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Original Research Article

Mycobacterium tuberculosis infection and diabetes mellitus-*mycobacterium tuberculosis* dual burden in subjects attending infectious diseases hospital Calabar, Nigeria

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ABSTRACT

Background: The rising global DM epidemic is driving the problem of TB control. This research determined glycemic control in TB only infected and DM-TB comorbidity and the consequence of the double burden on treatment outcome.
Methods: fifty M. TB infected subjects and fifty control subjects were enrolled into the study, all the participants gave consents. FPG and HbA1c were determined by Colorimetry. Data were analyzed using SPSS version 20.0 statistical package, differences between groups and variation among groups were determined by Student's t-test and ANOVA respectively while the association between variables by Pearson's correlation. Differences were considered statistically significant at $p<0.05$.
Results: The mean FPG and HbA1c levels of TB subjects were significantly ($P<0.05$) higher than those of the control. The mean BMI of the TB infected subjects was significantly lower ($p=0.001$) than that of the controls. The mean age, FPG and HbA1c of TB subjects at the beginning phase of treatment were significantly lower ($p<0.05$) than those of subjects at the continuation phase of treatment. The mean age, FPG and HbA1c of subjects with DM-M.TB coexistence were significantly ($p<0.05$) higher than those of the M.TB only infected subjects. BMI of the DM-M.TB comorbidity subjects was lower than that of the M.TB only infected subjects ($p=0.109$). A significant positive correlation was obtained between HbA1C and FPG in M.tb infected subjects. ($r=0.910$, $p=0.001$). A negative correlation obtained between HbA1C and BMI in M.tb infected subjects. ($r=0.267$, $p=0.061$).
Conclusion: Infection with *mycobacterium tuberculosis* poses a risk to DM and vice versa, which may adversely affect treatment outcome and control of both diseases. Firm efforts to control DM may likely have a significant valuable effect on TB treatment outcome.

Keywords: Diabetes, Diabetes mellitus-tuberculosis dual burden, Tuberculosis

INTRODUCTION

Mycobacterium tuberculosis (M. tb), the agent that causes tuberculosis (tb), is one of the most successful human pathogens. Despite the creditable progress recorded in the control of tuberculosis (TB), it continues to be a huge global health threat.[1,2] Diabetes mellitus (DM) is a significant risk factor for active tuberculosis (TB), which equally undesirably affect TB treatment outcome. The emerging global DM epidemic is driving the problem of TB. In achieving the long term goal of curing TB; the problem of DM needs to be addressed as well, as numerous studies have pointed towards the unsuccessful TB treatment outcome in DM-TB patients

compared to TB only infected subjects.[3-5] A major policy for ending TB should therefore target this twin burden.

Globally in 2016, there were an estimated 10.4 million incident cases of TB, equivalent to 140 cases per 100, 000 population, 10% of which were people living with HIV, claiming roughly 1. 7million lives in 2016 and 1.6 million lives in 2017.[6-8] In the past 200 years, TB claimed the lives of more than one billion people; more deaths than from malaria, influenza, smallpox, HIV/AIDS, cholera and plague put together. Of these incident cases of TB in 2016, malnutrition, HIV, diabetes and smoking related TB was acknowledged to be 1.9 million, 1.0 million, 0.8 million and 0.8 million correspondingly.[8,9] The relative significance of the diverse risk factors for TB is continually being modified by the global epidemiological and demographic shifts lending a major challenge to TB control programmes.[10]

The global diabetes mellitus (DM) epidemic has been recognized as one of the major determinants of TB epidemics posing a significant bottleneck to the TB control programme.[11-13] Meaning that; the rising prevalence of DM constitutes a major setback to TB control and vice versa.[14,15] This may partly be due to the risk of uncontrolled hyperglycemia for diabetes and TB in these immune compromised subjects.[5,16,17] The International Diabetes Federation (IDF) estimated that, globally in 2017, there were 451 million (age 18-99 years) people with diabetes and 5 million deaths due to diabetes worldwide.[18] These figures were projected to increase to 693 million by 2045.[19]

