DIABETES MELLITUS AMONG PATIENTS WITH TUBERCULOSIS ATTENDING TB CLINICS IN DAR ES SALAAM

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MMed (Internal Medicine) Dissertation
Muhimbili University of Health and Allied Sciences
October, 2017

Muhimbili University of Health and Allied Sciences

Department of Internal Medicine

DIABETES MELLITUS AMONG PATIENTS WITH TUBERCULOSIS ATTENDING TB CLINICS IN DAR ES SALAAM

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A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Masters of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences.

Muhimbili University of Health and Allied Sciences
October, 2017

CERTIFICATION

The undersigned certify that, he has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled, ***"Diabetes mellitus among patients with tuberculosis attending TB clinics in Dar es Salaam"***, in (partial) fulfillment of the requirement for the degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied Sciences.

…….

Prof. Kisali Pallangyo

(Supervisor)

……

Date

DECLARATION AND COPYRIGHT

I, **Dr. Henrika Herman Kimambo**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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ACKNOWLEDGEMENTS

I wish to express my sincere gratitude to all those who in different ways they made the production of this dissertation possible.

First and foremost I would like to thank the Almighty GOD for the gift of life and health he has been granting me and all those who made this dissertation possible.

My sincere gratitude should extend to my employer Muhimbili National Hospital and TRIM-TB for funding this study.

I would like thank my supervisor Professor Kisali Pallangyo, for his guidance, patience and for taking much of his valuable time to contribute, guide and follow up this dissertation.

My sincere gratitude should also be extended to Dr C Moshiro, Dr R Mpembeni and Dr M Kazaura from the department of biostatistics (MUHAS) for their contribution and guidance in fulfillment of this dissertation.

I would like to thank all the staff members of the TB clinics at Temeke, Amana, Mwananyamala and Mbagala hospital for their support and contribution in the fulfillment of this dissertation.

I would like to thank my colleague Dr Johannes Ngemera who worked with me tirelessly in data collection.

Last but not least, I would like to thank all the patients who participated in this study for their tolerance despite the hard time they were going through.

DEDICATION

To Dr Elimath Martin my husband and our children Meshack, Gloria and Jeremy

To my parents Mr. and Mrs. H Kimambo

To Professor Kisali Pallangyo, my supervisor

ABSTRACT

Background: A bi-directional interaction between diabetes mellitus and tuberculosis is well established and has been likened to that between HIV and TB. Whereas HIV screening is standard of care test in sub Saharan Africa TB programs, the same as yet is not true for diabetes mellitus (DM). Sub Saharan Africa, a region with high TB infection rates, is going through an epidemiological transition period with rapidly rising prevalence of diabetes with majority being undiagnosed. We aimed at characterizing TB patients with DM in order to identify factors associated with TB-DM dual disease among patients attending TB treatment clinics in Dar es Salaam.

Objective: To determine the prevalence and describe the characteristics associated with diabetes mellitus among patients with tuberculosis attending TB clinics in Dar-es-salaam

Methodology: This was a clinic based descriptive cross sectional study among TB patient's ≥18years. Demographic information was collected and anthropometric measurements taken. Patients were then tested for diabetes using fasting blood glucose followed by 2hrs post prandial glucose (2h-PPG) after a 75g oral glucose load for those with impaired fasting blood glucose. The association between diabetes and clinical characteristics of the patients were examined using logistic regression analyses.

Results: A total of 660 TB patients were recruited into the study among whom 25(3.8%) were known diabetics. 39/635 (6.1%) patients were diagnosed to have DM and in additional 147/635(23.1%) patients had impaired fasting blood glucose. Therefore overall 64/660 (9.7%) of subjects had DM. Diabetes mellitus was more prevalent (15.6%) among TB patients aged ≥45years (p=0.01). Other independent risk factors for DM, on multivariate analysis were, a positive family history of DM (OR 2.8, 95%CI 1.52-5.06) p=0.001and overweight (OR 2.5, 95%CI 1.14-5.34) p=0.02.

Conclusions: Diabetes Mellitus was a frequent co morbid condition among TB patients in Dar es Salaam and majority of these TB patients had undiagnosed DM. Screening for DM should be advocated among TB patients aged ≥45 years, those who are overweight or obese and with family history of DM.

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LIST OF ABBREVIATIONS

ADA	American diabetic association
BMI	Body mass index
CAD	Coronary artery disease
CVD	Cerebral vascular disease
CSF	Cerebral spinal fluid
CT	Computed tomography
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
DOTS	Direct observed treatment
ESR	Erythrocytes sedimentation rate
EPTB	Extra pulmonary tuberculosis
FBG	Fasting blood glucose
FNAC	Fine needle aspiration cytology
GDM	Gestation diabetes mellitus
HbA1C	Glycated hemoglobin concentration
HCV	Hepatitis c virus
HLA	Human leukocytes antigen
HIV	Human immunodeficiency virus
HAART	Highly active antiretroviral therapy
IDF	International diabetic federation
IL	Interleukin
LAM	Lipoarrabinomanaan
MDR	Multidrug resistant tuberculosis
MHC	Major histocompatibility complex
MGIT	Mycobacterium growth indicator tube
MNH	Muhimbili national hospital
MOHSW	Ministry of health and social welfare
MTB	Mycobacterium tuberculosis

NADPH	Nicotinamide adenine di-nucleotide phosphate
NTLP	National tuberculosis and leprosy programme
OGTT	Oral glucose tolerance taste
PAD	Peripheral vascular disease
PCR	Polymerase chain reaction
PLWHI	People living with HIV
PI	Principal investigator
PTB	Pulmonary tuberculosis
RBG	Random blood glucose
TB	Tuberculosis
TNF	Tumor necrotic factor

CHAPTER ONE

1.0 INTRODUCTION

1.1 DIABETES MELLITUS

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the common phenotype of hyperglycemia. The disease was first recognized in 1500 BC by ancient Egyptians and the term diabetes was used by Greeks to describe a person with urinary frequency in whom urine also taste sweet(1).

Several distinct types of DM exist which results from complex interaction of genetics and environmental factors. The metabolic dys-regulation that occurs in DM leads to secondary pathophysiological changes in multiple organ systems which in turn increases likely hood of developing disease to patients and increased burden to the health care system in general.

1.1.1 Classification of Diabetes Mellitus

Currently diabetes mellitus is categorized into four types based on the etiology. Type 1 DM, type 2 DM, gestational diabetes mellitus (GDM) and other types of diabetes(2). Type 1 DM account for 5 to 10% of all cases(3). It is primarily due to pancreatic beta cell destruction attributed to either autoimmune process or unknown cause (idiopathic). Type 2 DM is the most common form and account for 90 to 95% of all cases(3). It is characterized by disorder of insulin action or secretion either of which can be the predominant feature. Both are usually present by the time type 2 DM manifest clinically. Obesity, physical inactivity, impaired glucose metabolism, GDM, family history of diabetes, older age, race/ethnicity are all associated with increased risk of developing type 2 DM.GDM is carbohydrates intolerance resulting in hyperglycemia of variable severity with onset or first recognized during pregnancy. It does not exclude the possibility that glucose intolerance may antedate pregnancy but may be previously unrecognized.

1.1.2 Disease Burden due to DM

Diabetes mellitus is now a world major health problem with its prevalence increasing with time. Data released by International diabetes federation (IDF) in 2012 show that there were estimated 371 individual with DM at that time and about 80% of these were people living in low to middle income countries (LMICs)(4). In 2015 there were 415 million people with DM in the world and the number was estimated to increase to 642 by 2040(5). The prevalence of diabetes has been significantly increasing in Tanzania since the 1980s when the prevalence was reported to be 0.9% in rural areas(6). In community survey conducted two decade ago the prevalence of diabetes was reported to be <2% and >5% in rural and urban areas respectively(7). The prevalence among Asian population was found to be higher >9%(8).There is no recently conducted prevalence survey but according to data from IDF(2015) and WHO(2016) the prevalence of diabetes in adult aged 20-79yrs was 3.5 % and 4.3% respectively(5)(9).

