ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IV April 2024

Evaluation of Creatine Kinase-MB Activity and Cortisol Level in Hypertensive *Mycobacterium Tuberculosis* Patients Receiving Treatment in Nnewi.

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DOI: https://doi.org/10.51244/IJRSI.2024.1104057

Received: 14 April 2024; Accepted: 19 April 2024; Published: 20 May 2024

ABSTRACT

Mycobacterium tuberculosis, the etiological agent of tuberculosis (TB), imposes a health challenge globally. Tuberculosis is an infectious disease that most often affects the lungs, and it spreads through the air when infected people cough, sneeze, or spit. This study was aimed at evaluating creatine kinase-MB (CK-MB) activity and cortisol levels in *Mycobacterium tuberculosis* patients receiving therapy at Nnewi. A cross-sectional study involved 90 participants consisting of 45 TB+ individuals and 45 healthy controls. A questionnaire was used to obtain the age, sex, and other vital information needed for the study. The body mass index (BMI) of the participants was calculated. Their systolic and diastolic blood pressure was obtained using an Accu-Answer automatic blood pressure monitor. *Ziehl-Nelseen (ZN) sputum smear microscopy determined Mycobacterium tuberculosis* infection and confirmed positive using GeneXpert. Plasma cortisol level was determined using an Enzyme-linked immunosorbent assay whereas plasma CK-MB activity was determined spectrophotometrically. Independent t-test and Pearson`s correlation coefficient were used for statistical analysis. Significant levels were considered at $p < 0.05$. Data was presented as mean ± standard deviation. The mean value of the diastolic blood pressure (DBP) of the TB+ participants was significantly lower (75.53 ± 14.04) compared with the control (81.53 ± 6.10) ($p < 0.05$). No significant difference was observed in the mean values of plasma cortisol and CK-MB activity (9.37±1.26) (18.99±1.26) of the TB+ participants compared with control (9.28±6.92) (18.81±1.45) ($p>0.05$). There was a moderate positive correlation between systolic blood pressure (SBP) and DBP ($r = 0.50$; $p = 0.01$) in the test group and a strong positive correlation between SBP and DBP in the control. SBP and cortisol showed a moderate positive correlation with DBP and cortisol in the test group. In conclusion, there was no predisposition to acute myocardial infarction and inflammation in the subjects studied.

Keywords: Creatine Kinase-Mb, Cortisol, Hypertensive, *Mycobacterium tuberculosis* Nnewi.

INTRODUCTION

Tuberculosis (TB) is a contagious illness primarily targeting the respiratory system, predominantly the lungs, resulting from infection with Mycobacterium tuberculosis. Transmission occurs via airborne particles expelled when infected individuals cough, sneeze, or expectorate [1]. Pulmonary tuberculosis (PTB), instigated by Mycobacterium tuberculosis (MTB), represents a significant global health challenge [2].

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According to the World Health Organization (WHO) in 2023, approximately 25% of the world's population is believed to have contracted tuberculosis (TB) bacteria. Roughly 5–10% of individuals infected with TB will eventually exhibit symptoms and progress to TB disease. It's important to note that individuals who are infected but asymptomatic cannot spread the disease. TB disease is typically managed with antibiotics, and without proper treatment, it can be fatal. Moreover, mounting evidence suggests that various infections, including Mycobacterium tuberculosis, contribute to the development of cardiovascular disease (CVD) [3].

Some researchers have identified a connection between latent tuberculosis and acute myocardial infarction (AMI) [4]. This association is believed to stem from findings showing ongoing activation of the immune system in both latent and active tuberculosis [5]. Monocytes/macrophages, lymphocytes, and cytokines, which play key roles in cell-mediated immune responses against Mycobacterium tuberculosis, are also significant contributors to the development of atherosclerosis. This suggests a potential pathogenic role of tuberculosis in cardiovascular disease (CVD) through mechanisms like those seen with other pathogens that establish chronic infection and latency [4, 5].