According to the WHO, about 15% of TB cases globally can be endorsed to DM.[20,21] with substantial variation between 10-20% depending on the resident epidemiology of TB.[22] TB exploits condition such as presence of long–standing poorly controlled diabetes. Whether diabetes mellitus predisposes one to infection with M.tb or infection with M.tb is a risk to development of abnormal glucose regulation and diabetes is not fully clear, however, the coexistence of these diseases may result in poor treatment outcome and control of the diseases.

A systematic review that quantified the increased risk of developing TB among people with type 2 diabetes found that DM increases the likelihood of developing TB by 2- to 3-fold.[23] Diabetes mellitus (DM) poses a significant risk to the development of active tuberculosis (TB) and complicates its treatment. Several studies have shown that patients with TB have higher rates of DM than the general population.[24,25] This has been attributed to the possible interference of TB infection with glycemic control.[26,27]

Diabetes and tuberculosis have had a long historical association, the strength of the link between the two diseases have been demonstrated by various studies. The effect of DM on TB was the key concern of investigators in the early 20 century, but with the emergence of proper treatment for both diseases in the second half of the century this was rather ignored.[28] With the increasing prevalence of TB, particularly Multi Drug Resistant TB (MDR-TB) and DM cases in the world, the relationship is evolving again as an important public health concern.

The difficulty in complete eradication of M.tb may be partly due to DM setting the stage for easy transmission and establishment of new infection in uninfected subjects, interference with treatment and development of drug resistant strains, reactivation of latent TB, relapses after complete treatment and worsening of the characteristic features of TB burden. Effective M.tb control is threatened by other multiple dynamic factors such as HIV epidemic, emerging multidrug-resistant tuberculosis and poorly controlled diabetes.

Diabetes and Tuberculosis treatment and control may mask each other at different levels. The diabetes mellitus-*mycobacterium tuberculosis* (DM–M.TB) double burden may not only confer an increased risk to the development of new and recurrent TB disease but could also increase the risk of poor TB treatment outcome and rate of recurrent disease after successful completion of treatment.[29] TB affects DM in many aspects. Although the definite pathophysiological mechanism of the effect of DM as a predisposing risk factor for TB is not clearly understood, it has been suggested that depressed cellular immunity, dysfunction of alveolar macrophages, low levels of interferon gamma, pulmonary microangiopathy, and micronutrient deficiency may be contributing factors.[30]

About 95% of patients with tuberculosis (TB) and 70% of patients with diabetes mellitus (DM) live in the low and middle income countries.[31] The epidemic growth of DM occurs in developing countries where TB is highly endemic. Consequently, DM and TB are increasingly present together suggesting the need for a rehabilitated interest in this topic.[32]

The thrust of treatment programmes for tuberculosis is to avoid treatment failure and to prevent emergence of drug resistant strains, however, this target is being challenged by the coexistence of DM in a large number of TB infected subjects. Global progress depends on major advances in TB and diabetes mellitus prevention and care in countries endemic in the diseases. WHO had recommended a collaborative framework for the clinical management and control of DM-TB comorbidity. The essential intervention schemes identified include establishing mechanisms of collaboration between TB and DM control programmes, detection and management of TB in patients with DM, and detection and management of DM in TB patients.[33]

This research aims to determine the level glycemic control in TB only and DM-TB comorbidity and the consequence of the double burden on glycemic control at different phases of treatment.

METHODS

Study location

This study was conducted in Calabar, Cross River State, in subjects attending Infectious Diseases Hospital, Calabar.

Subject selection

fifty M.TB infected subjects and fifty control subjects were enrolled into the study, all the participants gave consents

Inclusion criteria

Subjects between the ages of 20-65 years; diagnosed with *mycobacterium tuberculosis* infection, and had begun treatment, attending infectious diseases hospital, Calabar, Cross River State, and who gave consent were included in the study.