1.1.3 Pathophysiology of DM

Type 1 DM is the culmination of lymphocytic infiltration and destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas(10). As beta-cell mass declines, insulin secretion decreases until the available insulin no longer is adequate to maintain normal blood glucose levels. When 80-90% of the beta cells are destroyed, hyperglycemia develops and diabetes may be diagnosed(10). Patients need exogenous insulin to reverse this catabolic condition, prevent ketosis, decrease hyperglucagonemia, and normalize lipid and protein metabolism. Currently, autoimmunity is considered the major factor in the pathophysiology of type 1 DM. Approximately 85% of type 1 DM patients have circulating islet cell antibodies, and the majorities have detectable anti-insulin antibodies before receiving insulin therapy. The most commonly found islet cell antibodies are those directed against glutamic acid decarboxylase (GAD)(10). Polymorphisms of the class II human leukocyte antigen (HLA) genes that encode DR and DQ are the major genetic determinants of type 1 DM with 95% of type 1 DM patients having either HLA-DR3 or HLA-DR4.

Type 2 DM is characterized by a combination of peripheral insulin resistance and inadequate insulin secretion by pancreatic beta cells. Insulin resistance, which has been

attributed to elevated levels of free fatty acids and pro-inflammatory cytokines in plasma, leads to decreased glucose transport into muscle cells, elevated hepatic glucose production and increased breakdown of fat(11)**.** A role for excess glucagon cannot be underestimated; indeed, Type 2 DM is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hyperglucagonemia and hence the consequent hyperglycemia(11).

1.1.4 Clinical Presentation and Complications

Many patients have insidious onset of hyperglycemia and are asymptomatic initially particularly type 2 DM. The classical symptoms of DM are polyuria, polydypsia, polyphagia, nocturia, fatigue and weight loss. All these symptoms reflect abnormal glucose, fat and protein metabolism associated with insulin deficiency and insulin resistance seen in diabetics. Patients with DM are prone to both acute and chronic complications of the disease. Acute complications include diabetic ketoacidosis (DKA) commonly seen in type 1 DM patients and hyper-osmolar non ketotic diabetic coma (HHS) which occur in patients with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and electrolytes imbalance and acid-base abnormalities. Chronic hyperglycemia in patients with DM is mostly responsible for chronic complications that affect multiple organ systems. These chronic complications are responsible for majority of morbidity and mortality seen in diabetic patients(10).

Common proposed theories on mechanism on how hyperglycemia cause chronic complications in diabetics are formation of advanced glycosylation end products, activation of sorbital pathway, and increased formation of diacylglycerol followed by activation of protein kinase and increased flux of hexosamine pathway(10). Most of these mechanisms lead into formation of growth factors and reactive oxygen species which cause cellular and organ dysfunction. Macrovascular complications of DM include coronary artery disease, peripheral vascular disease and cerebral vascular disease and the microvascular complications include diabetic retinopathy, nephropathy and neuropathy. Non-vascular complications include diabetic gastroparesis, genitourinary

complications, increased risk to bacterial, viral and fungal infections and skin complications(10).

1.1.5 Diabetes Mellitus and Infections

DM has been associated with reduced response of T cells, neutrophil function, and disorders of humoral immunity(12)(13)(14). Consequently, DM increases the susceptibility to infections, both the most common ones as well as uncommon infections such as rhinocerebral mucormycosis, malignant otitis externa and gangrenous cholecystitis which are almost exclusively confined to people with diabetes mellitus(14). Such infections in addition to the repercussions associated with its infectivity may trigger DM complications such as hypoglycemia and ketoacidosis. Mechanisms responsible for increased risk to infections in diabetes are as detailed hereunder.

1.1.5.1 Complement

Although some studies have detected a deficiency of the C4 component in DM(15)(16) this reduction of C4 is probably associated with polymorphonuclear dysfunction and reduced cytokine response(12)(15).

1.1.5.2 Inflammatory cytokines

Mononuclear cells and monocytes of persons with DM secrete less interleukin-1 (IL-1) and IL-6 in response to stimulation by lipopolysaccharides(12)(14). It appears that the low production of interleukins is a consequence of an intrinsic defect in the cells of individuals with DM(12)(17). However, other studies reported that the increased glycation could inhibit the production of IL-10 by myeloid cells, as well as that of interferon gamma (IFN-γ) and tumor necrosis factor (TNF)-α by T cells. Glycation would also reduce the expression of class I major histocompatibility complex (MHC) on the surface of myeloid cells, impairing cell immunity(18).

1.1.5.3 Polymorphonuclear and mononuclear leukocytes

Decreased mobilization of polymorphonuclear leukocytes, chemotaxis and phagocytic activity may occur during hyperglycemia(14)(19)(20). The hyperglycemic environment also blocks the antimicrobial function by inhibiting glucose-6-phosphate dehydrogenase(G6PD), increasing apoptosis of polymorphonuclear leukocytes and reducing polymorphonuclear leukocyte transmigration through the endothelium(14). In tissues that do not need insulin for glucose transport, the hyperglycemic environment increases intracellular glucose levels, which are then metabolized using nicotinamide adenine di-nucleotide phosphate (NADPH) as a cofactor. The decrease in the levels of NADPH prevents the regeneration of molecules that play a key role in antioxidant mechanisms of the cell, thereby increasing the susceptibility to oxidative stress.

Regarding the mononuclear lymphocytes, some studies had demonstrated that when the glycosylated hemoglobin (HbA1c) is <8.0%, the proliferative function of CD4 T lymphocytes and their response to antigens is not impaired(14).

1.1.5.4 Antibodies

Glycation of immunoglobulin occurs in patients with diabetes in proportion with the increase in HbA1c, and this may harm the biological function of the antibodies(14). However, the clinical relevance of these observations is not clear, since the response of antibodies after vaccination and to common infections is adequate in persons with DM(14).

1.1.5.5 Major infections associated with Diabetes Mellitus

Respiratory tract infections are responsible for a significant number of medical appointments by persons with DM compared to those without DM(14). The most frequent respiratory infections associated with DM are caused by Streptococcus pneumoniae and influenza virus(19). Patients with diabetes are at higher risk of contracting tuberculosis than individuals without DM(21). Some studies have reported that persons with DM are more likely to develop multi- drug resistant tuberculosis and that treatment failures and death are more frequent in these patients(22). The association of these two diseases poses a major burden to the health public system, especially in the

developing countries where tuberculosis is one of the most important causes of bacterial infection and the prevalence of type 2 DM is increasing. Urinary tract infections (UTIs) are more prevalent in individuals with DM and may evolve to complications and/or serious manifestations(23). Acute pyelonephritis is 4–5 times more common in individuals with DM. Most infections are caused by Escherichia coli or Proteus sp(19). The clinical presentation is similar to that of non-diabetic individuals, except for the bilateral renal involvement(14). Additionally, persons with DM are at increased risk for complications such as perinephric and/or renal abscesses, emphysematous pyelonephritis (EP) and renal papillary necrosis(14)(19). Several studies, from different countries, have reported that 13–33% of patients with HCV infection have diabetes, mostly type 2 DM (24). Persons with DM are more predisposed to skin and soft tissue infections such as folliculitis, furunculosis, and subcutaneous abscesses. These infections may break out during the course of the disease or may be the first sign of DM presentation and can also be more severe in these populations(14).Invasive external otitis is an infection of the external auditory canal that can extend to the skull base and adjacent regions(19). It often affects elderly diabetic individuals and the etiologic agent is usually Pseudomonas aeruginosa. Mucormycosis is a rare opportunistic and invasive infection caused by fungi of the class Zygomycetes. Approximately 50% of the cases in individuals with mucormycosis have DM.

1.2 TUBERCULOSIS

Tuberculosis (TB) is a chronic bacterial infection caused by mycobacterium tuberculosis (MTB) that most often affects the lungs. These micro-organisms usually enter the body by inhalation through the lungs. Basically there are two types, pulmonary tuberculosis (PTB) which affects the lungs and is the commonest form of TB and the infectious form of the disease and extra pulmonary tuberculosis (EPTB) in which the disease affects organs other than the lungs. TB may affect any part of the body.

1.2.1 Tuberculosis disease burden

About one third of the world's population is infected with Mycobacterium tuberculosis. Among the communicable diseases, TB is the second leading cause of death worldwide

after HIV-AIDS, killing nearly two million people each year. There were an estimated eight million to nine million new cases of TB in 2000, but less than one half were actually reported. Most cases (5 million to 6 million) occur in those aged 15 to 49 years, with significant socioeconomic impact(25). Sub-Saharan Africa has the highest incidence rate (approximately 300/100,000 population/year)(26). Ongoing intensified efforts against TB through introduction of Direct observed treatment strategy(DOTS) in 1994 followed by stop TB strategy in 2006 led to significant global decrease in incidence, prevalence and mortality of TB between 2000 and 2014. However the burden of disease including mortality due to TB remained high in most sub-Saharan African countries including Tanzania(27).

