OSTEOPOROSIS AMONG TUBERCULOSIS PATIENTS IN PENANG, MALAYSIA: EVALUATION OF TREATMENT OUTCOMES, KNOWLEDGE AND HEALTH BELIEFS

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by

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LIST OF ABBREVIATIONS

AFB	Acid-Fast Bacilli
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANOVA	One-Way Analysis of Variance
BMI	Body Mass Index
BMD	Bone Mineral Density
BQI	Bone Quality Index
BUA	Broadband Ultrasound Attenuation
CRC	Clinical Research Centre
CXR	Chest X-ray
DOTS	Directly Observed Treatment Short Course
DXA	Dual Energy X-ray Absorptiometry
eBMD	Estimated Bone Mineral Density
ESR	Erythrocyte Sedimentation Rate
EMB	Ethambutol
EPTB	Extrapulmonary Tuberculosis
HBM	Health Belief Model
HPF	High Power Field
HPP	Hospital Pulau Pinang
HIV/AIDS	Human I^{mm}unodeficiency Viruses
INF-gamma	Interferon-gamma
IVDU	Intravenous Drug Users
INH	Isoniazid

KAP	Knowledge, Attitude and Practice
MREC	Medical Research Ethics Committee
MTB	Mycobacterium tuberculosis
NIH	National Institute of Health
NTP	National Tuberculosis Program
NCDs	Non-communicable Diseases
OHBS	Osteoporosis Health Belief Scale
OKT	Osteoporosis Knowledge Test
PZA	Pyrazinamide
QUS	Quantitative Ultrasound
RBC	Red Blood Cells
RT	Respiratory TB
RMP	Rifampicin
SOS	Speed of Sound
SI	Stiffness Index
TB	Tuberculosis
WBC	White Blood Cells
WHO	World Health Organisation
Xpert MTB/RIF	Gene Xpert MTB/RIF

LIST OF SYMBOLS

dL	Decilitre
kg	Kilogram
KHz	Kilohertz
gm	Gram
L	Litre
mm^3	Cubic Millimeters
MHz	Megahertz
μmol	Micromole
mg	Milligram
mL	Millilitre
m^2	Square metre
IU/L	International unit per litre
g/cm^2	Grams per Square Centimetre

OSTEOPOROSIS DALAM KALANGAN PESAKIT TUBERKULOSIS DI PULAU PINANG, MALAYSIA: PENILAIAN HASIL RAWATAN, PENGETAHUAN DAN KEPERCAYAAN TERHADAP KESIHATAN

ABSTRAK

Tuberkulosis (TB) adalah salah satu jangkitan manusia paling kuno, dengan bukti genetik lebih dari 17000 tahun dan penyakit berjangkit kedua yang paling banyak dikenalpasti di Malaysia. Osteoporosis, yang dicirikan oleh pengurangan jisim tulang dan kemerosotan mikro-arsitektur tisu tulang, masih kurang didiagnosis dan ditangani di Malaysia dan kelazimannya tidak diketahui atau didokumentasikan. TB dan osteoporosis adalah penyakit kronik dan hubungan antara mereka adalah kompleks. Penyelidikan mengenai jangkitan bersama ini masih belum ada. Kejadian osteoporosis, perkaitan dengan TB, pengetahuan dan kepercayaan kesihatan adalah penting bagi semua program pengurusan osteoporosis dan juga pra-syarat untuk mewujudkan peningkatan tingkah laku yang diinginkan. Tujuan kajian ini adalah untuk menilai prevalensi osteopenia dan osteoporosis, kadar penukaran sputum yang tertunda dan hasil rawatan berkenaan dengan osteoporosis dan tahap pengetahuan, keyakinan kesihatan terhadap osteoporosis di kalangan pesakit TB di Pinang. Sebanyak 430 pesakit TB didaftarkan di klinik pernafasan Hospital Palau Pinang. Penyebaran BMD, osteopenia dan osteoporosis normal di kalangan populasi kajian pada diagnosis adalah 24.8%, 41.6%, dan 33.4%, pada akhir fasa intensif adalah 27.0%, 33.9%, 39.1% dan pada akhir rawatan masing-masing adalah 28.1%, 42.9%, 29.0%. QUS (BMD normal, osteopenia dan osteoporosis) secara subjektif ditentukan oleh kombinasi faktor kognitif dan tingkah laku, serta data sosio-demografi. Peramal bebas yang mempunyai hubungan yang signifikan secara statistik untuk membezakan