Exclusion criteria

Pregnant women and those who were newly diagnosed and had not commenced treatment and those who did not give consent were excluded.

Study design

This study was a case control study, conducted between March–September 2018, to understand the state of glycemic control in TB only and DM-TB comorbidity subjects at different phases of treatment. Ethical approval was received from the research ethical committee of the University of Calabar Teaching Hospital (UCTH). Informed consent was obtained from all the participants.

Sample collection and analysis

A standard venipuncture method was used to obtain six milliliters (6ml) of blood from all the subjects. Two millilitres (2ml) of the blood was transferred into fluoride-oxalate bottle and four millilitres (4ml) into K2EDTA for estimation of fasting plasma glucose and glycated haemoglobin concentrations respectively. Fasting plasma glucose was determined by glucose oxidase method of Barham and Trinders (1971), glycated hemoglobin by Ion Exchange Resin method of Trivelli et al., 1971.

Statistical analysis

Data generated were analyzed using SPSS version 20.0 statistical package, differences between groups were determined using Student's t-test, variations among groups by ANOVA and relationship between parameters using Pearson's correlation, differences were considered significant at $P<0.05$.

RESULTS

The mean fasting plasma glucose and glycated hemoglobin levels of TB subjects (5.68±1.43mmol/L, 6.53±2.23%) were significantly ($p<0.05$) higher than those of the control (4.40±0.63 mmol/L, 5.73±0.64%) respectively. The mean BMI of the TB infected subjects (21.31±3.32kg/m^2) was significantly lower ($p=0.001$) than that of the control (25.65±2.84 kg/m^2). The mean age of TB infected subject was not significantly different from that of the control, Table 1.

Table 2 shows the mean age, body mass index (BMI), fasting plasma glucose and glycated hemoglobin of *Mycobacterium tuberculosis* infected subjects at the beginning phase of treatment, continuation phase and the control.

The mean age, body mass index (BMI), fasting plasma glucose and glycated hemoglobin of TB infected subjects at the beginning phase of treatment were (35.93±6.12 years, 21.91±3.06 kg/m^2, 4.95±1.09 mmol/L and 5.35±1.17%) respectively while those of subjects at the continuation phase of treatment were (44.36±9.97 years, 21.08±3.42 kg/m^2, 5.96±1.47 mmol/L and 6.99±2.39%) and those of control were 38.68 ±7.15 years, 25.65±2.84 kg/m^2, 4.40±0.63mmol/L, 5.73±0.64% respectively. The mean FPG and HbA1C level of those at the continuation phase of treatment were significantly ($p<0.05$) higher than that of those at the beginning phase of treatment and the control. The mean BMI of the control was significantly ($p<0.05$) higher than either of the groups on treatment. The mean age, FPG and HbA1c of subjects with DM-M.TB coexistence were significantly ($p<0.05$) higher than those of the M.TB only infected subjects. BMI of the DM-M.TB comorbidity subjects was lower than that of the M.TB only infected subjects ($p=0.109$), table 3.

A significant positive correlation was obtained between HbA1C and FPG in M.tb infected subjects. ($r=0.910$, $p=0.001$), figure 1. A negative correlation was observed between HbA1C and BMI in M.tb infected subjects. ($r=0.267$, $p=0.061$) figure 2.

Among the M.tb infected subjects, thirty per cent of the M.tb infected subjects were HIV sero-positive, 24% were females, 76% males. Fifty four per cent had normal glycemic control and 38% had poor glycemic control.

Fourteen per cent were underweight, 62% were normal weight and 24% overweight. Of the 28% at the beginning phase of treatment 2% had poor glycemic control and 34% of those in the continuation phase of treatment had poor glycemic control.