Mycobacteria are types of bacteria that live and reproduce inside certain cells of the body called macrophages. To eliminate these mycobacteria, the body's cells, including macrophages, neutrophils, and monocytes, produce large quantities of reactive oxygen species. However, this defensive mechanism can inadvertently cause damage to the body's tissues through inflammation. In individuals with compromised antioxidant capacity, such as those with HIV infection, this inflammatory response may be exacerbated, potentially leading to suppression of the immune system [6, 7]. Researchers have shown that patients with TB have a higher proportion of hypertension than controls without TB [8, 9, 10]. Tuberculosis (TB) has been linked to hypertension, particularly in individuals with prolonged TB infection. The underlying mechanism involves the immunological response triggered by TB, characterized by the destruction of parenchymal cells in the lung tissue. This response may contribute to the development of hypertension [8,9,10,11]. A comprehensive review published in PLoS Medicine in 2008, as highlighted by Smeeth et al. (2008) [12], and Vignesh et al. (2021) [9], elaborates on this association. It proposes that the chronic inflammatory reaction accompanying TB infection can induce vascular dysfunction, ultimately leading to hypertension.

Lifestyle choices are recognized to impact the likelihood of hypertension and cardiovascular disease (CVD). However, it is plausible that persistent infections, such as tuberculosis (TB), also play a role in the onset of these conditions through various mechanisms. Furthermore, there could be a bidirectional relationship where hypertension increases the risk of contracting TB [10].

Concerning the potential link between TB and hypertension, it has been suggested that the activation of immune responses may hinder endothelial function, thereby elevating the risk of CVD and potential hypertension [11, 13]. TB could lead to damage in lung tissue, affecting the vascular structure and causing conditions like vasculitis and endarteritis, ultimately resulting in a reduction in the cross-sectional area of pulmonary blood vessels and consequent pulmonary hypertension [1]. Additionally, hypertension may ensue if TB infection in the kidneys destroys renal tissue, leading to impaired renal function and compromised blood pressure regulation [14].

Cortisol, a steroid hormone, serves as the ultimate output of the well-established hypothalamic–pituitary–adrenal (HPA) axis, a fundamental component of the human neuroendocrine system. This system, along with others, regulates various bodily functions under the direction of the hypothalamus and pituitary gland. Cortisol possesses lipophilic properties, enabling it to traverse the plasma membrane of target cells independently, without necessitating a membrane transporter [15].

In a study featured in Clinical and Vaccine Immunology, tuberculosis (TB) demonstrates a correlation with elevated cortisol levels. Individuals afflicted with active TB exhibited heightened cortisol concentrations in

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comparison to those with latent TB infection or individuals free of TB. Researchers postulate that this phenomenon may stem from the immune response triggered by TB, which has the potential to induce cortisol production [16].

As a result, tuberculosis (TB) is linked to changes in the hypothalamic-pituitary-adrenal (HPA) axis, leading to higher levels of cortisol in the bloodstream [17,18]. Nevertheless, certain research has indicated that tuberculosis can induce adrenal insufficiency through either direct infection of the adrenal gland or because of anti-tuberculous treatment, resulting in decreased cortisol levels [16, 18].

Creatine kinase is a specialized enzyme found within the interior of cells in the heart, brain, and skeletal muscle. When the cell membrane of the heart is compromised due to low oxygen levels (hypoxia), creatine kinase MB (CK-MB), a specific variant of creatine kinase, is released from the cell's interior (cytosol) into the bloodstream. CK-MB is loosely attached to the contractile apparatus of the heart muscle, and the severity of damage to the heart tissue influences its concentration in the blood. This release into circulation is a passive process [19].