Tanzania is among 22 high TB burden countries in the world and has the 8th highest burden in Africa(26). WHO estimates the prevalence of all form of TB in 2013 at 172(92-277) per 100,000 population and the incidence at 164(157-170) per 100,000 with an estimated case detection of 79% (77-83). TB mortality was estimated to be at 12 per 100,000 for both HIV positive and negative individual(26). According to the first national TB prevalence survey which was completed in 2012 the prevalence of bacteriological confirmed TB was 295 per 100,000 in adult population above 15 years(28). The prevalence was higher in rural compared to urban area, in men compared to women, in older people compared to younger individual and in people with lower socio-economical status than those with higher socio-economical status.

1.2.2 Natural history of tuberculosis

TB transmission occurs almost exclusively from human to human; a prerequisite is having contact with a source case. More than 80% of new TB cases result from exposure to sputum smear-positive cases, although smear-negative, culture-positive cases can be responsible for up to 17% of new cases(29). Tuberculosis is spread by airborne droplet nuclei, which are 1- to 5-µm particles containing 1 to 400 bacilli each. They are expelled in the air by coughing, sneezing, singing, laughing, or talking, and remain suspended in the air for many hours. They can be inhaled and subsequently entrapped in the distal airways and alveoli. There, bacilli are ingested by local macrophages, multiply within the cells and, within 2 weeks, are transported through the lymphatics to establish

secondary sites (lymphohematogenous spread). After inhalation, the pathogenic bacilli start to replicate slowly and continuously and lead to the development of a cellular immunity in about 4 to 6 weeks. T lymphocytes and local (pulmonary and lymphatic node) macrophages represent key players in limiting further spread of bacilli in the host. This can be seen at the pathologic level, where the bacilli are in the center of necrotizing (caseating) and non-necrotizing (noncaseating) granulomas, surrounded by lymphocytes and macrophages(10).The infected macrophages release interleukins 12 and 18 (IL-12 and IL-18), which stimulate CD4-positive T lymphocytes to secrete IFN-γ (interferon gamma), which in turn activate the macrophage phagocytosis of M. tuberculosis and the release of TNF-α. TNF-α has an important role in granuloma formation and the control of infection(10). Some of the bacilli remain viable, or dormant, for many years. This stage is called latent TB infection (LTBI), which is generally an asymptomatic, radiological undetected process in humans. Sometimes, a primary complex (Ghon complex) can be seen radiographically, mostly in the lower and middle lobes, and comprises the primary lesion, hilar lymphadenopathy, with or without a lymphangitic track. Later, the primary lesion tends to become calcified and can be identified on chest radiographs for decades(10).

Under certain conditions of immature or dysregulated immunity, alveolar macrophages and the subsequent biologic cascade could fail in limiting the mycobacterium proliferation, leading to primary progressive tuberculosis; this is seen mostly in children younger than 5 years or in HIV-positive or profoundly immunosuppressed individuals. Factors known to influence this unfavorable course are patient's age, nutritional status, host immunity, and bacterial infective load(10)(30).

1.2.3 **Biological interactions between DM and TB**

DM increases the general risk to infections. DM impair cell mediated immunity by impairing the function and activation of microphages, monocytes and lymphocytes with additional potential role played by pulmonary microangiopathy, renal dysfunction and vitamin deficiencies(12) There are fewer T lymphocytes and reduced neutrophil count in diabetics.

A reduced Th1 immune response, TNF alpha production, IL-1 beta and IL- 6 production is seen in people with concomitant TB and DM as compared to non diabetic individual(12)(22)(31). Th1 cytokines play a vital role in control and inhibition of mycobacterium tuberculosis bacilli. The decrease in T lymphocytes number and activity is primarily responsible for increased susceptibility of diabetics to TB. Macrophage function is also inhibited in diabetics with an impaired production of reactive oxygen species and phagocytic and chemotactic function. It is important to remember that T lymphocytes and local (pulmonary and lymphatic node) macrophages play a key role in limiting further spread of bacilli in individuals who are infected with MTB. This immune dysfunction in diabetics results into failure in limiting the mycobacterium proliferation, leading to development of TB disease.

Also hyperglycemia has been assumed to favor growth, viability and propagation of tubercle bacilli. It is also thought that the concomitant increase of dextrose in tissues results in decreased resistant to infections in situ and impair repair capacity. Predilection to infection is also attributed to local tissue acidosis and electrolytes imbalance. Patients with uncontrolled hyperglycemia appeared to be at an higher risk than those with controlled hyperglycemia, this suggest that uncontrolled hyperglycemia play important role in interaction between TB and DM(32)(33).

1.3 LITERATURE REVIEW

1.3.1 DM is a risk factor of active tuberculosis infection

In general, infectious diseases are more frequent and/or serious in patients with diabetes mellitus, which potentially increases their morbidity and mortality(19). Diabetes is an independent risk factor for all lower respiratory tract infections including those due to MTB. In a meta-analysis which included 13 observational studies, random effects meta-analysis of 3 cohort studies showed that DM was associated with an increased risk of TB (relative risk 3.11) and 8 case-control studies were heterogeneous and odds ratios ranged from 1.16 to 7.83(34). Studies have shown that patients with type 1 DM are more susceptible than those with type 2 DM. This higher susceptibility may be related to a longer duration of disease or could be due to the fact that control of hyperglycemia is more difficult among type 1DM as compared to type 2 DM(35). A study done in Tanzania showed that patient with type1DM has three to five fold increased risk of developing TB than type 2 DM patients(36). Higher prevalence of type 2 DM compared to type 1 DM makes it important risk factor for TB as type 1 DM. Higher prevalence of type 2 DM among patients with diabetes in TB population has been documented in several studies(37)(38)(39). A review of several studies on screening of DM among TB patients concluded that both type1DM and type 2 DM are associated with increased risk of TB and type 2 DM is most often undiagnosed(40).Type 2 DM is often asymptomatic and development of TB may be the first sign of its presence. DM among TB patients is often undiagnosed particularly in LMIC due to weak healthy systems. Several studies revealed higher prevalence of undiagnosed DM among TB patients (21)(41)(42)(43) and all these studies were conducted in LMICS. In populations with a higher incidence of TB, DM is a more important risk factor for TB. Overall, the risk of tuberculosis attributed to diabetes is 15%(44). At an individual level, Acquired immunodeficiency syndrome (AIDS) is a more potent risk factor for TB in comparison to DM, but the high frequency of DM at the population level makes its effect on the TB burden increasing. In communities with a high burden of HIV infection, the effect of DM may be masked by HIV(22).

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1.3.2 Burden of DM among TB patients

Prevalence of diabetes among patients with tuberculosis varies widely in different regions and depends on prevalence of both TB and DM on those areas. Highest prevalence is reported in regions with high DM prevalence. A systematic review of screening studies conducted in different settings found the prevalence of DM among TB patients to range from 1.9% to 35% with this proportion being influenced by burden of both TB and diabetes in those setting(40). Fewer studies that has been conducted in Tanzania reported the prevalence of diabetes among TB patients to be 6.7%,16.7% and 16.4%(41)(45)(46). Majority of diabetic patients among TB cases were found to be newly diagnose in most of the studies(21)(41)(42)(43). A study done in Tanzania in 1990, 73% of all diagnosed with diabetes among TB patients were new cases(41). Screening helps in early detection of these patients who need extra attention and care for better TB treatment outcome and prevention of chronic diabetes complication.

Different diagnostic methods have been used but no data are available on most suitable method of diagnosing DM through screening among TB patients. Different studies prefer different diagnostics test including fasting plasma glucose (FPG), random blood glucose (RBG), oral glucose tolerance test (OGTT), urine glucose and glycosylated hemoglobin concentration HbA1c(33)(38)(47). In a study done in Guinea in 2006 symptoms of hyperglycemia led to the diagnosis of all diabetic cases identified in that study(37). Measurements of 2 hours PG has been reported to be more sensitive than FPG and RBG. HbA1c can provide the mean blood glucose concentration of 3month prior to the test, now recommended by WHO and ADA as a diagnostic test for DM in the general population. HbA1c is expensive and not widely available in LMICs. Transient hyperglycemia is frequent in active tuberculosis and diagnosis of diabetes need confirmation after TB treatment(48).Screening is recommended to be done early during TB diagnosis and be repeated later after treatment. Transient hyperglycemia always regresses after starting treatment. In a study done in 1990 using OGTT as diagnostic criteria 28% of TB patients who initially were diagnosed to have DM had normal glucose tolerance after repeated test following completion of TB treatment(41).