Fifty six per cent were not diabetic while 44% were diabetic. Eighty one per cent of the diabetics had poor glycemic control while 42% of the subjects were TB-DM comorbid.

Table 1: Mean age, Body Mass Index (BMI), Fasting Plasma Glucose (FPG) and glycated hemoglobin (HbA1C) in *mycobacterium Tuberculosis* (M.TB) and control subjects.

Parameters	TB subjects (n=50)	Controls (n=50)	Cal.T	P- value
Age (yrs)	42.00±9.78	38.68±7.15	1.938	0.056
BMI (Kg/m^2)	21.31±3.32	25.65±2.84	7.023	0.001
FPG (mmol/L)	5.68±1.43	4.40±0.63	5.750	0.001
HbA1C (%)	6.53±2.23	5.73±0.64	2.429	0.017

Significant at p<0.05
BMI=Body Mass Index, FPG=Fasting Plasma Glucose, HbA1C=glycated hemoglobin

Table 2: Mean age, BMI, fasting plasma glucose and glycated hemoglobin in *Mycobacterium tuberculosis* infected subjects at the beginning phase of treatment, continuation phase and the control.

Parameters	Beginning phase (n=14)	Continuation phase (n=36)	Control (n=50)	Cal. F	p-value
Age (Yrs)	35.93±6.12	44.36±9.97	38.68±7.15	7.434	0.001
BMI(Kg/m^2)	21.91±3.06	21.08±3.42	25.65±2.84	24.959	0.001
FPG	4.96±1.09	5.96±1.46	4.40±0.63	22.274	0.001
HbA1C	5.35±1.17	6.99±2.39	5.73±0.64	8.776	0.001

*significant at p<0.05, age, BMI = body mass index, FPG = fasting plasma glucose, HbA1C = glycated hemoglobin.

Table 3: Mean age, BMI, fasting plasma glucose and glycated hemoglobin levels in *Mycobacterium tuberculosis* infected only and Diabetes mellitus-*Mycobacterium tuberculosis* comorbidity subjects.

parameters	TB only subjects (n=29)	DM-TB comorbidity (n=21)	Cal.T	P- value
AGE (yrs)	39.0±6.41	46.12±12.07	2.709	0.009
BMI (Kg/m^2)	21.95±3.27	20.43±3.24	1.634	0.109
FPG (mmol/L)	4.56±0.60	7.21±0.49	16.517	0.000
HbA1C (%)	4.88±0.93	8.80±1.30	12.284	0.000