Studies have indicated that heightened activity of creatine kinase, which plays a pivotal role in regulating energy metabolism, contributes to the development of elevated blood pressure [20]. Creatine kinase facilitates the rapid production of adenosine triphosphate (ATP), a crucial molecule for powering energy-intensive processes such as cardiovascular contraction. Additionally, it counteracts the effects of nitric oxide on bodily functions. It is believed that increased activity of creatine kinase, particularly in the small arteries that regulate blood flow resistance, may amplify pressure responses, and consequently raise blood pressure levels [21]. CK-MB (creatine kinase-MB) is also associated with failure of antihypertensive treatment [20, 22]. Hence, CK-MB is believed to play a crucial role in pressure reactions by aiding in the augmentation of systemic vascular resistance (SVR) and stroke volume (SV). This is because the enzyme is closely associated with cytosolic ATPases that are pivotal in cardiovascular contractility and sodium retention. Notably, Ca2+-AT, which regenerates ATP in the reaction, is one such ATPase [21, 23].

METHODS

Study participants

Sample size.

The sample size was calculated using G* Power software version 3. 0. 10 (Universität Dusseldorf, Germany). Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.90, and a medium effect size of 0.4. Based on these, the calculated total sample size of 58 has 90% power to detect a difference of 0.4 at a significance level of 0.05. To take care of possible attrition, a total sample size of 90 was used for this study.

This was a cross-sectional study conducted at Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Anambra State, Nigeria, and involved tuberculosis-infected participants, who are undergoing treatment, and participants who are not infected with tuberculosis, who fall within the age range of 16-65 years. A total of 90 individuals were recruited for this study, which includes 45 tuberculosis-positive participants who are undergoing therapy which serve as the test group, and 45 participants who are not infected with the tuberculosis disease and will serve as the control group. A questionnaire was prepared and given to the participants to ascertain their medical condition and any other underlying pathology that may affect the research, including their sociodemographic data. Subjects who were suffering from any form of kidney or liver disease were exempted from this study. The ethical approval for this research was obtained from the Nnamdi Azikiwe University Teaching Hospital ethics committee by the Helsinki Declaration by the World Medical Association (WMA) on the ethical principles for medical research involving human

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subjects. Informed consent was sought and obtained from subjects before the study. The systolic and diastolic blood pressures, height, and weight of all the subjects were measured, and the corresponding BMIs were determined. Five milliliters (5mL) of venous blood were collected aseptically from each participant, through venipuncture, and the blood was dispensed into a plain container. The blood was centrifuged at 4000rpm for 5 minutes. The serum was extracted and used for the estimation of Cortisol and Creatinine kinase-MB in the blood.

Statistical analysis

The statistical analysis was performed using independent student's t-tests and Spearman's coefficient of correlation. Values were deemed significant if, $p < 0.05$. The correlation of the parameters was determined using Pearson's correlation coefficient.

RESULTS

Table 1: No significant difference was observed in the mean values of plasma cortisol (ug/dl) and plasma CK-MB activity (iu/l) of the TB+ (test group) compared with non-TB (control) ($p > 0.05$).

Table 1: -The mean values of Cortisol and Creatinine kinase-MB activity in the groups (Mean ± Sd).

Parameter	**Test group.** (N = 45) mean ±S. D	**Control group.** (N = 45) mean ±S. D	**T-test**	**P- value**
Cortisol(µg/dL)	9.28±6.92	9.37±1.26	0.078	0.938
CK-MB (U/L)	18.81±1.45	18.99±1.26	0.617	0.539

Table 2: The mean value of DBP (mmHg) of the TB+ subjects was significantly lower compared with the control ($p < 0.05$). However, there were no significant differences in the mean values of SBP and BMI in the TB+ test group compared with the control ($p > 0.05$).

Table 2: Comparison of the body mass index and blood pressure in the groups (mean ± SD).

Parameter	**Test group.** N=45 mean ±S. D	**Control group.** N=45 mean ±S. D	**T-test**	**P- value**
SBP (mmHg)	120.24 ±6.15	119 ± 24.96	-0.162	0.87
DBP (mmHg)	81.53 ± 6.10	75.53 ± 14.04	-2.63	0.01
BMI (kg/m2)	21.83 ± 2.51	20.96 ± 3.75	-1.29	0.20

Table 3: There was a moderately positive correlation between SBP and DBP ($r = 0.50$, $p = 0.01$) in the test group, while SBP and cortisol also showed a positive correlation ($r = 0.51$; $p = 0.01$). DBP and BMI showed a negative correlation ($r = -0.50$; $p = 0.00$).

