IGRA and TST respectively. CD4 count was inversely proportional to the presence of LTBI amongst HIV patients using the TST method. Age and duration of illness were significantly associated with LTBI in diabetics (P<.05). Participation rates were higher among males, though females recorded a non significant higher prevalence on the two test methods.

Conclusion: There was a high prevalence of latent tuberculosis infection amongst HIV and Diabetic patients in Anambra State. IGRA and TST diagnostic results were not concordant with each other but IGRA appeared to be more specific than TST in diagnosing LTBI.

Keywords: Diabetes; HIV; latent tuberculosis; Anambra State.

ABBREVIATIONS

LTBI : Latent Tuberculosis Infection,
IGRAS : Interferon Gamma Release Assays,
TST : Tuberculin Skin Test,
NTBLCP: National Tuberculosis and Leprosy Control Program,
WHO : World Health Organization,
TB : Tuberculosis,
HIV : Human Immune deficiency Virus,
BCG : Bacillus Chalmette Guerin,
PPD : Purified Protein Derivative,
IFN.Y : Interferon Gamma,
ESAT-6 : Early Secreted Antigenic Target 6,
CFP-10 : Culture Filtrate Protein-10,
ELISA : Enzyme Linked Immunosorbent Assays,
PBMC : Peripheral Blood Mononuclear Cells,
CDC : Center for Disease Control and Prevention.

1. INTRODUCTION

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB [1]. A primary infection with Mycobacterium tuberculosis leads to clinical disease in only 10% of individuals. In the remaining cases, the ensuing immune response arrests further growth of M. tuberculosis. However, the pathogen is completely eradicated in only 10% people, while the immune response in the remaining 90% individuals only succeeds in containment of infection as some bacilli escape killing by blunting the microbicidal mechanisms of immune cells (such as phagosome – lysosome fusion, antigen presentation by MHC class I, class II, and CD1 molecules, production of nitric oxide, and other reactive nitrogen intermediates) and remain in non-replicating (dormant or latent) state in old lesions [2].

According to the World Health Organization (WHO), approximately 2–3 billion people in the world are latently infected with Mycobacterium tuberculosis and 5–15% of these people will suffer from reactivation of TB during their lifetime [3], with the majority developing TB disease within the first five years after initial infection [4]. Therefore, the treatment of LTBI directly influences the future global prevention of TB infection. However, the risk of developing TB disease following infection depends on several factors, the most important one being the immunological status of the host.

HIV co-infection is the most potent immunosuppressive risk factor for developing active TB disease [5]. The emergence of HIV has an unprecedented impact on the epidemiology of infectious disease in general and particularly on TB. In fact, HIV infection and TB are the pandemics which cause a higher number of deaths in the world annually, estimated at 1.8 and 1.2 – 1.5 million deaths respectively. Of the 8.8 million incident TB cases in 2010, 1.1 million (13%) were among people living with HIV [6]. Thus the emergence of HIV has not only increased TB incidence and TB associated mortality but it also has made the diagnosis of TB...
more difficult [7]. While the risk of developing TB disease among those infected only with *M. tuberculosis* is about 10% during their lifetime, among HIV positive patients infected with *Mycobacterium tuberculosis* it is in the order of 10% annually [8,9]. Thus the spread of the HIV infection has contributed to the extension of TB, which is the main cause of mortality in HIV patients. TB is also the most frequent AIDS defining illness globally, HIV co-infection exacerbates the severity of TB disease and also accelerates HIV replication in affected organs including lungs and pleura [10]. Cell mediated immunity is a crucial component in the host defense against *M. tuberculosis* that is weakened by HIV infection resulting in increased risks in reactivation of TB.

One of another factors facilitating or accelerating the phenomenon of conversion of latent to active form as well as reactivation of old TB disease is the increasing number of people with diabetes. Biological evidence supports the theory that diabetes directly impairs the innate and adaptive immune response, thereby accelerating the proliferation of TB.

