

# Endocrine dysfunction among adult patients with tuberculosis: An African experience

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### ABSTRACT

A broad spectrum of endocrine conditions has been reported among adult patients with tuberculosis in Africa. This review aims to describe the magnitude and pathogenesis of the following endocrinopathies among patients with tuberculosis in Africa: adrenal insufficiency, diabetes mellitus, disorders of calcium and vitamin D metabolism, thyroid dysfunction and hypogonadism. PubMed database and Google scholar were used to search for the relevant published English language studies and case reports relating to endocrine abnormalities and tuberculosis in Africa up to July 2013. The search terms used were endocrine dysfunction, endocrine abnormalities, adrenal insufficiency, diabetes mellitus, thyroid dysfunction, hypogonadism, disorders of calcium and vitamin D metabolism, tuberculosis, Africa. Reference lists of the identified articles were further used to identify other studies. Adrenal insufficiency, diabetes mellitus and calcium-vitamin D abnormalities were the most prevalent and frequently reported endocrine disorders among adult patients with tuberculosis in Africa. A meticulous endocrine evaluation among tuberculosis patients with suspected endocrine abnormalities should be encouraged in Africa and other high TB endemic regions. Treatment of these endocrine disorders has generally been shown to improve quality of life and reduce mortality.

**Key words:** Africa, endocrine dysfunction, tuberculosis

## INTRODUCTION

Tuberculosis (TB) is of notable public health significance globally with the greatest disease burden documented in sub-Saharan Africa (SSA). The World Health Organization (WHO) estimated about 8.7 million incident cases of TB with about 1.45 million deaths due to TB in 2011 globally.<sup>[1]</sup>

TB is associated with diffuse functional impairment of most endocrine organs. The spectrum of TB associated endocrinopathies is extensive. A minority of patients with TB present with clinically overt symptoms; hence, the need among clinicians to possess a high index of

suspicion for early diagnosis and initiation of appropriate treatment.

Adrenal, pituitary, thyroid, pancreatic, calcium, gonadal, and glucose abnormalities have been well-described among TB patients.<sup>[2-7]</sup> This review article will broadly focus on describing the extent and pathogenesis of adrenal insufficiency, diabetes mellitus (DM), disorders of calcium-vitamin D metabolism, thyroid dysfunction, and hypogonadism among African TB patients.

### Adrenal insufficiency

TB involvement of the adrenal glands is well-documented and is one of the commonest causes of adrenal insufficiency in developing countries with high TB prevalence.<sup>[8-10]</sup> Evaluation of adrenal function among TB patients is of great significance because cortisol deficiency is associated with unexplained sudden and early mortality.<sup>[11]</sup>

TB has a direct destructive effect of the adrenal glands leading to adrenal insufficiency. Chronic inflammatory conditions like TB are associated with increased levels of proinflammatory cytokines like tumor necrosis factor- $\alpha$ .

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These cytokines inhibit adrenal cortisol synthesis and adrenal insufficiency ensues. Anti-TB drugs like rifampicin also cause cortisol deficiency by inducing increased hepatic metabolism of cortisol.<sup>[11,12]</sup>

Adrenal insufficiency in the setting of TB can also occur secondary to coexisting adrenal infiltration by human immunodeficiency virus (HIV) coinfection and neoplasms like kaposi sarcoma and lymphomas.<sup>[11]</sup>

Studies from Africa on the degree of adrenal insufficiency among TB patients have reported varying prevalence ranging from 0% to 40%.<sup>[13-19]</sup> The reason for this disparity is the varying criteria for defining adrenal insufficiency and diagnostic methods used.

Odeniyi *et al.*,<sup>[16]</sup> in a study among 44 adults with smear positive TB in Nigeria documented a prevalence of subclinical adrenal insufficiency of 23% after a low dose 1  $\mu$  adrenocorticotrophin hormone (ACTH) stimulation test. Overt adrenal insufficiency was infrequent among the study cohort at baseline. There was no statistical difference noted between the basal cortisol levels of the TB patients and the 100 healthy controls (239.9 nmol/L vs. 229.1 nmol/L,  $P = 0.661$ ). This study demonstrates that an ACTH stimulation test may be a better test to confirm or exclude adrenal insufficiency in TB patients.