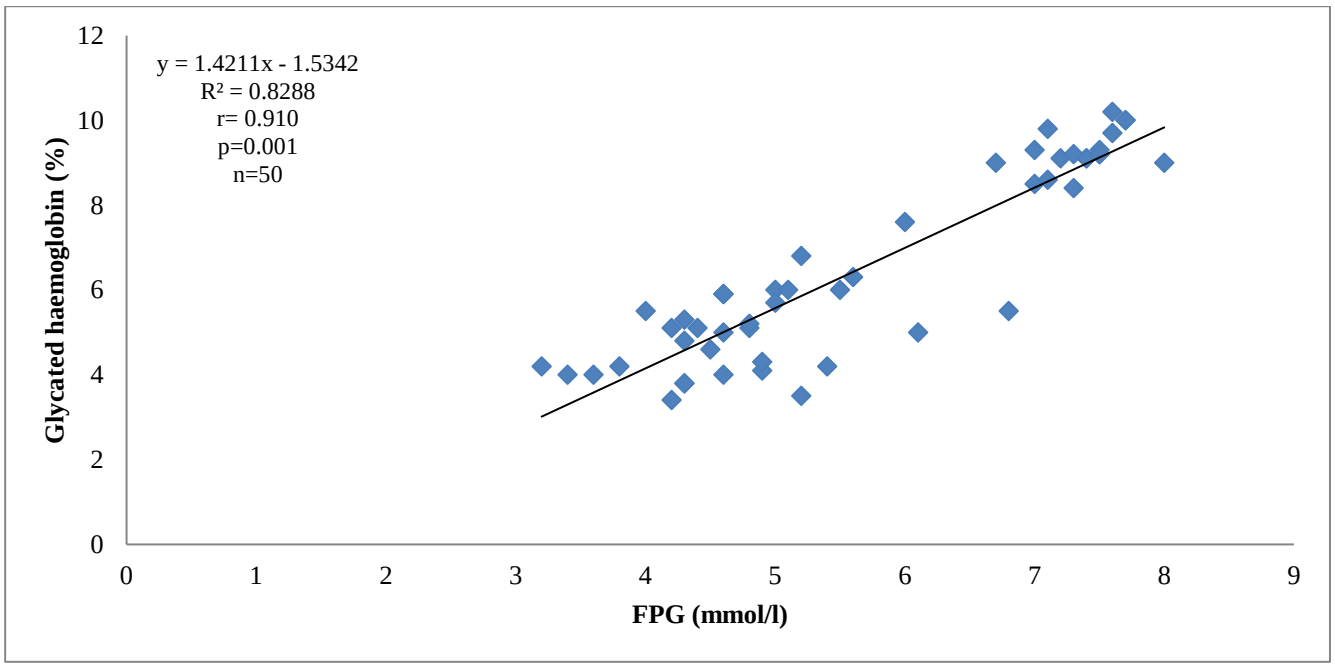

Figure 1: correlation of Glycated haemoglobin and FPG in MTB infected subjects.

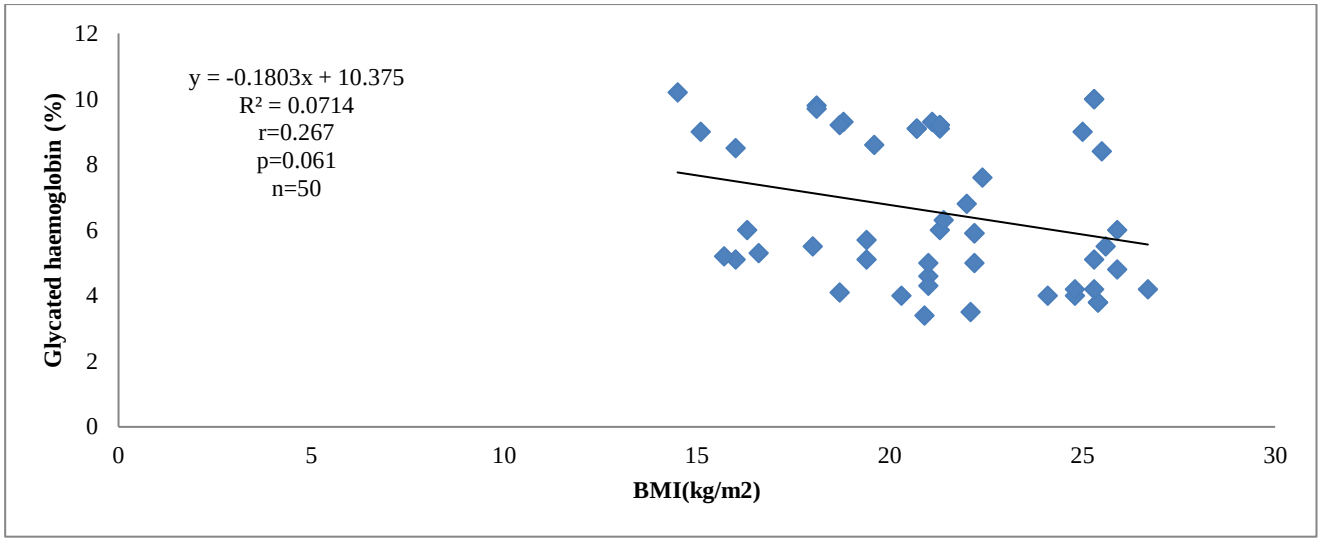

Figure 2: correlation of Glycated haemoglobin and BMI in MTB infected subjects.