kumpulan osteopenia dan osteoporosis dari BMD normal adalah usia, diabetes, lesi sinar-X dada (CXR). Sebanyak 80.6% peserta didiagnosis menghidap TB paru, di mana 63.1% daripadanya adalah kes positif sputum smear yang disahkan secara bakteriologi Di antara mereka, 27.4% mempunyai BMD normal, 33.8% dan 35.6% mempunyai osteopenia dan osteoporosis, masing-masing. Pada akhir fasa intensif, 11% pesakit gagal mencapai penukaran sputum smear. Dari jumlah tersebut, 8.3%, 8.8% dan 14.5% mempunyai BMD, osteopenia dan osteoporosis normalKajian itu tidak menemui kesan osteoporosis yang signifikan terhadap penukaran dahak. Prediksi penukaran sputum yang tertunda pada analisis multivariat adalah pesakit TB yang diundurkan, diabetes, lesi CXR yang jauh lebih maju, indeks jisim badan (BMI), dan sputum grading 3+. Kadar kejayaan rawatan TB adalah 69.1%. Sekiranya hasil rawatan TB yang tidak berjaya, hasil yang paling ketara adalah kematian 17.4%, dipindahkan keluar 9.5%, rawatan gagal bayar 3.5%, dan kegagalan rawatan 0.9%. Osteoporosis adalah faktor risiko bebas yang signifikan untuk jangkitan TB. Dari mereka, 21.1% pesakit dengan hasil rawatan yang tidak berjaya mempunyai BMD normal, 36.8% menderita osteopenia dan 42.1% menderita osteoporosis. Faktor lain yang berkaitan dengan hasil rawatan TB adalah pesakit negatif smear pulmonari, lesi CXR jauh lebih maju, HIV, pesakit tanpa bekas luka BCG, dan pesakit yang menjalani rawatan. Instrumen yang paling banyak digunakan untuk menilai pengetahuan dan keyakinan kesihatan osteoporosis adalah ujian pengetahuan osteoporosis (OKT) dan skala kepercayaan kesihatan osteoporosis (OHBS). Sebanyak 337 pesakit TB menunjukkan persetujuan mereka untuk mengambil bahagian dalam penilaian pengetahuan dan kesihatan. Hasil kajian menunjukkan bahawa 61.7% dan 72.5% pesakit TB mempunyai tahap pengetahuan dan kesihatan osteoporosis yang rendah. Disimpulkan bahawa keadaan kesihatan tulang membimbangkan di kalangan pesakit

TB. Hasil kajian ini sangat penting kerana ia menentukan faktor-faktor yang meramalkan keadaan kesihatan tulang dan membantu memulakan tingkah laku pencegahan osteoporosis di pusat-pusat rawatan TB. Penemuan kajian ini menunjukkan bahawa penilaian kesihatan tulang pesakit TB, pengetahuan dan kepercayaan kesihatan mereka terhadap osteoporosis sangat menjanjikan tetapi dapat ditingkatkan dengan memberikan perhatian yang signifikan dan menyoroti program pendidikan masa depan yang diperlukan untuk meningkatkan pengurusan klinikal osteoporosis.

OSTEOPOROSIS AMONG TUBERCULOSIS PATIENTS IN PENANG, MALAYSIA: EVALUATION OF TREATMENT OUTCOMES, KNOWLEGDE AND HEALTH BELIEFS