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Table 3: Association of the level of association between the parameters studied in the test group.

Parameters	r	p-value
SBP VS DBP	**0.05**	**0.01**
SBP VS CORTISOL	**0.51**	**0.01**
DBP VS BMI	**-0.51**	**0.001**

Table 4: There was a significant, strong positive correlation between SBP and DBP (r = 0.913; p = 0.00) in the control.

Table 4: Correlation of the level of association between the parameters studied in the control group.

PARAMETERS	r	p-value
SBP VS DBP	0.91	0.01

DISCUSSION

Mycobacterium tuberculosis, the etiological agent of tuberculosis, imposes a health challenge globally, and infects a large population, although active infections account only for a small percentage [16]. Though some degree of endocrine dysfunction is invariable in all patients with TB [18], clinically significant endocrinopathy other than glucose intolerance is rare. T.B. which is a bacterial infection that affects mostly the upper lobe of the lungs can spread to other parts of the body such as the adrenal glands causing adrenal tuberculosis (extra-pulmonary tuberculosis). A comparison of anthropometric measurement and blood pressure revealed that TB+ subjects had significantly lower mean values of DBP compared with the control ($p < 0.05$). However, no statistical differences were seen regarding BMI and SBP among the test group and the control participants ($p > 0.05$). The mean BMI values of the entire study groups were within the normal reference range, although the mean BMI of the TB+ participants was lower than that of the control. The lower mean levels of BMI observed in the test group might be the result of depletion in body lipids and free fatty acids associated with Mycobacterium tuberculosis infection and malnutrition. Previous studies have shown that active tuberculosis is known to have a strong relationship with low BMI, and this occurred only with pulmonary TB and not with extra-pulmonary tuberculosis, especially in treatment individuals [24, 25]. This indicates that active TB infection can lead to low BMI and low BMI can equally predispose to TB reactivation in the lungs [24, 26]. The finding agrees with previous studies conducted by Igbagboyemi et al., (2022) on "Assessment of Body Mass Index of tuberculosis patients on anti-tuberculosis drugs" in Ibadan, Oyo state, Nigeria, by [27] in Mozambique and by [3] in Nnewi, Anambra state, Nigeria on serum apolipoprotein-B increased among tuberculosis patients compared to control. The researchers discovered that most of the TB+ respondents involved in their studies had normal weight and BMI (18.5 – 24.9 Kg/M2). Healthy/normal BMI observed in the test subjects in the present study could be due to early detection of Mycobacterium tuberculosis before emaciation of the patients and this conserved their weight status before they began therapy. This is in line with the previous report by [28], which also found a significant relationship between BMI and anti-tuberculosis drugs. BMI increases over time as treatment progresses [29]. Another factor that might have helped the tuberculosis patients not to lose weight much was the implementation of TB directly observed treatment course which helped the patients conserve their weight due to enhanced treatment compliance. However, the present study disagrees with the study done by [30,24] on "the link between tuberculosis and body mass index. The study found that pulmonary tuberculosis was implicated in low BMI. The disparity could be because of different factors like demographic factors (age, gender, ethnicity, religion, household size, education, and occupation) which were not considered in this study. The mean blood pressure of the participants was within the normal range. The normal range for blood pressure is 90 – 120 mmHg for systolic blood pressure (SBP) and 60 – 80 mmHg for diastolic blood pressure (DBP) [8, 19]. The normal blood pressure observed among the