1.3.3 Characteristics or predictors of DM among TB patients

There is no direct evidence on the most cost effective approach to identify individuals with undiagnosed, symptom free diabetes in low resource settings. Predisposing factors for diabetes in LMICs have been poorly assessed. Interestingly, a number of these factors, such as tobacco, alcohol and malnutrition, are associated with both TB and diabetes**.**

Old age, obesity, physical inactivity, life style and family history of diabetes are risk factors for diabetes found among TB patients(37)(44). Age was the factor that was significantly associated with prevalence of DM among TB patients. Diabetic TB patients are usually 10-20 years older than those without DM as type 2 DM is associated with older age. In poor resource settings it might be worth focusing screening DM in TB patients above 40 years(43). Published studies found no difference in terms of gender between diabetic and non-diabetic patients(44). Central obesity and alcohol consumption has been reported to be common among TB-DM cases, but no difference has been reported on smoking habit between TB-DM patients compared to Non-diabetic TB patients(49).

Studies reported similar occurrence of symptoms of TB between diabetic and Non-diabetic TB patients(22)(37)(50)(51)(52).Weight loss and fatigue were frequently reported in patient with dual disease. Extra pulmonary TB was reported to be less common among diabetic patients compared to non diabetic(22)(37)(44)(50)(51)(52). There is contradiction in sputum smear results in TB patients with diabetes. Some studies reported higher rates of sputum smear negative among diabetics(53) while other studies reported high numbers of tubercle bacilli in sputum smear on TB-DM patients(22)(51)(54). Report from different studies on radiological presentation of TB in diabetic patients are conflicting, some reported similar radiological findings to TB patients with and without diabetes(53)(54)(55) while other studies reported presence of multiple cavities and nodular lesions on the lungs, with more lower lobe involvement, being common among DM-TB patients(51)(56)(57).In conclusion, based on systematic reviews of different available literature, TB patients with DM are usually older and have higher body weight, but it remains uncertain whether DM affects clinical presentation of

TB. Differences in patient selection and case definitions used for DM may explain some of the discrepancy between different studies(44).

1.4 PROBLEM STATEMENT

The prevalence of diabetes worldwide has increased by about 20% in the past three decades with particularly large rates in LMICs(58). Furthermore IDF predicts further increase in prevalence of DM especially in developing countries in the foreseeable future due to changes in life style, eating habits and other risk factors(59). Indeed reports from developing countries indicate a steadily increasing prevalence of DM among the general population. Ongoing intensified efforts against TB led to significant global decrease in incidence, prevalence and mortality of TB between 2000 and 2014. However the burden of disease including mortality due to TB remained high in most sub-Saharan African countries including Tanzania.

Diabetes is a risk factor for lower respiratory tract infection including those due to mycobacterium tuberculosis. The decrease in T lymphocytes number and activity is primarily responsible for increased susceptibility of diabetics to TB. Macrophage function is also inhibited in diabetics with an impaired production of reactive oxygen species and phagocytic and chemotactic function.

Fifteen percent of TB cases globally are estimated to be attributed to diabetes mellitus(44). The review of screening studies conducted in different settings found the prevalence of DM among TB patients to range from 1.9% to 35% with this proportion being influenced by burden of both TB and diabetes in those setting(40). Fewer studies that has been conducted in Tanzania reported the prevalence of diabetes among TB patients to be 6.7%,16.7% and 16.4%(41)(45)(46) Majority of diabetic patients among TB cases in conducted studies were asymptomatic for DM, had type 2 DM and were newly diagnosed(42)(43). TB-DM dual disease has been reported to be associated with TB relapse, TB treatment failure, increased mortality and poor control of diabetes mellitus in setting of chronic infections(51). The reported increasing prevalence of DM in Tanzania where there is high TB burden will most likely lead to increasing proportion of TB patients with DM which will negatively influence TB treatment outcome and affect Tuberculosis control . In particular there is a need to characterize TB patients with DM in order to identify them early and to treat both conditions not only to improve TB treatment outcome but also to prevent other complications associated with poorly controlled DM.

1.5 STUDY RATIONALE

The burden of Tuberculosis in Tanzania is high (295/100,000 population). On the other hand the prevalence of diabetes mellitus is reported to be increasing rapidly especially in low and middle income countries, Tanzania included. It is known that a high TB burden in a given population (Tanzania) is associated with high transmission rates in the population in question especially among those with DM who are also at increased risk of developing clinical TB following infection.

Furthermore, DM is associated with poor TB treatment outcomes, with higher rates of relapse, failure and death. Consequently, early detection of diabetes among TB patients and prompt treatment of both conditions is essential and could improve treatment outcomes and prevent development of other chronic complications of uncontrolled DM.

Prevalence of DM among TB patients and predictors or characteristics associated with DM among TB patients is largely unknown in Tanzania. The NTLP guidelines do not indicate weather TB patients should be screened for DM or who among TB patients should be screed for DM. Results from this study will provide current status on prevalence of DM among TB patients and which of these patients if any should be screened for DM. Early detection of these individual with TB-DM dual disease will help in TB control and prevention of chronic DM complication**.** Knowledge about risk factors for diabetes in TB patients may help in reserving costly and labor intensive diabetes diagnostics.

1.6 OBJECTIVES

1.6.1 Broad objective

To determine the prevalence and describe the characteristics associated with diabetes mellitus among patients with tuberculosis attending TB clinics in Dar-es-salaam.

1.6.2 Specific objectives

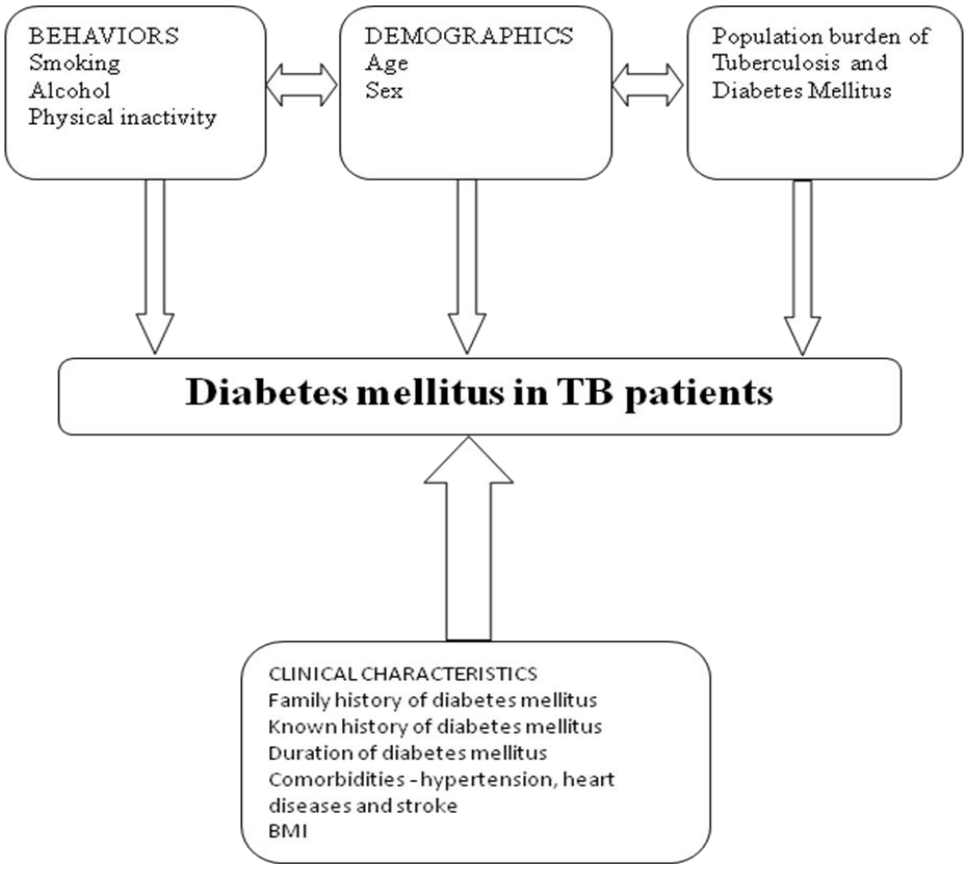
1. To determine the prevalence of diabetes mellitus among patients with tuberculosis attending TB clinics in Dar-es-salaam.
2. To determine the proportion of TB patients with impaired fasting glucose among patients with tuberculosis attending TB clinics in Dar-es-salaam.
3. To describe characteristics associated with diabetes mellitus among patients with tuberculosis attending TB clinics in Dar-es-salaam.