ABSTRACT

Tuberculosis (TB) is one of the most ancient human infections, with more than 17000 years of genetic evidence and the second most widely identified communicable disease in Malaysia. Osteoporosis, characterized by a reduction in the bone mass and micro-architectural deterioration of bone tissue, remains under-diagnosed and undertreated in Malaysia and the prevalence is not well known or documented. TB and osteoporosis are both chronic diseases and the research on this comorbid condition is scarce at present. Osteoporosis incidence, association with TB, knowledge, and health beliefs are pre-requisite for establishing desired behavioral improvements. Therefore, the present study aimed to assess the prevalence of osteopenia and osteoporosis, delayed sputum conversion rate and TB treatment outcomes among TB patients with weak bone health, the knowledge and health belief towards osteoporosis among study participants in Penang. A total of 430 TB patients were registered at the respiratory clinic of Hospital Pulau Penang. The prevalence of normal bone mineral density (BMD), osteopenia and osteoporosis among the study population at diagnosis was 24.8%, 41.6%, and 33.4%, at the end of the intensive phase was 27.0%, 33.9%, 39.1%, and at the end of treatment was 28.1%, 42.9%, 29.0%, respectively. Bone health (normal BMD, osteopenia, and osteoporosis) subjectively was determined by a combination of cognitive and behavioral factors, as well as socio-demographic data in the current study. The independent predictors that had a statistically significant relationship to distinguish TB with osteoporosis were age, diabetes, moderately

advanced chest X-ray (CXR) lesions. In the present study, greater numbers of participants (80.7%) were diagnosed with pulmonary TB, of which 63.1% were bacteriologically confirmed sputum smear-positive cases. At the end of the intensive phase, 11% of patients had failed to achieve sputum smear conversion. Of these, 8.3%, 8.8%, and 14.5% had normal BMD, osteopenia, and osteoporosis. The study found no significant effects of osteoporosis on sputum conversion. The predictors of delayed sputum conversion on multivariate analysis were retreated TB patients, diabetes, far advanced CXR lesion, body mass index (BMI), and sputum grading 3+. In the current study, the TB treatment success rate was 69.1%. In the case of unsuccessful TB treatment outcome, the most noticeable outcome was mortality 17.4%, transferred out 9.5%, defaulted 3.5%, and failure 0.9%. Osteoporosis was a significant independent risk factor for TB infection. Of them, 21.1% of patients with unsuccessful treatment outcomes had normal BMD, 36.8% had osteopenia and 42.1% had osteoporosis. The associated risk factors of TB treatment outcomes were pulmonary smear-negative patients, far advanced CXR lesions, HIV, patients without BCG scars, and retreated patients. Furthermore, the most widely used instruments to assess knowledge and health belief osteoporosis were the osteoporosis knowledge test (OKT) and osteoporosis health belief scale (OHBS).Total 337 TB patients showed their consent to participate in knowledge and health belief assessment. The study findings revealed that 61.7% patients had a low level of osteoporosis knowledge and 72.5% had low level health beliefs. It is concluded that the bone health condition is alarming among TB patients. The results of this study were of great importance as it specified the factors that predict bone health conditions.

CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 Tuberculosis

Tuberculosis (TB) is predicted to influence a human's health. It remains a significant cause of death worldwide, regardless of the discovery of its successful and in-expensive therapy (Glaziou et al., 2015). TB is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (*MTB*) which spreads through the air from person to person. TB primarily affects the respiratory organs, but it can also trigger other parts of the body, such as the brain, kidneys, spine, or intestines. However, the lungs are the predominant site of infection. Since respiratory droplets have been suspended in the air for many hours (figure 1.1), increases the risk of transmission is higher in crowded and low ventilated environments (Zaman, 2010). The severity of the disease depends on the involvement of both lungs (bilateral disease) and more of cavitary lesions, which are thought to be a significant source of transmission (Pai et al., 2016).

TB is one of the worst ancient human infections, with more than 17000 years of genetic evidence (Sandhu, 2011). Globally, TB is one of the primary causes of a single infectious agent, human immunodeficiency viruses (HIV). Millions of people suffering TB every year. In 2017, among HIV-negative people, TB accounted for approximately 1.3 million deaths (range, 1.2–1.4 million) 300,000 additional deaths (range, 266, 000–335, 000) among HIV-positive people caused by TB (WHO, 2018).

In developing countries, including Malaysia, TB continues to be the leading cause of comorbidities and mortality. TB is declining globally with the advent of chemotherapy since1940s while in the 1980s, standardized short courses were introduced. The declining trend of TB was observed in developed countries while this has not been apparent in developing countries (Chadha, 2009). Directly observed treatment (DOTS) is a standardized short course technique for the provision of primary TB diagnosis and cure. It is not solely a therapeutic solution to patients, but also a public health services management technique, including policy-making, case-identification by quality-assured bacteriology, short-term chemotherapy, patient compliance surveillance, appropriate medical supply, and sound systems of monitoring (Sandhu, 2011).