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participants in the present study confirms the normal plasma cortisol level and creatine kinase-MB (CK-MB) activity obtained in the study. It is a fact that active TB disease is associated with chronic inflammation especially when therapy has not been initiated [10]. Chronic inflammation can lead to hypertension and other cardiovascular diseases and increased plasma CK-MB has been implicated in hypertension [4] The normal blood pressure found among the TB+ participants in this study agrees with [31,10] in which they reported no association between hypertension/raised blood pressure and tuberculosis and no significant difference in the mean systolic and diastolic blood pressures of the TB correspondents compared with the control in their studies. However, this present report is at variance with an analysis of cross-sectional data from the 2011-2012 National Health and Nutrition Examination Survey (NHANES) on Tuberculosis infection and hypertension: Prevalence estimates from the US National Health and Nutrition Examination Survey conducted by[35] They reported a higher prevalence of hypertension (blood pressure ≥140/90 mmHg) among tuberculosis patients. The disparity could be attributed to changes in geographical location as the prevalence of hypertension is higher in the USA (48.1% in 2021) than in Nigeria (30.6% in 2021) [32, 33]. Dietary differences in this region, particularly in the amount of oil and salt used in food as well as high consumption of processed food may be the contributory factors. Another cohort study in Indonesia also found a significantly higher prevalence of hypertension among TB patients compared with control [10]. Geographical location and study design could be the contributory factors. Compared to the control, TB+ individuals revealed no significant difference in the mean values of plasma cortisol and CK-MB activity. This indicated that the plasma cortisol level and CK-MB activity of both the test participants (TB+) and the control are within the normal ranges (3- 25ug/l and 5-25U/L respectively). Active tuberculosis affects the adrenal gland mostly when the patient is not on anti-tuberculosis therapy [18]. M. tuberculosis complex spreads to the adrenal gland hematogenous. The adrenal gland is a common site of extrapulmonary tuberculosis. At least 90% of the adrenal gland must be destroyed before adrenal insufficiency occurs. Adrenal insufficiency should be verified by demonstrating depressed/reduced morning plasma cortisol levels with a diminished response to synthetic adrenocorticotropin (ACTH). Cortisol is an anti-inflammatory hormone as well as a stress hormone. Active tuberculosis especially when anti-tuberculosis therapy has not been initiated induces inflammation. Most of the TB+ participants involved in this research were already in therapy and this could be why their adrenal glands were not affected (as cortisol is a hormone of the adrenal gland). This indicates that the relative deficiency or activation of the HPA axis is less manifest in them. The normal plasma cortisol level observed in the test group is in line with the studies in active TB patients from Nigeria and South Africa. The researchers suggest that the TB+ individuals had normal plasma cortisol levels compared with the control [18, 34]. This was because of anti-tuberculosis therapy as their studies were also conducted on tuberculosis individuals already on treatment. However, the finding is at variance with that of Betterle and Morlin, (2019) [35,36]. Betterle and Morlin (2019) [35] reported that active TB causes adrenal insufficiency through bilateral destruction of the adrenal gland leading to low levels of serum cortisol. This could be due to differences in their methods of assessment of adrenal insufficiency in those subjects and the duration of the infection, that is, chronic tuberculosis infection. [36] in their study attributed the low plasma cortisol level observed among tuberculosis participants to TB treatment regimens involving rifampicin which accelerates cortisol metabolism (breakdown) resulting in low cortisol levels. Rifampicin is used for Drug sensitive-TB treatment categories 1 and 2. Additionally, lower plasma cortisol level was observed in drug-resistant TB compared with drug-sensitive TB subjects in their study, but the present study was majorly on drug-sensitive TB subjects. The present study is also in disparity with the study by [36] who opined that active TB activates the HPA axis rather than under activation leading to increased cortisol levels. In his study, both TB+ treatment naïve participants and TB+ subjects under therapy were recruited, and he discovered that the plasma cortisol levels of TB+ individuals not on treatment were significantly higher than those on treatment. This was a result of an enlarged adrenal gland because of stressful conditions caused by active tuberculosis seen among the TB+, not on treatment. This could also be the result of prolonged (chronic) tuberculosis infection without treatment. However, he reported that those tuberculosis subjects recovered after the treatment of tuberculosis.