In another case-control study by Mugusi *et al.*,<sup>[17]</sup> on 50 hospitalized patients with chronic pulmonary TB in Tanzania, an abnormal adrenal response was noted in 16 (32%) patients. Adrenal insufficiency in this study was defined as a 60-min cortisol response  $<21.7 \mu\text{g/dL}$  ( $<600 \text{ nmol/L}$ ) and/or an increment  $<10.8 \mu\text{g/dL}$  ( $<300 \text{ nmol/L}$ ) after an ACTH stimulation test. Hypotension is a common clinical sign associated with adrenal insufficiency as noted in this study. Patients with an impaired cortisol response were reported to have lower mean supine and erect diastolic blood pressures compared to those with a normal response (supine: 64 mm Hg vs. 74 mm Hg,  $P < 0.01$  and erect: 62 mm Hg vs. 73 mm Hg,  $P < 0.05$ ).

In South Africa, varying prevalence of adrenal insufficiency among TB patients has been documented. This could be explained by the differences in races being studied and study definitions of adrenal insufficiency. Ross *et al.*,<sup>[15]</sup> in a cross-sectional study to determine the specific etiology of Addison's disease in a large South African cohort found a prevalence of 8% among TB patients, while Soule<sup>[18]</sup> reported a prevalence of probable TB-related Addison's disease to be 34% (18%-active TB disease and 16%-old TB disease) among 50 hospitalized patients.

In another case-control study by Kaplan *et al.*,<sup>[14]</sup> to assess the magnitude of adrenal insufficiency and the effect of HIV coinfection on adrenal function in 21 healthy controls and 18 HIV positive and 22 HIV negative hospitalized TB patients, a very low frequency of hypoadrenalism of 1.6% (documented in 1 HIV negative TB patient) was reported. Adrenal insufficiency in this study was defined as a 30-min cortisol level  $\leq 414 \text{ nmol/L}$  after a 1  $\mu\text{g}$  ACTH stimulation test. HIV sero status did not significantly affect the serum cortisol levels after administration of the 1  $\mu\text{g}$  ACTH stimulation test.

Post *et al.*,<sup>[13]</sup> in another prospective study did not find any evidence of adrenal insufficiency among 50 hospitalized patients with newly diagnosed active pulmonary TB. In this study, adrenal insufficiency was defined as a peak cortisol concentration  $\leq 550 \text{ nmol/L}$  after a 250  $\mu\text{g}$  stimulation ACTH test irrespective of the basal cortisol levels.

Adrenal insufficiency is invariably accompanied by unspecific clinical features like fatigue, salt craving, myalgia, nausea and vomiting, abdominal pain, postural hypotension, and hyperpigmentation. Hyponatremia, hypoglycaemia, hyperkalemia, unexplained eosinophilia and mild prerenal azotaemia are the common biochemical findings.<sup>[11]</sup> Presence of any of these clinical features among TB patients should prompt evaluation of adrenal function using either measurement of basal early morning serum cortisol levels or an ACTH stimulation test.

Management of adrenal insufficiency involves long-term low dose oral glucocorticoid and mineral corticoid replacement therapy and timely initiation of anti-TB therapy with the standard regimen.<sup>[8]</sup>

Rifampicin, an integral drug in TB treatment, is a known potent inducer of the cytochrome P450 enzymes which may result in enhanced clearance of the endogenous cortisol produced by the adrenal cortex. This can precipitate an Addisonian crisis and early mortality in TB patients.<sup>[11]</sup> However, two prospective studies reported from South Africa<sup>[19]</sup> and Malawi,<sup>[20]</sup> though limited by the relatively small patient numbers, reported no impairment in adrenal function due to rifampicin. The latter study demonstrated no increase in mortality in TB patients in the early phases of treatment.<sup>[20]</sup>

### Diabetes mellitus

DM is now a recognized risk factor and common complication encountered among TB patients.<sup>[21,22]</sup> Recent evidence suggests that diabetic patients have an increased tendency to develop TB due to impaired cell-mediated immunity, renal failure, micronutrient deficiency, and pulmonary microangiopathy.<sup>[23]</sup> Chronic infections like TB

are associated with reactionary hyperglycemia which occurs due to increased production of counter-regulatory stress hormones like epinephrine, glucagon, cortisol, and growth hormone that act synergistically.<sup>[24]</sup> There are published case reports describing TB of the pancreas with ensuing brittle DM.<sup>[4]</sup>

The prevalence of DM among TB patients in the published African studies ranges from 2.1% to 16.4%.<sup>[25-31]</sup> This disparity in the prevalence could be explained by the varying diagnostic techniques used in the studies [75 g oral glucose tolerance test (OGTT), measurement of fasting and random blood sugar level]. Majority of these studies used a 75 g OGTT for diagnosis of DM.