1.1.2 Osteoporosis and Osteopenia (weak bone density)

Osteoporosis is a disease defined as reducing bone mass and weakening of bone microstructure and porous bones that compromised the bones strength and intensifies fracture risk leading to higher morbidity and mortality incidence. Hip, spine, and wrist bone fractures causing death in elderly populations (Compston, 2001). Currently, the estimated number of people affected by osteoporosis worldwide is enormous. Approximately >200 million people suffer from osteoporosis, irrespective of gender and race, the prevalence of osteoporosis will keep growing as the population ages. Globally, 1 in 3 women more than the age of 50 years and 1 in 5 men will be suffering osteoporotic fractures in their lifetime, according to the International Osteoporosis Foundation (Cooper et al., 1992; IOF, 2017; Sözen et al., 2017).

Osteopenia is the condition that begins as you lose bone mass and your bones get weaker (Eriksen, 2012). Osteopenia occurs when your bones are weaker than normal but not so weak that they shatter easily, as in the case of osteoporosis (Xu et al., 2020). Bone contents and strength can be determined by estimating bone mineral density (BMD). BMD is defined as the measurement of the extent of minerals in bones and reflecting the strength of bones as signified by calcium content (Carnevale et al., 2004). It can be measured by several techniques as quantitative ultrasound (QUS) (Cournil et al., 2012) and dual-energy X-ray absorptiometry (DXA) considered a gold technique. The results are represented as T-scores or Z-scores (Handa et al., 2008). According to the World Health Organization (WHO) diagnostic classification, T-score and Z-score are parameters to define the bone strength or weakness (osteopenia or osteoporosis).

WHO and the National Institute of Health (NIH) have classified BMD as normal, osteopenia, and osteoporosis based on T-score or Z-score.

- Normal bone density: if T-scores lies within the range of +1 or −1 of the young adult mean
- Osteopenia: if T-score lies between -1 to -2.5.
- Osteoporosis: if T- score is -2.5 or lowers.

Z-score is also used to measure BMD of age, sex, and the ethnicity-matched reference population. Low BMD is considered for a Z-score ≤ -2 SD (WHO, 2018).

Early osteoporosis is not usually diagnosed and remains asymptomatic; it does not become clinically evident until fractures occur. Hip fractures and vertebral fractures are strongly associated with decreasing the hip BMD and spine BMD, respectively, and have been considered as the prototypical osteoporotic fractures.

Though the frequency of all other fractures (non-hip, non-vertebral) is numerically much higher, and these fractures generally result in much higher economic costs for the population (Bouxsein et al., 2019).

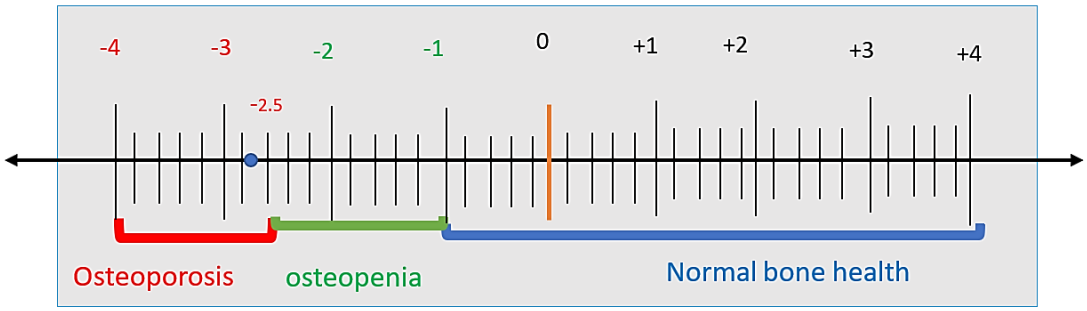

Figure 1.1 Classification of bone density measurements with reference to T-score. Modified from Understanding Bone density results: American bone health, 2020.
Source: https://americanbonehealth.org/bone-density/understanding-the-bone-density-t-score-and-z-score.