1.7 HYPOTHESIS

Patients with TB have higher chances of having diabetes mellitus (with known or unknown DM diagnosis).Association between TB and DM depends on patient's age, body weight, level of physical activities and family history of diabetes mellitus.

1.8 CONCEPTUAL FRAMEWORK

This conceptual framework summarizes factors that can affect the presence of DM among TB patients.



Source: Designed by Henrika Kimambo.

Figure 1: Conceptual framework for factors associated with DM among TB patients.

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design

This was a TB clinic based descriptive cross sectional study done to determine the prevalence of diabetes among patients with tuberculosis.

2.2 Study duration

The study was conducted for a period of 6 month (1st Sept 2016 to 31st Jan 2017).

2.3 Study area

The study was conducted at TB clinics in four hospitals in Dar-es-salaam that include Mwananyamala, Amana and Temeke and Mbagala hospital. The clinics where the study was conducted were conveniently accessible and represent TB clinics in three districts in Dar es Salaam. Each clinic receives about 30 TB patients per day. TB clinics provide diagnostic services for TB suspects, direct observed treatments to TB cases and follow-ups for patients on treatment.

2.4 Study population

Patients with pulmonary or extra-pulmonary tuberculosis attending TB clinics at above mentioned hospitals during the study period.

2.5 Inclusion criteria

TB patients who were eighteen years or older and on TB treatment

2.6 Exclusion criteria

Pregnant women with TB

2.7 Sample size calculation

The sample size was calculated using formula for sample size calculation on prevalence studies which was

$$n = \frac{Z^2 P (1-P)}{E^2}$$

Where by n - the sample size

Z -A standard normal variate at 5%type I error ($P<0.05$) it is 1.96

P-Expected proportion in population based on previous studies

E- Absolute error or precision

The sample size was calculated using the prevalence obtained by study done in Mwanza(45) which found the prevalence of diabetes in culture confirmed PTB cases to be 16.7% (n=803).

The power of this study was 80%, with an absolute error/precision of 3%, 10% non response rate/attrition rate.

Hence from the formula above the calculated sample size was 594.

The sample size calculated after considering 10% attrition rate was 660, calculated with formula below;

N=n x 100/ (100-f %)

f% is attrition rate, n=594, hence N=660

2.8 Key study definitions

BMI interpretation was according to WHO classification as shown in table1.

Table 1: WHO classification of BMI

Classification	**BMI in Kg/m^2**
Underweight	<18.5
Normal weight	18.5 – 24.9
Overweight	25 – 29.9
Obese	≥ 30

Table 2: ADA diabetic diagnostic criteria for diagnosis of DM (2009)

AIC≥6.5%.The test should be performed in a laboratory using method that is NGSP certified and standardize to the DCCT assay
FPG ≥ 126mg/dl(7.0mmol/l).Fasting is defined as no caloric intake for at least 8 hours.
2-h plasma glucose ≥ 200mg/dl(11.1) during an OGTT
RPG ≥ 200mg/dl(11.1mmol/l) in patient with classic symptoms of hyperglycemia or hyperglycemia crisis.

2.9 Sampling technique

We consecutively enroll TB patients on treatment for tuberculosis aged 18 years or above who consented to participate in the study.

2.10 Data Collection

Data was collected using an interviewer based structured questionnaire. A research assistant conducted face to face interviews and physical examination. Information collected included socio-demographic characteristics, symptom screen for diabetes, risk factors for type 2 diabetes including physical activity, alcohol consumption, cigarette smoking and a past medical history related to diabetes. We also collected information on sputum smear status, TB anatomical site, TB treatment category, and HIV status from the participants TB treatment cards.

We measured the participant's weight and height using standard equipment based at the TB clinics thereafter computed body mass index (BMI).

A capillary fingertip blood sample was collected from each patient for fasting blood glucose and two hour post prandial blood glucose assessment for participants with impaired fasting blood glucose using a the standard ACCU-CHECK blood glucose meter. All participants with impaired fasting blood glucose were given 75mg of oral glucose that was followed by a two-hour post-prandial collection of capillary blood sample for glucose testing. The American Diabetic Association (ADA) diagnostic criteria were used for diagnosis of diabetes(60). Diabetes was defined as either a fasting blood glucose level of >6.9mmol/L or a 2-hour postprandial glucose level of ≥11.1mmol/L for patients with impaired fasting glucose levels of 5.6mmol/L- 6.9mmol/L.

2.11 Data processing and analysis

Data were entered into EPI data software; checked for consistency, validity and missing information. Analysis was done using SPSS version 23.0. Continuous variables were summarized into frequency, mean and standard deviation. Categorical variables were analyzed by chi square test. Odds ratio and 95% CI were estimated using univariate and multivariate logistic regression analysis to identify the association between variables and occurrence of diabetes. P values <0.05 was considered statistically significant.

2.12 Ethical approval

Ethical clearance was obtained from the Research and Publications Committee of MUHAS. Permission to conduct this study was obtained from the District medical officers for each district hospital where the study was conducted. Only patients who consented to participate in the study were enrolled. Confidentiality on patient information was maintained.

CHAPTER THREE

3.0 RESULTS

3.1 Social demographic and clinical characteristics of the study participants

Of the 660 study participants enrolled, majority were male 416(63.0%). The mean age of the study participants was 39.2 years (S.D-14.3). The age range was between 18years and 85years and 220(33.3%) of participants were 45years and above. Majority of participants were married 355(53.8%), had primary education level 430(65.2%) and were employed 484(73.3%). Family history of DM was reported by 166(17.6%). One hundred and eight (27.3%) and 267(40.5%) had ever smoked and use alcohol respectively. Majority had low level of physical activities 3849(58%). (Table 3)

The mean BMI was 21.0 kg/m^2.HIV co-infection was documented in 212(32.1%) and 90.1% of them were on ART. Five hundred and seventy seven (87.4%) patients had pulmonary tuberculosis. Among patients with PTB 60.3% had positive sputum smear at the time of TB diagnosis. Drug resistant tuberculosis was documented in 14(2.1%) TB patients. Majority of participants were in continuation phase of Anti-TB therapy 391(59.2%). (Table 4)

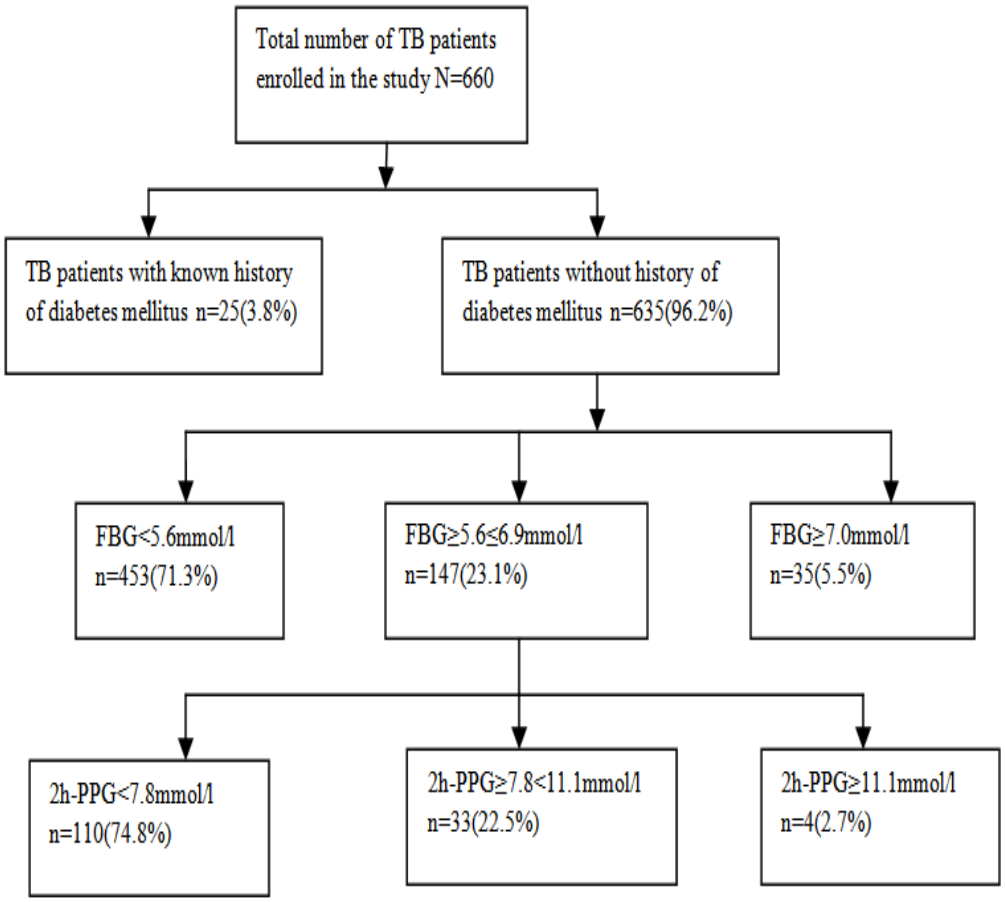


Figure 2.0: Recruitment flow chart

Table 3: Socio-demographic Characteristics of Study Participants (N=660)