The earliest study in Africa by Marais<sup>[25]</sup> in South Africa among 436 TB patients reported a prevalence of 2.1%. In another cross-sectional study done in Tanzania by Mugusi *et al.*,<sup>[26]</sup> assessing glucose tolerance using a 75 g OGTT in 506 hospitalized patients with sputum-positive pulmonary TB found an initial prevalence of 6.7%. Oluboyo and Erasmus<sup>[27]</sup> in a study among 54 Nigerians with active pulmonary TB found 3 (5.6%) and 20 (37%) patients to have DM and impaired glucose tolerance, respectively, following a 75g OGTT.

In Conakry, Guinea<sup>[28]</sup> using fasting capillary blood sugar testing, the prevalence of DM among TB patients was 3.35%. Four (31%) patients had not been diagnosed with DM prior to the study. DM in this study was significantly associated with an increased age ( $P < 0.0001$ ), obesity ( $P < 0.005$ ), sedentary lifestyle ( $P < 0.0004$ ), and previous family history of diabetes ( $P < 0.04$ ) or obesity ( $P < 0.04$ ).

In another cross-sectional study performed in Nigeria to determine the prevalence of DM in 351 TB patients by measuring the fasting blood sugar level, DM as defined by levels  $\geq 126$  mg/dL was noted in 20 patients (5.7%).<sup>[30]</sup> Half of these patients were not known diabetic patients prior to initiation of TB treatment. Significantly, diabetic patients with TB coinfection were noted to have a higher mean age than those with only TB disease ( $41.5 \pm 13.9$  years vs.  $34.15 \pm 13$  years,  $P = 0.02$ ). No significant statistical difference was noted between these two groups in relation to duration of cough and sputum positivity.

In another study performed in Uganda, a prevalence of DM of 8.5% was reported among 260 hospitalised adult TB patients.<sup>[29]</sup> DM in this study was defined as a random blood sugar level  $\geq 200$  mg/dL in the presence of the usual signs and symptoms of DM like polyuria. Of the 22 TB patients diagnosed with DM, only 5 (22.7%) were known diabetics at baseline. DM in this study on multivariate

analysis was significantly associated with a raised mean serum alanine transaminase (ALT) concentration  $\geq 80$  U/L [odds ratio (OR): 11.42 95% confidence interval (CI): 2.15-60.59,  $P = 0.004$ ] and paradoxically, HIV had a protective effect (OR: 0.17 95% CI: 0.06-0.51,  $P = 0.002$ ).

This association between raised mean ALT concentrations and DM in TB patients has not been described in any African studies. Increased serum ALT concentrations are a strong predictor of insulin resistance<sup>[32]</sup> in addition to signifying direct hepatocellular damage either due to hepatotropic viruses like hepatitis C or hepatosteatorosis which have been demonstrated to be associated with DM.<sup>[33-35]</sup> However, in this study, assessment for hepatitis B, C, or hepatosteatorosis was not done.

The largest African study to date examining the prevalence and clinical predictors of DM in TB patients by Faurholt-Jepsen *et al.*,<sup>[31]</sup> performed in Mwanza, Tanzania reported a relatively high prevalence of DM of 16.4% ( $n = 197$ ) among 1205 patients. In this study, age of 45-55 years and high waist circumference, that is,  $>90$  cm for both sexes (OR: 4.94, 95%CI: 2.34-10.42,  $P < 0.001$ ) were strong predictors of diabetes among TB patients. Additionally, severe underweight was also associated with DM among male TB patients (OR: 2.52, 95%CI: 1.34-4.74,  $P = 0.004$ ).

Infections like TB are often associated with reactionary hyperglycemia that may resolve following appropriate treatment hence lowering rates of factual DM.<sup>[24]</sup> In the study by Mugusi *et al.*,<sup>[26]</sup> a documented decrease in the crude diabetes prevalence rate from 6.5% to 4% was noted following a repeat OGTT on 25 patients with an initial diagnosis of DM. In another similar study by Oluboyo and Erasmus<sup>[27]</sup> an OGTT after 3 months of anti-TB treatment later found only one patient to be frankly diabetic compared with three at initiation of anti TB therapy.