1.2 Geography of Malaysia

Malaysia is located in the Southeast Asia region. It is consists of two parts: Peninsular Malaysia to the west, lying between Singapore and Thailand, and the Sabah and Sarawak states, which are situated in the eastern part of the island shared by Indonesia and Borneo. Malaysia is divided into 13 states and including Kuala Lumpur (legislative capital) and one federal republic (Wilayah Persekutuan), and Labuan and Putrajaya (administrative capital). Malaysia lies entirely in the equatorial zone and is ranked as an intermediate TB burden country. The estimated population in 2020 is 29.7 million, 29% of which lives in the rural area (Aquastate, 2011). The average population density of Malaysia's capital Kuala Lumpur is 84 inhabitants/km^2.

1.3 Osteoporosis and TB in Malaysia

1.3.1 TB in Malaysia

The TB incidence rate in the country has fluctuated substantially between 2012 and 2019 (world bank, 2019). TB is the second most commonly reported communicable disease in Malaysia in 2001(Dony et al., 2004). The latest value of TB incidence (per 100,000 people) in Malaysia was 92.00 as of 2016. Over the past 16 years, the value for this indicator fluctuated between 68.00 in 2002 and 92.00 in 2016 (WHO, 2015). Ten to fourteen percent of TB cases were classified as extrapulmonary TB (EPTB) at tertiary care respiratory clinics (Khan et al., 2019; Nissapatorn et al., 2004). About 14% of PTB patients had also extrapulmonary involvement. Almost 20% of EPTB cases are diagnosed with HIV co-infection (Mohammad & Naing, 2004).

1.3.2 Osteoporosis in Malaysia

Osteoporosis is continued to be one of the most prevalent and costly diseases across Asia, with a rapidly increasing and aging population (Yeap et al., 2013). The osteoporosis prevalence rate increases markedly in those above 50 years of age among postmenopausal women in Asia (Gallagher & Tella, 2014; Ji & Yu, 2015). Another study reported that the prevalence of osteoporosis among postmenopausal women in central Malaysia was 24.1% (Lim et al., 2005). In Malaysia, the proportion of over the age of 60 years population will upsurge from 1.4 million in 1999 to approximately 3.3 million by 2020 (Mafauzy, 2000; Noor, 2002) and the aged population is more susceptible to osteoporosis. For over the last three decades, due to the fast-growing urbanization and economic situation in Malaysia, there has been a change observed in the diet and lifestyle with a rise in chronic diseases proportion (Tee, 1999). Therefore, fractures caused by osteoporosis can also be expected to burden the healthcare system

if effective and appropriate intervention and management are not carried out (Cotté et al., 2008).

1.4 Pharmacological link between TB and Osteoporosis

The pathogenesis of osteoporosis in TB-infected individuals has not been established. There are several mechanisms at the cellular level that linked osteoporosis with TB (Yeh et al., 2016). The interconnection between *MTB* and nonimmune cells, like the bone cells (osteocyte, osteoblast, and osteoclast), is not directly weakening or destroying, but indirectly cause a disturbance in the form of metabolism disruption and interruption in the growth of the bone cell (Florencio-Silva et al., 2015). The existence of *MTB* in the microenvironment of bone enlightens the link between bacteria and the nonimmune cells, which indicates the presence of bacteria in the organic and inorganic environment of bone (Jabir et al., 2017).

MTB utilizes the proteins as a medium to grow obtained from the bone cell's metabolism. The denaturation of protein compounds into simpler compounds and the availability of oxygen supply help to develop a new microenvironment that will be used by the bacteria (Jabir et al., 2017). Immune response and TB infection will cause a microvascular obstruction and result in bone cells necrosis as well as damage to the hard and soft tissues of bone. Bone cells death will subsequently generate discontinuity or gap among the bones structure and leads towards osteoporosis (Jabir et al., 2017).

Traditional pathophysiological models of osteoporosis concentrate on endocrine pathways such as estrogen or vitamin D deficiency and also secondary hyperparathyroidism (Cândido & Bressan, 2014). Osteoporosis is an anabolic bone disruption caused by osteoclastic cellular bone resorption which is not compensated

by osteoblastic bones formation (Kogawa et al., 2010). This leads to frail and weak bones, which increasing the fracture possibility. In bone metabolism, vitamin D plays an indirect role by regulating the plasma phosphorus and calcium in the body (Krela-Kaźmierczak et al., 2015). Vitamin D involves increasing the expression of RANKL, in osteoblast and inhibiting osteoclast activity, and combating the elevated level of PTH, endorsing bone formation, and preventing and treating osteoporosis (Krela-Kaźmierczak et al., 2015). Similarly, inadequate vitamin D is accompanied by the risk of TB infection, patients who had less concentration of vitamin D are associated with a 5-fold worse TB prognosis and greater susceptibility to developing TB (Holick, 2006; Talat et al., 2010).