Characteristic		n	%
Sex	Male	416	63
	Female	244	37
Age groups (years)	≤24	87	13.2
	25-34	181	27.4
	35-44	172	26.1
	≥45	220	33.3
Mean age(years) & standard deviation	39.2±14.25		
Highest education level	No formal education	65	9.8
	Primary	430	65.2
	Secondary	121	18.3
	College	44	6.7
Marital Status	Single	188	28.5
	Married	355	53.8
	Divorced	117	17.7
Occupation	Unemployed	145	22
	Employed	484	73.3
	Retired	31	4.7
Family history of diabetes	Yes	116	17.6
Cigarette smoking	Ever smoked	180	27.3
Alcohol use	Ever used	267	40.5
Physical Activity	Low	383	58
	Moderate	252	38.2
	High	25	3.8

Table 4: Clinical Characteristics of Study Participants (N=660)

Characteristic		n	%
Body mass Index Kg/M^2	Underweight	173	26.3
	Normal	398	60.4
Missing(n=1)	Overweight	66	10.0
	Obesity	22	3.3
Mean Body mass Index Kg/M^2	21.3		
Polyuria		110	16.7
Polyphagia		68	10.3
Polydypsia		82	12.4
Nocturia		151	22.9
Loss of weight		479	72.6
Fatigue		375	56.8
Blurred vision		100	15.2
Fasting blood glucose levels			
In mmol/L (n-635)	Normal	453	71.3
	Impaired fasting glucose	147	23.1
	Diabetes	35	5.5
Oral glucose tolerance test (n=147)	Normal	110	74.8
	Impaired glucose tolerance	33	22.5
	Diabetes	4	2.7
Sputum Acid fast bacilli status	Positive	398	60.3
Tuberculosis anatomical site	Pulmonary	577	87.4
TB treatment category	First line	578	87.6
	First line re-treatment	68	10.3
	Second line	14	2.1
Tuberculosis treatment phase	Intensive	269	40.8
	Continuation	391	59.2
HIV status	Infected	212	32.1
On HIV treatment	Yes	191	90.1

3.2 Prevalence of DM and IFG among TB patients

The recruitment flow diagram (Figure 2) summarizes the flow of study participants. Twenty five of 660 (3.8%) TB patients enrolled in the study were known to suffer from DM. Of the 635 study participants with no history of DM, 39 (6.1%), were newly diagnosed diabetics giving overall prevalence of diabetes in this population of 9.7%, 95%CI (7.4-12.0). The prevalence of IFG was 23.1%, 95%CI (19.6-26.6). OGTT was done to 147 patients with IFG, 33(22.5%) out of 147 patients with impaired fasting glucose had impaired glucose tolerance and 4(2.7%) had diabetes mellitus. (Table 4)

3.3 Characteristics of TB patients with DM

Table 5 summarizes the characteristics of study subjects with DM, age of >44 years was associated with a higher prevalence (54.7% Table 5) of diabetes among TB patients ($p<0.001$). DM was more prevalent in TB patients who had a normal BMI 54% compared to patients who were underweight 20.6%, overweight 19% or obese 6.3% ($p=0.031$). There was no association between DM and clinical type of TB or results of sputum smear for acid fast bacilli.

Table 5: Characteristics of study subject with diabetes

Characteristic		Diabetes n=64	Non-diabetes n=596	Total	p-value
Sex	Male	43 (67.2%)	373 (62.6%)	416 (63.0%)	
	Female	21(32.8%)	223(37.4%)	244(37%)	0.499
Mean age		44.9	38.6	39.2	0.001
Age group in years	≤ 24	3 (4.7%)	84 (14.1%)	87 (13.2%)	
	25-34	10 (15.6%)	171 (28.7%)	181 (27.4%)	
	35-44	16 (25.0%)	156 (26.2%)	172 (26.1%)	0.001
	>44	35 (54.7%)	185 (31.0%)	220 (33.3%)	
Marital status	Never married	11 (17.2%)	177 (29.7%)	188 (28.5%)	
	Married	43 (67.2%)	312 (52.3%)	355 (53.8%)	0.057
	Divorced	10 (15.6%)	107 (18.0%)	117 (17.7%)	
Highest education level	No formal education	3(4.4%)	62 (10.4%)	65 (9.8%)	
	Primary	47 (73.4%)	383 (64.3%)	430 (65.2%)	0.32
	Secondary	9 (7.8%)	112 (18.8%)	121 (18.3%)	
	College	5 (7.8%)	39 (6.5%)	44 (6.7%)	
Occupation	Unemployed	11 (17.2%)	134 (22.5%)	145 (22.0%)	
	Employed	49 (76.0%)	435 (72.9%)	484 (73.3%)	0.708
	Retired	4 (6.3%)	27 (4.5%)	31 (4.7%)	
Family history of diabetes	Yes	24 (37.5%)	92 (15.4%)	116 (17.6%)	
	No	40 (62.5%)	504 (84.6%)	544 (82.4%)	<0.001
Cigarette smoking	Ever smoked	18 (28.1%)	162 (27.2%)	180 (27.3%)	
	Never smoked	46 (71.9%)	434 (72.8%)	480 (72.7%)	0.69
Alcohol use	Ever used	26 (40.6%)	241 (40.4%)	267 (40.5%)	
	Never used	38 (59.4%)	355 (59.6%)	393 (59.5%)	0.791
Physical Activity	Low	36 (56.3%)	347 (58.2%)	383 (58.0%)	
	Moderate	23 (35.9%)	229 (38.4%)	252 (38.2%)	0.206
	High	5 (7.8%)	20 (3.4%)	25 (3.8%)	
Body mass Index Kg/M^2	Underweight	13 (20.6%)	160 (26.8%)	173 (26.3%)	
	Normal	34 (54.0%)	364 (61.1%)	398 (60.4%)	0.031
	Overweight	12 (19.0%)	54 (9.1%)	66 (10.0%)	
	Obesity	4 (6.3%)	18 (3.0%)	22 (3.3%)	
Sputum smear for AFB	Positive	41(64.1%)	357(59.9%)	398(60.3%)	0.52
	Negative	23(35.9%)	239(40.1%)	262(39.7%)	
Anatomical site of TB	PTB	57(89.1%)	520(87.2%)	577(87.4%)	0.68
	EPTB	7(10.9%)	76(12.8%)	83(12.6%)	

3.4 Predictors of DM among TB patients

The predictors for diabetes in patients with TB were as summarized in Table 6. In univariate analysis there was a trend indicating that an increase in age was associated with an increase in risk for diabetes with age of >44 years having an odd of 5.3 (95% CI: 1.58-17.71). Most symptoms of diabetes were associated with increased odds for diabetes on univariate analysis however after controlling for other factors this association was lost. After controlling for other factors age >44 years {OR 5.18, 95% CI [1.45-18.55]}, a family history of diabetes {OR 2.96, 95% CI [1.59-5.53]} and overweight {OR 2.53,95% CI [1.12-5.35]} were associated with an increased risk for diabetes while, low physical activity {OR 0.25, 95% CI [0.08-0.79]} moderate physical activity {OR 0.25, 95% CI [0.79-0.82]} and HIV {OR 0.35, 95% CI [0.17-0.73]} seemed to decrease the risk for diabetes in TB patients.(Table 6)