Compelling evidence shows that DM alters the clinical presentation of TB and its outcomes in terms of causing delayed sputum/culture conversion, increased case fatality, and treatment failure.<sup>[36]</sup> In a large cross-sectional study by Faurholt-Jepsen *et al.*,<sup>[37]</sup> performed in Mwanza, Tanzania among 1250 urban TB patients, DM was associated with small changes in TB manifestations. TB patients with DM comorbidity had a higher neutrophil count ( $0.5 \times 10^9$  cells/L, 95% CI: 0.2-0.9,  $P = 0.001$ ) than nondiabetic TB patients. Serum C-reactive protein (18.8 mg/L, 95% CI: 8.2-29.4,  $P = 0.001$ ) and alpha-1-acid glycoprotein (0.2 g/L, 95% CI: 0.03-0.3,  $P = 0.02$ ) as acute phase reactants were also similarly higher in patients with diabetes. Self-report of fever as a symptom of TB was also more frequent among

diabetics with TB patients compared with those without DM (OR: 2.9, 95% CI: 1.5; 5.7,  $P = 0.002$ ). There was no difference in mycobacterium TB positive culture status and HIV sero positivity between the two groups.

In relation to clinical recovery or treatment outcome in the same study, patients with TB-DM comorbidity experienced a slower improvement in weight and haemoglobin concentrations compared to those with TB alone at 2 and 5 months of follow-up.<sup>[38]</sup>

Faurholt-Jepsen *et al.*,<sup>[39]</sup> in a prospective cohort study of the same study population also demonstrated that DM is a strong predictor of early mortality during anti TB treatment. In the initial 100 days, diabetes was associated with a fivefold increased risk of mortality [relative ratio (RR): 5.09, 95% CI: 2.36-11.02,  $P < 0.001$ ] among HIV uninfected, and a twofold increase among HIV coinfecting patients (RR: 2.33 95% CI: 1.20-4.53,  $P = 0.012$ ). However, it was not associated with long-term mortality.

Screening of TB patients for DM in Africa and other TB endemic regions using either a 75g OGTT, measurement of glycosylated hemoglobin, fasting or random blood sugar level, is therefore, of paramount importance; because DM is associated with adverse clinical outcomes and greatly alters clinical presentation. Screening for DM is also advised before initiation of anti-TB therapy and later in the course of the disease (preferably 3 months after initiation of therapy) to exclude reactionary hyperglycaemia that resolves with treatment.<sup>[40,41]</sup>

Treatment of DM among patients with TB should involve the use of insulin or oral hypoglycaemic agents (OHAs) in order to achieve the optimal goals of therapy, that is, maintaining an HbA1c of  $<7\%$ , random blood sugar level  $<180$  mg/dL or a FBG level  $<120$  mg/dl.<sup>[42]</sup> However, therapeutic doses of most glucose lowering drugs may need to be increased during the initial phases of TB treatment. This is because rifampicin induces an acute transient hyperglycemia due to its effect of augmenting intestinal absorption of glucose.<sup>[43]</sup> Due to its cytochrome P450 enzyme inducing properties, it also augments hepatic metabolism of most OHAs.<sup>[44]</sup> Patients should receive standard anti-TB therapy of 6 or 8 months depending on the regimen used with pyridoxine supplementation.

### Disorders of calcium and vitamin D metabolism

Hypercalcemia is known to be associated with chronic granulomatous diseases like TB. This is due to increased tissue conversion of 25-hydroxyvitamin D3 (25(OH) D3) to 1,25-dihydroxyvitamin D3 (1,25(OH) 2D3) or calcitriol.<sup>[45]</sup> The frequency of hypercalcemia among TB patients in

Africa varies among countries mainly due to the differences in the prevalence of coexisting vitamin D deficiency (VDD) and extent of calcium intake.

To my knowledge, hypercalcemia among African TB patients has been documented in 3 published studies.<sup>[46-48]</sup> Dosumu and Momoh<sup>[48]</sup> in a cross-sectional study to determine the prevalence of hypercalcemia among 120 newly diagnosed TB patients in Nigeria found a prevalence of 27.5%. However, only 12% of the patients had symptomatic hypercalcemia warranting medical intervention.

Majority of the African studies have documented no occurrence of hypercalcemia with corrected hypocalcaemia predominating.<sup>[49-54]</sup> This high frequency of hypocalcaemia is due to the high prevalence of coexisting VDD among African TB patients. Vitamin D has a physiological role of increasing intestinal absorption of calcium.<sup>[45]</sup>

VDD has been described among African TB patients living in developed countries<sup>[55]</sup> and in Africa. The prevalence of VDD among TB patients in Africa is reported to range from 8.5% to 62.7%.<sup>[49-54,56]</sup> This discrepancy in the frequency is probably due to the differences in geographical locations of the countries, dietary habits, baseline HIV coinfection, and techniques of vitamin D measurement.