Moreover, endocrine alterations and inflammatory cytokines such as IL6 (Interleukin 6), CRP (C- reactive protein), and TNF-α (Tumour necrosis factor-alpha), are directly involved in pathogenic mechanisms and also produced during infection that may improve bone turnover by activation of osteoclastogenesis (Kany et al., 2019).

Respiratory TB (RT) is one of the diseases that characterized the development of granulomas, mediated by interferon-gamma (IFN-gamma) cellular immune reactions, which control inflammatory reactions increased by TB (Kim et al., 1998). IFN-gamma expressions showed a positive linkage to bone fracture (Chen et al., 2017). as well as stimulates the release of neopterin. Therefore, neopterin elevation has also been associated with a high risk of hip fracture (Apalset et al., 2014). These previous findings revealed the association of RT with bone fracture, even in absence of comorbidities or steroid use. Holloway et al., (2013) studied that skeletal lesions grow and cultivate with bone fracture such as compression fracture in 3 to 5% of active TB

cases, in accordance with our study (Holloway et al., 2013). However, this hypothesis warrants further research. The mechanisms mentioned above are primary evidence of the interrelations of osteoporosis and TB, which urges us to study the synergistic impact of both diseases on patients.

1.5 Risk factors of Osteoporosis among TB patients

Osteoporosis is a public health hazard that aggravates the economic burdens and affects the financial resources for preventive and therapeutical programs (Sözen et al., 2017). Bone mass declines steadily and painlessly, leading to weak, frail, brittle bones that are vulnerable to fracture (NIH, 2019). Compared to other major illnesses, the fractures prevalence raises the mortality risk in men than women, and usually fracture survivors suffer poor quality of life and do not live independently (Haentjens et al., 2010). Osteoporosis thus became a common concern for public health. Women ≥ 50 years of age have a four times higher rate of osteoporosis and a two times higher rate of osteopenia, and they tend to have fractures 5 - 10 years earlier compared with men but mortality risk is higher among men (Alswat, 2017).

It is not restricted to increased risk in the elderly but in all age ranges. Osteoporosis among The population was associated with predictors such as older age, lower income, female gender, asthma, and chronic obstructive pulmonary disease (COPD) (Chen et al., 2017). Another study also indicated that the predictors of osteoporosis among TB patients were history of TB, scars on chest x-ray (CXR), smoking, alcohol, parathyroid hormone level, and education level (Choi et al., 2017).

1.6 TB and Osteoporosis knowledge and health belief

1.6.1 TB Knowledge

Knowledge regarding any illness or disorder is essential for rehabilitation and the good quality of life of patients. Knowledge is also recognized as a crucial factor in determining an individual's attitudes and practices. TB-related knowledge and awareness have been more widely observed among the affluent, educated, and senior community members (Solliman, 2012). Moreover, since the 1920s, TB has remained an occupational hazard and due to the number of TB outbreaks in healthcare, there is a need to focus on improving TB information and awareness among TB patients and their caregivers as well as healthcare workers (Wahab et al., 2016). Hence, low knowledge of TB, poor awareness of risk factors and lack of access to treatment facilities, and stigma have been documented as influencing factors against adequate TB care. Poor knowledge and perception of TB are prevalent in most developing countries, resulting in delayed diagnosis and treatment. Though, it is believed that the low case identification rate is suspected to be due to inadequate knowledge of the disease and it is perceived to be a serious challenge to TB control programs (Biya et al., 2014). TB control strategies cannot be successful unless erroneous beliefs among people are acknowledged and modified. Health education considers being a vital tool for promoting patient satisfaction and encourage their commitment to TB prevention (Nyasulu et al., 2018). In Malaysia, several studies are done for evaluating TB knowledge, attitude, and practices at the community level, at health care workers and professionals, at student level but there is scarce data about TB knowledge among TB patients (Mohamed, 2017; Ramli et al., 2018; Salleh et al., 2018; Wahab et al., 2016).