Table 6: Predicators for Diabetes among TB patients

Predicator		Diabetes	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Age group years	≤ 24	3 (4.7%)	Ref	
	25-34	10 (15.6%)	1.64 (0.44-6.11)	1.77 (0.45-6.99)
	35-44	16 (25.0%)	2.87 (0.81-10.14)	3.66 (0.96-13.86)
	>44	35 (54.7%)	5.30 (1.58-17.71)	5.18 (1.45-18.55)
Sex	Male	43 (67.2%)	Ref	
	Female	21(32.8%)	0.82 (0.47-1.41)	0.97 (0.47-1.99)
Polyuria	No	40 (62.5%)	Ref	
	Yes	24 (37.5%)	3.56 (2.04-6.20)	1.43 (0.45-4.53)
Polyphagia	No	45 (70.3%)	Ref	
	Yes	19 (29.7%)	4.71 (2.56-8.68)	2.55 (0.68-9.53)
Polydypsia	No	44 (68.8%)	Ref	
	Yes	20 (31.35)	3.91 (2.17-7.06)	1.10 (0.26-4.64)
Nocturia	No	38 (59.4%)	Ref	
	Yes	26 (40.6%)	2.58 (1.51-4.41)	1.08 (0.46-2.56)
Weight loss	No	17 (26.6%)	Ref	
	Yes	47 (73.4%)	1.05 (0.59-1.88)	1.59 (0.73-3.49)
Fatigue	No	24 (37.5%)	Ref	
	Yes	40 (62.5%)	1.30 (0.76-2.21)	0.86 (0.44-1.67)
Blurred Vision	No	46 (71.9%)	Ref	
	Yes	18 (28.1%)	2.45 (1.36-4.44)	1.59 (0.79-3.18)
Family history of Diabetes	No	40(62.5%)	Ref	
	Yes	24 (37.5%)	3.29 (1.89-5.71)	2.96 (1.59-5.53)
Cigarette Smoking	Never	46 (71.9%)	Ref	
	Stopped	16 (25.0%)	1.15 (0.63-2.10)	0.79 (0.36-1.75)
	Current	2 (3.1%)	0.61 (0.14-2.63)	0.44 (0.85-2.27)
Alcohol consumption			Ref	
	Never	38 (59.4%)		
	Stopped	25 (39.1%)	1.05 (0.61-1.78)	1.34 (0.15-11.96)
	Current	1 (1.6%)	0.52 (0.07-3.99)	0.90 (0.09-8.28)
Physical Activity	Low	36 (56.3%)	0.41 (0.15-1.170	0.25 (0.08-0.79)
	Moderate	23 (35.9%)	0.40 (0.14-1.17)	0.25 (0.79-0.82)
	Vigorous	5 (7.8%)	Ref	
HIV	Negative	53 (82.8%)	Ref	
	Positive	11 (17.2%)	0.41 (0.21-0.79)	0.35 (0.17-0.73)
Body mass index (kg/m^2)	Normal	34 (54.0%)	Ref	
	Underweight	13(20.6%)	0.9 (0.59-1.70)	1.11 (0.51-5.12)
	Overweight	12 (19.0%)	2.33 (1.15-4.84)	2.53 (1.12-5.35)
	Obesity	4 (6.3%)	2.43 (0.81-7.43)	3.21 (0.93 – 11.1)

CHAPTER FOUR

4.0 DISCUSSION

4.1 Prevalence of diabetes among TB patients

This clinic based descriptive cross-section study demonstrated that about 10% of patients attending TB clinics in Dar-es-salaam had diabetes mellitus (DM). Interestingly only one third of them reported to be aware of having DM and two thirds were not known to have diabetes. The prevalence of Diabetes mellitus found in this study is higher than the estimated prevalence of 3.5% and 4.3% among adults aged 20-79years by 2015 IDF and 2016 WHO country profile respectively(9)(61).

The observed high prevalence of DM among TB patients in this study is in keeping with findings from other recent studies done in Ethiopia (15.8%), Uganda (8.5%), Nigeria (12.3%) and Mwanza, Tanzania 16.4%(43)(46)(62)(63).The prevalence of DM among TB patients in the published African studies ranges from 2.1% to 16.7%(37)(43)(46)(62)(63)(64)(65)(66). The different prevalence rates could be explained by the varying diagnostic techniques used in these studies, socio-demographic characteristics of source populations and the prevalence of both TB and DM in the respective general populations in which the studies were performed.

Similar studies from other parts of the world have reported remarkably higher prevalence rates of DM among TB patients. In Asia the documented prevalence varies from 9.5%-44%(38)(51)(67)(68)(69). A multi centre study done in Texas, USA and Mexico reported prevalence of 39% and 36% respectively(21). This higher prevalence rates could probably be due to the higher background prevalence of DM in the general population in those respective countries.

Two thirds (39/64) of the TB patients with diabetes mellitus in this study had no prior history of the disease i.e. they were diagnosed during this study. Similar observations have been reported in other studies(21)(22)(41)(42)(43). The presence of undiagnosed DM in these individuals could be among the factors that predisposed them to develop active TB. A high index of suspicion, routine enquiry for DM symptoms among TB

patients may identify some patients but many will be missed. Hence routine testing for blood glucose is required to confirm/exclude DM.

The overall prevalence of Impaired Fasting Glucose (IFG) among TB patients in this study of 23.1% is higher than the IDF estimated population prevalence of 9.1% for Tanzania(61). In addition population based survey) in Tanzania reported IFG prevalence rates of 3.6% and 4.7% among men and women respectively(7). The prevalence reported in this study is higher than reported from Indonesia (3.7%) but lower than that reported in studies done in Guinea Conakry (31%), Ethiopia (26.7%), Mwanza, Tanzania (37.6%) and India (24.5%)(37)(43)(46)(68). The high IFG found in TB patients may be attributed to stress hyperglycemia because of TB co-morbidity; it is nonetheless an indicator of future risk. Appropriate changes in lifestyle, health promotion and follow-up may prevent or delay the onset of T2DM in a substantial number of these cases.

4.2 Predictors of diabetes among TB patients

Age above 45 years, family history of diabetes and overweight are independently associated with DM among the study participants. The increase in proportion of TB patients with DM by age in this study is comparable to estimated increased prevalence of DM by age in the general population(61). Several studies have found association between increasing age, overweight, obesity and physical inactivity with DM among TB patients(21)(37)(38)(67). This study didn't demonstrate an association between obesity and DM among TB patients probably because of few numbers of obese participants (3.3%) in the study. Family history of DM was associated with DM among TB patients in this study similar to findings from other studies(37)(67). There was no difference in prevalence of DM among men and women with TB which is consistence with finding reported in other studies(46)(62). In contrast other studies reported higher prevalence of DM among male TB patients(39)(43). TB-DM patients did not present with classical symptoms of DM namely polyuria and polydypsia, this is in contrast to the study done in Guinea Conakry in 2006 where by questioning led to finding of symptoms of hyperglycemia in all newly diagnosed cases of DM(37).Significant weight loss and fatigue observed in this study could be much explained by active TB.

The analysis of this study found a negative relationship between DM and HIV co-infection among TB patients. This finding is consistent with findings in other two studies where HIV was reported to be protective(45)(62). The relationship is in contrast with the fact that HIV and ART are strongly associated with higher prevalence of metabolic syndrome and DM(70). In addition higher incidence of new onset DM in HIV infected individuals has been reported(71). Further investigations are needed to explore this association.

The major challenge in making diagnosis of DM among TB patients is the influence of infection induced hyperglycemia particularly at the time of TB diagnosis or early after initiation of anti-TB medication. This can lead into over diagnosis of DM in patients with active TB. Indeed blood glucose in the diabetic range levels, among some TB patients, have been shown to decrease to normal range during the course of TB treatment(41)(65).Screening for DM in TB patients should be done early at TB diagnosis or at the time for initiation of anti-TB, hyperglycemia should be controlled and these patients should be followed up after the course of anti-TB for confirmation of DM. All patients with diabetic range blood glucose in this study were referred to diabetic clinic for follow up and confirmation of DM.

CHAPTER FIVE

5.0 STRENGTH AND LIMITATIONS

5.1 Strength of the study

Screening for DM at TB clinics in our study was feasible and led to detection of unknown DM cases and patients with impaired glucose tolerance. All 39 TB cases with DM were sent to diabetic clinics for treatment and follow-up.

5.2 Study limitations

An OGTT is more sensitive in detecting DM than other glucose tests but it was difficult to perform this test to all study participants because of the study setting. The study didn't involve follow up of study participants with impaired glucose tolerance test if these participants are a potential for future diabetes or the impaired glucose tolerance was a response to TB induced hyperglycemia. It would be of interest to re-examine these participants after they have completed TB treatment.

CHAPTER SIX

6.0 CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

DM was a frequent co morbid condition among TB patients in Dar es Salaam and majority of these TB patients with DM had undiagnosed diabetes mellitus. Age ≥45years, positive family history of DM and overweight were factors independently associated with DM among TB patients. These findings were similar to previous studies conducted elsewhere. Screening for DM among TB patients should be advocated to TB patients above 45years who are overweight or obese and with positive family history of diabetes mellitus.