Darker skin pigmentation, chronic infections like HIV, malabsorption, lower sunshine exposure, and renal and liver dysfunction have been described as risk factors for VDD.<sup>[57]</sup> Unequivocal evidence suggests a very close link between VDD and TB.<sup>[58]</sup> Adequate vitamin D levels in form of calcitriol are associated with increased production of cathelicidin by the immune cells. This is an antimicrobial peptide with proven antimycobacterial effects.<sup>[59]</sup> Calcitriol is also very essential in reducing the viability of *Mycobacterium* TB bacilli. This is by enhancing the process of fusion of the phagosome and lysosome in infected macrophages and increasing intra cellular oxidative stress.<sup>[60]</sup>

Due to the high prevalence of VDD among TB patients, additional research in form of randomized clinical trials to evaluate the effect of oral vitamin D and calcium replacement therapy on clinical outcomes and prevention of TB in Africa are justified.

### Thyroid dysfunction

Protracted critical illness is often associated with a disruption of the hypothalamic-pituitary-thyroid axis, resulting in reduced stimulation of the thyrotropes and impairment of thyroid hormones release.<sup>[61]</sup> Case reports of TB of the thyroid gland with subsequent destructive thyroiditis and thyroid dysfunction have also been documented.<sup>[3,62]</sup>

Thyroid dysfunction among adult patients with TB has been described in the African context.

Sick euthyroid syndrome is the most frequently encountered biochemical abnormality. In a cross-sectional study of 50 hospitalized patients with active TB in South Africa, 46 (92%) patients were found to have sick euthyroid syndrome.<sup>[13]</sup> The sick euthyroid syndrome in this study was defined as a serum free triiodothyronine (T3) concentration less than 3.3 pmol/L in the absence of clinical or biochemical features of primary or secondary hypothyroidism.

Kaplan *et al.*,<sup>[14]</sup> in another cross-sectional study done in South Africa reported a prevalence of sick euthyroid syndrome of 42% among 40 patients with active TB. Two (5%) patients had a biochemical picture of subclinical hypothyroidism. A reduced thyroid stimulating hormone level was noted to be significantly associated with HIV sero positivity (1.57 vs. 3.39 mIU/L,  $P < 0.006$ ) in this study. HIV sero status did not have any significant effect on the free thyroxine (T4) and triiodo thyronine (T3) concentrations.

A case report from Somalia documented a unique case of TB of the thyroid gland in an euthyroid young patient presenting as a thyroid mass.<sup>[62]</sup>

Alterations in thyroid gland function among critically ill patients have been highly associated with adverse patient outcomes and increased mortality.<sup>[61]</sup> Screening and treatment of thyroid dysfunction among suspected TB patients will, therefore, aid in determining and improving the prognosis. Thyroxine replacement therapy in critically ill patients with sick euthyroid syndrome is a very controversial issue and is not advocated. Usually, sick euthyroid syndrome resolves spontaneously with treatment of underlying disease.<sup>[61]</sup> Thyroxine replacement is recommended in all cases of hypothyroidism and selected cases of sub clinical hypothyroidism.<sup>[63]</sup>

### Hypogonadism

There are few studies on the magnitude of hypogonadism among TB patients in Africa. Male hypogonadism (primary and secondary) is a common endocrinopathy among TB patients especially in the setting of HIV coinfection. Two South African studies by Post *et al.*,<sup>[13]</sup> and Kaplan *et al.*,<sup>[14]</sup> reported prevalence of male hypogonadism among TB patients to be 73% and 88%, respectively. The prevalence of HIV sero positivity in the studies was 4% and 45%, respectively. The former study demonstrated a significant positive correlation between total serum testosterone levels and free serum T3 concentrations ( $P < 0.01$ ) and body mass index ( $P < 0.01$ ).<sup>[13]</sup>

Male hypogonadism is associated with unspecific clinical features like loss of libido, erectile dysfunction, increased body fat mass, reduced muscle mass and strength, gynecomastia, and reduced bone mineral density. Screening with an early morning serum free testosterone level is recommended in male TB patients suspected to have hypogonadism. Replacement therapy in cases of testosterone deficiency is highly advised to improve sexual performance and reduce the risks of pathological fractures, dyslipidemia, dysglycemia, obesity, and hypertension.<sup>[64]</sup>

## CONCLUSION

TB-associated endocrinopathies are not infrequent. Clinically, overt manifestations of these conditions are, however, unusual. Awareness about the occurrence of these endocrine disorders among adult patients with TB should be emphasized among clinicians working in the Africa and other high TB endemic regions. There is a compelling need to urgently recognize and efficiently manage these endocrinopathies, because early management is associated with improvement in the quality of life and reduction of mortality.

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