1.6.2 Osteoporosis knowledge

In the Asian region, osteoporosis is often left undiagnosed and untreated (IOF, 2017) and the increasing prevalence of osteoporosis in the Asian continent has also increased health expenditures on the disease (Haq et al., 2015). Assessment of osteoporosis knowledge is therefore required in the Asian region. Osteoporosis is a rising health issue because of severe nutritional deficiencies (NIH, 2019) as well as a lack of sufficient information about osteoporosis (Spencer, 2007). Literature about knowledge on bone health and its related risk factors has not been established among adults in the Malaysian community (Nadiah et al., 2010). The significant hurdles associated with osteoporosis management including the limited level of community knowledge and expertise and low priority for health professionals to implement effective preventive and curative programs (Cindaş & Savaş, 2004; Yeap et al., 2010)

1.6.3 Osteoporosis health belief

Osteoporosis health beliefs are part of theoretical models which predict improvements in preventive and therapeutical behaviors of osteoporosis (Nguyen, 2014). The Health Belief Model (HBM) is a theoretical model that can be used for directing health care promotion and disease prevention initiatives. It is used to clarify and forecasts the changes in health behaviors as perceived vulnerability, susceptibility, seriousness, and perceived benefits and barriers (Jones et al., 2015). Based on HBM, people change their behavior when they understand that the disease is serious. Otherwise, they might not turn to healthy practices. The structures of the HBM include perceived severity, perceived susceptibility, perceived benefits, perceived barriers, modifying variables, and cues to action (Razmara et al., 2018). A detailed understanding of knowledge, beliefs, dietary and lifestyle habits concerning bone

health status and osteoporosis prevention among individuals will eventually help to make better choices on how to optimize bone health (Jeihooni et al., 2015). Furthermore, osteoporosis knowledge and health belief are essential to all osteoporosis treatment programs and are also a necessity for achieving the desired behaviour improvements. Literature review on knowledge and health belief of osteoporosis has been conducted among the diabetic population of Malaysia (Abdulameer et al., 2019) but lacking among TB patients in Malaysia.

1.7 Rationale of the study

Osteoporosis in Malaysia is a rising health issue with a high economic burden and disability cost. In Malaysia, osteoporosis leading to hip fracture has been estimated at 27,000 people per year. The incidence of hip fracture is over 90 per 100,000 persons among 50 years old, and the cost of immediate hospitalization was 22 million Ringgit in 1997 (IOF, 2013).

Malaysia is a multiracial territory having three main ethnic groups, including Malays, Chinese, and Indians. It is well known that certain diseases affect a particular ethnic group more than others. A factor that represents cultural, social, dietary, geographical, and other differences among races, is significant in the study of disease incidence (Villa, 1994). Ethnic-specific data would be more useful than a sizeable racial overview, as BMD and incidence of osteoporosis differ among Asian ethnic groups (Villa & Nelson, 1996). The most significant medical consequence of osteoporosis is the fragility fracture which, without proper treatment, causes severe medical and psychosocial complications. The overall cost of osteoporosis treatment and associated fractures is rising (Loh & Shong, 2007).

Although the incidence of TB has declined worldwide, it remains a global health problem. East-Asia region covers 44% of the total TB incidence burden. In Malaysia, TB is a significant health problem with the current incidence rate of 92/100,000, and TB-related mortality rate is 4.1/100,000 population annually (WHO, 2019). TB is concomitant with a breakdown in the immune system that clarifies an established link between active TB disease and non-communicable diseases (NCDs) that may be the significant weakening factor of the immune system. Comorbid NCDs like osteopenia and osteoporosis augment adverse impacts on humans in the current era. The combining effect of them also results in a "double burden of disease" in developing countries (Bates et al., 2015).

Recent studies have reported the prevalence of osteoporosis among TB patients in Asian regions. RT is associated with bone fracture, even without comorbidities or steroid use reported in 3 to 5% of active cases of TB (Holloway et al., 2013). The male respiratory TB patients group had a 57% higher risk of fragility fracture compared to the non-RT (Yeh et al., 2016). Female TB patients were more likely at risk of osteoporosis than male TB patients (Chen et al., 2017). Hence, the highest prevalence of osteopenia and osteoporosis among TB patients described up to 58.6% and 14.6%, respectively (Choi et al., 2017). Several mechanisms have been proposed for TB-related osteoporosis. The pathophysiology of TB-induced osteoporosis is still arguable.