6.2 Recommendation

TB patient's aged ≥45 years with a positive family history of DM who are overweight or obese should be screened for diabetes mellitus. Patients with hyperglycemia should be followed up for confirmation of DM because stress induced hyperglycemia usually regressed following initiation of anti-TB treatment.

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APPENDIX I

QUESTIONNAIRE

Serial NO……. Date……

Mobile phone NO……

Residential address (street/house NO)…….

SOCIAL DERMOGRAPHIC DATA

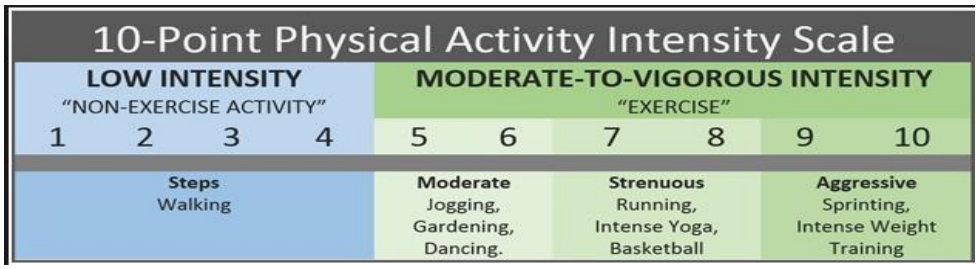
1. Age -------
2. Sex
    a. Male
    b. Female
3. Marital Status
    a. Single
    b. Married
    c. Divorced
    d. Separated
    e. Widowed
    f. Cohabiting
4. Education level
    a. No formal education
    b. Primary school education
    c. Secondary school education
    d. College/University education
5. Occupation
    a. unemployed
    b. self employed
    c. Government/private employed
    d. Student
    e. Retired

PART B: DM Screening

6. Symptoms of Diabetes (Yes/NO for each symptom)
    a. polyuria
    b. polyphagia
    c. polydypsia
    d. Nocturia
    e. un-intentional weight loss
    f. Fatigue
    g. blurring vision(constant/intermittent)
7. Past medical history
    a. DM----------if yes, Year of diagnosis&medication----------
    b. HTN-------if yes, year of diagnosis&medication----------
    c. Heart disease----------if yes, year of diagnosis&medication----------
    d. stroke----------if yes ,year of diagnosis&medication----------
8. Family medical history of DM
    a. Yes
    b. No (if No go to Qn 10)
9. If yes in Qn 8 above then DM is present in
    a. one parents
    b. Both Parents
    c. Grand parents
    d. Others
10. History of cigarette smoking
    a. Never smoked
    b. Stopped smoking
    c. Current smoker
11. History of alcohol consumption
    a. Never taken alcohol
    b. Stopped taking alcohol
    c. Current alcohol use

12. Level of physical activities before illness (using 10 points physical intensity scale below)

a. Low intensity
b. Moderate intensity
c. Vigorous intensity



Physical activity intensity scale adopted from: www.dansplan.com

13. Measurements

Weight (kg) …….

Height (cm) ……

BMI …….

FBG (mmol/l) …….

OGTT (if FPG ranges from 5.6mmol/l to 6.9mmol/l) …….

PART C: TB HISTORY

14. Sputum smear status at diagnosis

a. Smear positive
b. Smear negative

15. HIV Status

a. Positive; if yes then go to Qn16,but if the answer is b or c then go to Qn 17
b. Negative
c. Unknown

16. History of using HAART

a. Yes
b. No

17. Anatomical site of disease

a. PTB
b. EPTB
c. PTB+EPTB

18. TB treatment group
    a. New case
    b. Relapse patient
    c. Treatment after failure Patient
    d. Treatment after lost of follow-up
    e. Drug resistant patient
19. Treatment regimen
    a. I(1^{st}line)
    b. II(1^{st}line) retreatment
    c. III(2^{nd}line drug)
20. TB drugs treatment phase
    a. Intensive phase
    b. Continuation phase

APPENDIX II: INFORMED CONCENT FORM (ENGLISH VERSION)

Consent to participate in the study titled "Prevalence of diabetes among patients with tuberculosis attending TB clinics in Dar-es-salaam".

Greetings: I am Dr Henrika Kimambo, a postgraduate student doing a research on prevalence of diabetes among patients with tuberculosis attending TB clinics in Dar-es-salaam.

Purpose of the study: To determine the prevalence and factors associated with diabetes among TB patients.

What participation involved: If you agreed to participate in this study, your medical information will be used for research purpose.

Confidentiality: All information collected will be entered into computer with only an identification number, No name included.

Risk: we expect no harm to happen to you during the course of this study.

Right to withdrawal: Taking part in this study is completely voluntary and refusal to participate or withdrawal will not involve penalty or loss of any benefits to which you're entitled.

Benefits: The results from this study will be used as evidence based information for proposing routine screening of diabetes among all TB patients.

Who to contact : If you have any questions regarding this study, feel free to contact me, the investigator, Dr Henrika Herman Kimambo, MUHAS,PO BOX 65001, Dar-es-salaam, Tanzania. Mobile phone 0713 401745. E mail: henrika_k@yahoo.com

If you have any questions concerning your right as a participant, you may contact Prof Kisali Pallangyo, supervisor of the study, MUHAS, PO Box 65000, Dar es salaam, Tanzania. Mobile phone 0713 224 052. E mail: Kpallangyo@gmail.com

Signature

Do you agree; Patient/Relative…….

Participants does not agree……...

I' …… have read the consent form and my question have been answered and agree to participate in this study.

Signature: Participant/Relatives……..

Signature of investigator……

Date of signed consent……..

APPENDEX II: INFORMED CONSENT FORM (SWAHILI VERTION)

Ruhusa ya kushiriki utafiti kuhusu "Ukubwa wa tatizo la ugonjwa wa kisukari kwa wagonjwa wenye kifua kikuu wanaohudhuria vituo vya tiba ya kifua kikuu na ukoma katika hospitali za Amana, Mwananyamala, Temeke na Mbagala.

Mimi naitwa Dr Henrika Herman Kimambo ni mwanafunzi wa udhamili chuo kikuu cha tiba Muhimbili. Ninafanya utafiti kuangalia wingi wa ugonjwa wa kisukari kwa wagonjwa wenye kifua kikuu.

Dhumuni la utafiti huu : Kujua wingi wa ugonjwa wa kisukari na Kupata taarifa muhimu juu ya viashiria vya uwepo wa ugonjwa wa kisukari kwa wagonjwa wenye kifua kikuu.

Ushiriki : Kama unakubali kushiriki huu,taarifa zako za matibabu zitatumika kwenye utafiti huu.

Usiri : Taarifa zote za uchunguzi zitaingizwa kwenye kompyuta na nambari ya utambulisho; jina halitanukuliwa.

Madhara : Tunategemea kwamba hakuna madhara yoyote yatokanayo na utafiti huu.

Haki ya kujitoa kwenye utafiti : Kushiriki katika utafiti huu ni hiari na kutokubali kushiriki au kujitoa hautaadhibiwa au kupoteza haki yako ya matibabu.

Kutokea kwa madhara : Tunategemea kwamba hakuna madhara yoyote yatokanayo na utafiti huu. Hata hivyo kama madhara ya mwili yakitokea kutokana na utafiti huu utatibiwa kilingana na kanuni na taratibu za matibabu ya Tanzania.

Faida za kushiriki kwenye utafiti: Kama utakubali kushiriki kwenye utafiti huu, faida utakazopata ni pamoja na kuonwa na kufuatiliwa kwa ukaribu na daktari anayefanya utafiti.Tunatumaini kwamba taarifa zinazopatikana zitawanufaisha wengine pia.

Kwa mawasiliano zaidi: Kama una maswali kuhusu utafiti huu uwe huru kuwasiliana na mtafiti , Dr Henrika Herman Kimambo,Chuo kikuu cha afya na tiba Muhimbili, P.O Box 65001, simu 0713401745,barua pepe: henrika_k@yahoo.com

Kama una swali kuhusu haki yako kama mshiriki wasiliana na Prof K Pallangyo,msimamizi wa utafiti, P.O Box 65001,simu 0713 224 052, barua pepe: Kpallangyo@gmail.com

Saini:

Je, umekubali kushiriki? .....

Mshiriki hajakubali kushiriki ……

Mimi …… Nimesoma maelezo na kuyaelewa vizuri,
na nimekubali kushiriki kwenye utafiti huu.

Sahihi ya mshiriki ……

Sahihi ya mtafiti ……..

Tarehe ……