DISCUSSION

From this study the significantly higher fasting plasma glucose and glycated haemoglobin levels in MTB infected subjects compared with the MTB non-infected subjects may suggest that infection with MTB may predispose one to abnormal glucose control and development of diabetes mellitus. On the other hand hyperglycemia may complicate M.tb treatment and affective M.tb control in subjects with DM-M.Tb comorbidity. These findings are similar to that of Riza et al., who reported poorly controlled DM increasing the risk of TB and unfavorable TB treatment outcomes.[15] DM-TB joint framework evolving into a bi-directional screening approach for both diseases if implemented may reduce the dual burden of DM-TB comorbidity, the possibility has been established in other studies reported by Lin et al., and Li et al, The significantly higher mean age of the TB subjects compared with the control suggests that age may be a risk to development of DM and TB due to decreasing cellular immune system in this cohort.[34,35]

The suppressed immune condition developed in diabetic condition, makes the individual become more predisposed to MTB infection and a number of other diseases linked with immune compromised status with consequent treatment failure. This observation is similar to that reported by Sulaiman et al., Workneh et al., and tororo, who reported that the reason may be related to decrease in immune status in older age individuals that make them more susceptible to develop both TB and DM.[36-38] The significantly lower BMI in the Mtb infected cohort compared with the control may be as a result of poor appetite, malnutrition in Mtb infected subjects. This finding is in line with that of Sherry and Evan; who reported malnutrition and undernutrition as factors that lead to reactivation of latent TB, by playing key roles in TB subversion of the immune system and leading to an increase in metabolism and a decrease in appetite that complicate the already present malnutrition.[39] The significantly lower BMI in TB subjects compared with control, those in the continuation phase of treatment compared with those at the beginning phase of treatment and control, and those with TB-DM comorbidity compared with M.TB only infected subjects may be due to presence of malnutrition with continued muscle wasting resulting from loss of appetite, enhanced nutrient requirement and metabolic derangement in these groups. Similar findings have been reported in studies by Wang, et al., who stated that weight loss may be due to poorly controlled DM and metabolic decomposition which takes away the initial protection against TB offered by weight gain in diabetic which becomes risk factor to TB.[40] This finding is in accordance with that by Viswanathan et al., who reported both lower and higher BMI as an increased risk factor for DM-TB comorbidity.[41]

TB infected patients, those on continuation phase of treatment and those with TB-DM comorbidity were older in age compared with the control, those at the beginning phase of treatment and the TB only infected groups. This Suggests that age may be a risk factor for TB, DM and TB-DM comorbidity. FPG and glycated haemoglobin increased congruently in TB and TB-DM comorbidity. This may suggest that normal levels of glucose produce a normal amount of glycated hemoglobin. As the average amount of plasma glucose increases the fraction of glycated hemoglobin increases in a likely manner. In diabetes mellitus, higher amount of glycated hemoglobin, indicating poorer control of blood glucose levels, which have been linked with compromised immune system, TB infection, cardiovascular disease, nephropathy and neuropathy. Impaired immunity in diabetic patients is

thought to contribute to the evolution of latent TB infection to active cases

CONCLUSION

The global epidemic of diabetes may have adverse consequences on treatment outcome and effective control of TB. There seem to be ongoing derangement in glycemic control in TB subjects on treatment. Vigorous screening for DM in patients with TB or vice versa is advocated, which may possibly improve the early diagnosis and control of TB, DM and DM-TB double burden. Glucose control should be stringently preserved, especially, at the beginning intensive phase of treatment for better outcome in patients with TB and DM-TB comorbidity. Resolute efforts to control DM may likely have a significant valuable effect on TB management outcome.

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