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CK-M B is a marker for acute myocardial infarction (AMI) and hypertension can predispose to acute myocardial infarction (AMI). In this study, the normal value of CK-MB in both the TB+ participants and the control is an indication that the subjects were free from myocardial infarction at the time of the study. [4] reviewed the research on possible mechanisms underlying the association between TB and cardiovascular disease (CVD) and suggested that TB disease is associated with chronic inflammation which through the triggering of a complex cascade of immunological responses may lead to the formation of an atherosclerotic plaque. It has been shown that antibodies produced against mycobacterial HSP can cross-react with HSP expressed on host endothelial cells during an infection, resulting in an autoimmune response targeted against cells of the vessel wall. The severity of myocardial injury determines the plasma CK-MB level. The enzyme enters circulation by passive diffusion from infarct myocardium cells [34]. Following the onset of symptoms of myocardial infarction, CK-MB increases in serum within 3-6 hours; the peak levels occur between 16 and 30 hours and disappear from the serum at a more rapid rate. The research conducted in Gabon was of a different opinion as the researcher found significantly reduced levels of CK-MB in patients with active TB disease [37]. The discrepancy could be attributed to factors like study design as their study was a cross-sectional study with a longer duration from January 2019 to December 2020, sample storage, and geographical factors. However, many researchers attributed increased levels of CK-MB to myocardial infarction and other cardiovascular diseases like hypertension other than pulmonary tuberculosis [38]. Furthermore, a moderate positive correlation existed between SBP and DBP in the TB+ participants ($p = 0.01$) (Table 4.3) whereas a strong positive correlation was seen between SBP and DBP in the control ($p = 0.00$) (Table 4.4). This agrees with the findings by [8] who found an association between systolic blood pressure and diastolic blood pressure in tuberculosis subjects and control. This implies that DBP increases with an increase in SBP and vice versa among the participants. SBP and DBP also exhibited no statistical association with BMI in the control unlike in the test group where there was a negative correlation between SBP with BMI and DBP with BMI respectively. However, Cortisol and CK-MB had no association in both the test group (TB+) and the control ($p > 0.05$). This implies that an increase or decrease in plasma cortisol level did not affect the plasma CK-MB activity in both the test and the control. Both cortisol and CK-MB had no statistical correlation with BMI in both the control and test subjects. This is because an increase or decrease in serum cortisol level and CK-MB activity do not affect BMI.

CONCLUSION

The study revealed that individuals with tuberculosis (TB+) had lower diastolic blood pressure compared to the control group, but there were no significant differences in serum cortisol level, CK-MB activity, systolic blood pressure, or BMI between the two groups. The TB+ group showed normal levels of serum cortisol and CK-MB, likely due to anti-tuberculosis therapy. A healthy BMI was noted in the TB+ group, possibly due to prior TB medication. No statistical relationship was found between serum cortisol and CK-MB. The study didn't include sex and age in the analysis due to a lack of age matching during sample collection. Overall, the study didn't find a predisposition to acute myocardial infarction or inflammation among participants.

ACKNOWLEDGMENTS

The authors would like to pay their most profound gratitude to the management and staff of Nnamdi Azikiwe University Teaching Hospital, Nnewi, and Reene Medical Diagnostic Laboratory, Awada, Anambra State, for the laboratory analyses of all biochemical parameters.

Conflicts of Interest:

None declared

Author contributions:

ACI, EOI and CCO conceived and designed the research proposal. TAI and NO performed sample collection, experiments, and data analysis. ACI, and JCA contributed to the final version of the manuscript. All authors have read and approved the final manuscript.

Data availability

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

Funding:

No funding sources.

Ethical approval:

The study was approved by the Ethics Committee of the Faculty of Health Sciences and Technology, Nnamdi Azikiwe University, Nnewi, Anambra State, Nigeria NAUTH/CS/66/VOL.16/VER.3/203/2023/052

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ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue IV April 2024

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