In spite of frequent studies about the link between diabetes and active TB, the effect of diabetes on the frequency of latent tuberculosis infection has been less investigated. The few existing reports about a higher prevalence of latent tuberculosis infection among diabetes have been co-founded by an absence of control groups. Currently, a golden standard for the diagnosis of the LTBI is lacking. Because the amount of *Mycobacterium tuberculosis* is small in LTBI patients, diagnosis of LTBI mainly depends on the immune reaction of the host rather than the bacteria itself. There are two currently available screening tests for LTBI: the tuberculin skin test (TST) and interferon gamma release assays (IGRAs) which include the QuantiFERON-TB Gold and the T-SPOT TB test. to survey the epidemiology and diagnosis of Latent Tuberculosis Infection (LTBI) amongst HIV and Diabetic patients in Anambra state of Nigeria using Tuberculin Skin Test (TST) and interferon Gamma Release Assay (IGRA), prevalences of LTBI among different categories of HIV patients, diabetics of different durations as well some demographic indices were also ascertained in this work.

2. METHODOLOGY

2.1 Study Area

Anambra State is situated within longitude 6° 30’ E to longitude 7° 10’ and latitude 6° 15’ to 7° 07’. It has a land mass of 4,416 sq.km spread across 21 local government areas. The State is bordered by Delta State to the west, Imo State to the south, Enugu State to the east and Kogi State to the north. The State has a total estimated population of 4million people (2004 estimate). This was a multicenter study covering three general hospitals in Anamba State. The hospitals were chosen from the three senatorial zones in the state. They were Nnamdi Azikiwe Teaching Hospital, Nnewi, Onitsha General Hospital and Chukwuemeka Odumegwu Ojukwu Teaching Hospital, Awka which represented Anambra South, Anambra North and Anamba Central Senatorial Zones respectively. The hospitals have specialist health professionals and serve as referral centers for other hospitals. They have modern state of the art health facilities and are integrated with the National Tuberculosis and Leprosy Control Program. They are all provide DOTs services.

2.2 Study Design

This study conducted from February 2016 to April 2018 involved HIV positive and Diabetic patients. A total of 480 participants (240 from each risk group) were enrolled as well as 240 apparently healthy participants from the general population within the environment who served as controls. Out of the study population, males were 270 while females were 210. For the controls; 115 were males, while 125 were females.

2.3 Sample Size

Specimen collection: 720 participants were totally enrolled. 240 patients from diabetic clinic, 240 from HIV clinic and 240 from the general population within the hospital environment that have neither diabetes nor HIV (controls). All
2.4 Specimen Analyses

**2.4.1 HIV Screening**: Each patient was screened for HIV 1/II according to the national algorithm [11].

**2.4.2 CD4 Count Estimation (CyFlow SL3, Partec, Germany)**: CD4 count was done for each HIV patient to assess the correlation between CD4 count and Latent TB. CD4 count was done using a cyflow from Partec. Twenty μL of whole blood and 20 μL of CD4-PE (Partec, Germany) monoclonal antibody were added to the sample tube (Partec, Germany). After incubation, 800 μL of no lyse buffer (Partec, Germany) was added into the sample tube. The stained sample was then acquired on the CyFlow SL_3. The acquired data was analyzed using the inbuilt CyView software by gating on the histogram of CD4+ T cells. The histogram and absolute counts are displayed and printed automatically. The results were printed and stored after review.

**2.4.3 Diabetes Screening**: Point-of-Care Glucose Meter (Accu Chek Active) was used to screen the participants for diabetes. It was used according to manufacturers instruction [12].

**2.4.4 Interferon Gamma Release Assay (T-Spot TB)**: The T-Spot TB is the interferon gamma release assay used in this research work [13]:

**Step 1: Cell Isolation**: Whole blood sample was collected into a lithium heparin tube and mixed thoroughly by inverting the tube 5 – to times. The tubes were centrifuged at 1800 relative centrifugal force (RCF) for 30 minutes at room temperature to isolate polymorph nuclear blood cells (PMBC).

**Step 2: Washing and counting of cells**: Cells were washed using a standard culture medium (AIM-V). The white cloudy band of PMBC was collected using a pipette and transferred to a 15 ml conical centrifuge tube. The volume was made up to 10 ml with cell culture medium and centrifuged at 600 RCF for 7 minutes. The supernatant was poured off and the pellets re-suspended in the medium. Centrifugation was repeated at 350 RCF for another 7 minutes after which the pellets were re-suspended in 0.7 ml cell culture medium. An appropriate aliquot was placed unto a haemocytometer and the cells in the grid counted. After counting, the cells were diluted to 250,000 cells/100μL.

**Step 3: Adding of antigens and controls**: The T-Spot-TB test requires 4 wells to be used for each patient’s sample. A nil control and a positive control which were run with each individual sample. The samples were arranged vertically on the plate.

- Nil control (AIM-V)
- Panel A (ESAT-6)
- Panel B (CFP-10)
- Positive control (PHA)

50 μl of AIM-V cell culture medium was added to each nil control well. 50 μl of positive control solution, 50 μl of ESAT-6 and 50 μl of CFP-10 were also added to the required wells. To each of the 4 wells used for a patient’s sample, 100 μl of the patient’s final cell suspension (containing 250, 000 cells) was added and the plate incubated in a humidified incubator at 37°C with 5% CO₂ for 18 hours.

**Step 4: Adding of secondary antibody conjugate**: The plates were removed from the incubator and the cell culture medium discarded by flicking the content into an appropriate container. 200 μl phosphate buffered saline (PBS) solution added to each well. The PBS was later discarded and the washing repeated 3 times. 50 μl working strength conjugate reagent solution added to each well and incubated at 2-8°C for 1 hour.

**Step 5: Adding of substrate solution**: The conjugate was discarded and the wells washed four times with PBS solution. 50 μl substrate solution was added to each well and incubated at room temperature for 7 minutes. The plates were washed with distilled water to stop the reaction. The plates were allowed to dry by standing then in a well ventilated area.

**Step 6: Reading of wells**: The number of distinct, dark blue spots on the membrane of each well were counted and recorded.

**Result Interpretation and Assay Criteria**: The test is positive if (panel A-Nil) and/ or (panel B-Nil) ≥ 8 spots. The test is negative if both (panel A-Nil) and (panel B-Nil) ≤ 4 spots.
Tuberculin Skin Test (TST): A tuberculin skin test was administered by the Mantoux method [14].

0.1 ml of Purified Protein Derivative (PPD) was injected intra-cutaneously in the volar area of the forearm. A waterproof ink mark was drawn around the injection site so as to avoid difficulty especially when the level of induration was small. The reaction was read after 48-72 hours. The size of the reaction was determined by measurement of the induration (palpable, raised, hardened area or swelling).

The area of induration was measured transversely across the forearm (left to right, not up and down) with a caliper and recorded to the nearest millimeter. A measurement equal to or more than 10 mm was considered positive for non HIV participants while measurement of 5mm or above was regarded as positive for HIV – positive participants.

2.5 Statistical Analysis

Epi Info version 6.1. was used to cross check the filing of the questionnaire, Data analysis was done with R Programming and SPSS version 22. Pearson chi – square was used to check for independence among study variables. Correlation between TST and IGRA was assessed with Spearman’s correlation test. Statistical significance was accepted at P<0.05.

3. RESULTS

Table 1 shows that the overall prevalence of Latent Tuberculosis Infection (LTBI) were 24.4% and 22.5% for IGRA and TST respectively. Among the hospitals, the highest number of positive cases was seen in Onitsha General Hospital with 31% prevalence recoded in the IGRA method, while on the contrary the TST method had the least prevalence of 19% in the same hospital. On the other hand , Chukwuemeka Odumegwu Ojukwu Teaching Hospital had the highest prevalence in the TST method with 25.4%.

The results of the two health group is shown in Table 2 which depicts that the HIV group had 35% and 20% for IGRA and TST respectively in their overall prevalence, this was significant (P<0.05) when compared with the controls which had 2.5% and 4% respectively to IGRA and TST. The diabetic group on the other hand had 13.8% and 25% for IGRA and TST respectively, this also was statistically significant (P<0.05) in comparison to its control group with 1.6% each for both IGRA and TST.

Table 3 shows the concordant/discordant variables between the two test methods. Concordance here is defined as when a test subject is simultaneously positive to both IGRA and TST, while discordant is when a test subject is positive to only one of the test methods. By this definition 44(18.3%) HIV patients were concordant; this value was 52% of the highest positive number in the HIV group. Forty (16.7%) and 4(1.7%) were discordant in this group to IGRA and TST respectively. in the diabetic group, 30(12.5%) were concordant, this was 50% of the highest positive number also 3 and 30 were discordant for IGRA and TST respectively in the group. From this Table it can also be garnered that out of the 480 patients, 43(8.95%) and 34(7) patients constituting the discordant Fig in IGRA and TST respectively.

The prevalence of LTBI on the HIV group was categorized on CD4 counts of the patients, the aim being to know whether LTBI was decreasing as the CD4 count was increasing. This can be deduced from Fig. 1 which shows that the prevalence of LTBI among the HIV positive participants was 35% for IGRA and 20% for TST. TST patients with low CD4 count of less than 200 cells /mm$^3$ had the least antibody response of 9% which increased to 21.2% in patients with CD4 count between 200-400 cells /mm$^3$. Patients with CD4 count above 400 recorded 42.4%. This was not the case for IGRA as there was minimal effect of CD4 count on the prevalence recorded.

Fig. 2 shows the prevalence among diabetics stratified according to the year of diagnosis. The overall prevalence was 13.8% and 25% for IGRA and TST respectively. There was relative increase in prevalence according to year of diagnosis as patients that were diagnosed more than 7 years ago had the highest prevalence rate compared to other groups. The difference between the different diabetic cohorts were statistically significant (P<0.05) to each other for both the IGRA and TST methods.

Participation rates were higher among males. Out of 480 participants, males were 270 while females were 210, though females had higher positive percentage values with 26% and 24% for
both IGRA and TST respectively compared to 23% and 21% from their male counterpart. This difference was not significant ($P > .05$). This is shown in Fig. 3.

### Table 1. Distribution of latent TB in the various hospitals

<table>
<thead>
<tr>
<th>Hospitals</th>
<th>No. studied</th>
<th>Positive IGRA(%)</th>
<th>Positive TST(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOTTH</td>
<td>240</td>
<td>59(24.6)</td>
<td>61(25.4)</td>
</tr>
<tr>
<td>NAUTH</td>
<td>172</td>
<td>37(21.5)</td>
<td>34(19.8)</td>
</tr>
<tr>
<td>Onitsha Gen. Hosp.</td>
<td>68</td>
<td>21(31)</td>
<td>13(19)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>480</strong></td>
<td><strong>117(24.4)</strong></td>
<td><strong>108(22.5)</strong></td>
</tr>
</tbody>
</table>

### Table 2. Latent TB amongst the risk groups

<table>
<thead>
<tr>
<th>Risk groups</th>
<th>No. studied</th>
<th>Positive IGRA(%)</th>
<th>Positive TST(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV patients</td>
<td>240</td>
<td>84(35)</td>
<td>48(20)</td>
</tr>
<tr>
<td>HIV Controls</td>
<td>120</td>
<td>3(2.5)</td>
<td>5(4)</td>
</tr>
<tr>
<td>Diabetics</td>
<td>240</td>
<td>33(13.8)</td>
<td>60(25)</td>
</tr>
<tr>
<td>Diabetic Controls</td>
<td>120</td>
<td>2(1.6)</td>
<td>2(1.6)</td>
</tr>
</tbody>
</table>
Fig. 3. LTBI on the Sexes

Table 3. Discordant variables amongst the risk groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Concordant</th>
<th>Discordant</th>
<th>Total Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IGRA/TST(%)</td>
<td>IGRA alone(%)</td>
<td>TST alone(%)</td>
</tr>
<tr>
<td>HIV</td>
<td>44(18.3)</td>
<td>40(16.7)</td>
<td>4(1.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30(12.5)</td>
<td>3(1.25)</td>
<td>30(12.5)</td>
</tr>
<tr>
<td>Total</td>
<td>74(15.4)</td>
<td>43(8.95)</td>
<td>34(7)</td>
</tr>
</tbody>
</table>

4. DISCUSSION

The two test methods used in diagnosing Latent Tuberculosis Infection were significantly associated with LTBI diagnosis compared with the controls. Conversely this inferred that LTBI infection was high in the two groups worked on with HIV group having higher prevalence in IGRA method compared to TST method, on the contrary the diabetics had a higher TST prevalence than IGRA patients.

The prevalence of Latent Tuberculosis Infection (LTBI) found in the study was high and was consistent with other African settings that found the prevalence of LTBI to be ranging from 31% in Ethiopia and to 40% in Zambia [15]. The prevalence rates of 24.4% and 22.5% recorded in the study was lower than the 76% prevalence reported by Adjor et al. [16] in the Sylvanus Olympia Teaching Hospital of Iome using TST but higher than the prevalence of 4.6% recorded by Brock et al. [17] in Denmark using IGRA. There was a significant difference between the prevalence rates of both tests and the control ($P<0.05$). This high prevalence is not surprising as Nigeria is among the high TB burden nations.

Our findings suggest that there is a willy-nilly reactions to the two methods used for LTBI diagnosis for both the HIV and diabetics, in HIV positive individuals, we found that IGRA prevalence was significantly greater ($P<0.05$) than TST in the diagnosis of LTBI. Previous studies had shown that IGRA has higher specificity than TST in low TB incidence settings but did not specifically assess the contribution of IGRA to the diagnosis of LTBI in patients with HIV infection. Therefore, the study expands upon the evaluation of IGRA and offer relevant information on its potential usefulness. In this study, only 9% of patients with low CD4 count (< 200 cells /mm$^3$) had positive TST result, while 35% IGRA patients were positive for the same cohort, almost the same proportion was obtained in CD4 200 – 400 cells /mm$^3$ group but a different picture in CD4 above 400 cells /mm$^3$ group though TST was higher than IGRA ,there was a non significant difference between the methods ($P>0.05$). The above could be as a result of cutaneous anergy on the interpretation of TST result and highlights the difficulties of LTBI diagnosis in immune – suppressed patients. Similar result was reported by Saunders et al. [18] whose studies also found that among HIV
infected patients with negative tuberculin tests, the incidence of active tuberculosis was higher in those who were anergic compared to those who were TST negative [19,20,21]. The above explanation infers that TST should be performed only in HIV patients with CD4+ > 400 cells, while IGRA should be performed for those who have difficulties returning for a second visit, those vaccinated with BCG or those with low CDA count <200).

In the diabetics, the results from the TST was significantly higher than that of IGRA (P<.05). The difference between these two just like their HIV counterparts could be as a result of the pathological test principle with each favoring the detection of LTBI based on the pathology of the ailment. Another reason is that decreased production of interferon gamma and other cytokines with reduced chemotaxis in neutrophils of diabetic patient were thought to play a role in increasing the propensity of diabetic patients to developing active TB [22,23]. The above factors were apparent from this work because there was significant increase in the prevalence of LTBI with increase in the duration of diabetes. Apart from a reported prevalence of 28.2% among people with latent tuberculosis infection in their study [24], there is paucity of data to compare this research work with, but there are several study reports from different parts of the world showing higher prevalence of diabetes among TB patients than the general population. Jabbar et al. [25] in Pakistan reported 10 times higher prevalence of diabetes in Tb patients compared to their general population. A case control study conducted among newly diagnosed pulmonary TB patients attending a hospital in Bangalore for 2 years with age and sex matched subjects, showed diabetes as one of the risk factors for the incidence of pulmonary TB and reported an odd ratio of 2.44 [26]. Jeon and Murray [27] have done a systematic review of 13 studies related to TB and diabetes. The authors reported an odd ratio ranging from 1.16 to 7.83 from case control studies and relative risk of 3.11 from cohort studies thereby indicating that diabetic subjects are three times at higher risk of acquiring TB.

Noteworthy was a discordance in the overall results between the two diagnostic methods with IGRA having the better of the upper hand in the diagnosis of LTBI. This might be due to the differences between the principles of the detection methods, because as a blood assay, the IGRA which is more specific requires a single patient visit, and being an in-vitro test, does not boost anamnestic immune responses and the interpretation is less subjective than the TST, and also less affected by prior BCG vaccination and reactivity to non-tuberculous mycobacteria than the TST. Also the instance of false positive might be high in TST group as a result of BCG vaccination at birth of all the participants. The pathology of the two diseases and unforeseen technical glitches were factors that could also lead to discrepancy in the results obtained. These discordant results indicated that dual sequential testing with TST and IGRA, may be the optimal approach for LTBI screening in HIV and diabetic patients. This also implies that neither test can be used in place of the other.

Thus, these methodologies should be used to complement each other, the method should be selected depending on patient’s characteristics. Females had a higher prevalence rate in the two methods used but the difference was not significant (P>0.05).

5. CONCLUSION AND RECOMMENDATIONS

The results suggest that TST and IGRA assay, both being immunological markers of Mycobacterium tuberculosis exposure, measuring cellular immune response to Tuberculosis antigen have dissimilar performances with IGRA favoring HIV diagnosis and TST favoring diabetes. However, currently as these are only two diagnostic tests available for diagnosis of LTBI, use of either test in high burden countries can be recommended only after acknowledging their cost, logistics, population to be tested, and individual preferences in resource limited and high TB burden countries. The compulsory prophylactic treatment of latent tuberculosis in confirmed HIV patients as it is recommended by WHO and implemented by National Tuberculosis and Leprosy Control Program (NTBLCP) seems to be a step in the right direction towards containing latent tuberculosis from transforming into full blown contagious form of tuberculosis. In line with the same intention, targeted screening programs should be targeted towards people living with diabetes > 10 years old.

What is already known on this topic

- That TST and IGRA assay are both immunological markers of Mycobacterium tuberculosis exposure
- That participants that have had BCG vaccine often give a conflicting result
What this study adds

- There is still no gold standard method of LTBI diagnosis in both the diabetic and HIV patients.
- Choice of test method depends on the group or individual to be tested.
- Both IGRA and TST can be used on the same patient to maximize their diagnostic values.

CONSENT AND ETHICAL APPROVAL

Samples were collected from only participants who voluntarily gave informed consent and were able to submit themselves to blood sample collection for Interferon Gamma Release Assay (IGRA) and Tuberculin Skin Test (TST). Other considerations were that Participants must be 18 years and above, those who had evidence of active TB, as well as those who had received chemoprophylaxis or TST within the last six months were excluded. Participants from the above risk groups that have a compounding risk factor(s) were also excluded. Also Participants from the general population (control) must not have either HIV, Diabetes or evidence of active TB. This research was approved by the university ethical committee of Chukwuemeka Odumegwu Ojukwu University, Uli, Anambra state. Also the various hospitals ethical committees gave their written approvals.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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