The previously mentioned studies were based on retrospective study design and provide limited information about the impact of osteoporosis on TB. There is a lack of information about osteoporosis prevalence among TB types and some other essential aspects, including sputum conversion rate, treatment outcomes are also missing, which are the most critical indicators of TB treatment efficiency. Several

studies are available on sputum conversion rate, delayed sputum conversion, and associated risk factors among TB worldwide but there is limited data on sputum conversion rate among TB patients who were also affected with osteoporosis. Simultaneously, the data about osteoporosis effect on the TB treatment success rate was also lacking. The following reasons urge us to design this comprehensive study. The purpose of this prospective study is to evaluate these essential parameters to illustrate the impact of osteoporosis on TB patients.

1.8 Significance of the study

Osteoporosis and TB educational intervention programs have been offered and conducted at the community level. Despite all these, osteoporosis is still underdiagnosed, undertreated, under-reported, and their correlation is inadequately researched in the clinical setups (Nguyen, 2014). Moreover, osteoporosis diagnosis in Malaysia is significantly less reported than in other Asian regions (Kung et al., 2013). Primary prevention strategies must be improved and aimed at populations at high risk of developing osteoporosis. While osteoporosis is deemed an inevitable disease, it is still vitally important to take effective action to deal with this disease. Particularly lifestyle habits, physical exercise, healthy diet, weight control, and vitamin D intake affect the development of osteoporosis as well as TB progression (Huang et al., 2016; Kearns & Tangpricha, 2014; Yeap et al., 2013). Primary prevention strategies need to be enhanced in high-risk groups at developing osteoporosis (Tung & Lee, 2006). If no comprehensive prevention strategies are implemented, the cost expenditure of osteoporosis and fractures is estimated to increase by double or triple by 2040 in the US (Vondracek & Linnebur, 2009).

1. Through this study, health professionals and authorities will have a clearer picture of the incidence of osteoporosis among TB patients which will help us to cope with this comorbid condition by making new interventions. The findings of the study would emphasize the introduction of osteoporosis screening as an essential component for all TB patients in Malaysian practice. Based on osteoporosis screening patients can be managed accordingly along with TB treatment.
2. The current study will help pharmacists, clinicians, and program managers:
    i. Reduce TB infection by indicating risk factors of TB and an increase in treatment success rate by looking into the predictors of unsuccessful treatment outcomes among TB patients with osteoporosis patients.
    ii. Differentiate the delayed sputum conversion rate among TB with osteoporosis patients and TB without osteoporosis patients. It will also give information about predicting factors of delayed-sputum quality among smear-positive PTB patients.
    iii. Examine patient perceptions of osteoporosis, identify patients with poor osteoporosis knowledge, health beliefs as well as identify patients with low bone mass. The results will help in future planning of training programs for patients with osteoporosis and help health care providers to focus on these patients with high-risk factors for developing osteoporosis or low bone mass.
3. In Malaysia, TB knowledge, attitude and practices studies among TB patients were lacking, it might be because of common perception if the patient is suffering from any diseases becomes aware of this particular disease.

This study would prove to be significant to estimate the level of knowledge of TB patients regarding TB as well as osteoporosis. This precise evaluation will result in enhancing the awareness of osteoporosis for the well-being of TB patients.

1.9 Research objectives

1.9.1 Objectives of the study

The main objective of this research project was to investigate the prevalence of low bone mass among TB patients and to determine knowledge, attitude, and practices of TB and osteoporosis, health beliefs, and the association of these factors to bone health.

The aims of this study are:

Specific Objectives:

- To evaluate the prevalence and risk factors associated with osteoporosis among TB (PTB & EPTB) patients.

General Objectives:

- To determine the rate and predictors of delayed sputum conversion with weak bone density in TB patients.
- To evaluate the risk factors of unsuccessful treatment outcomes among TB patients with weak bone density in TB patients.
- To evaluate knowledge, attitude, and practices towards TB and osteoporosis knowledge among TB patients.
- To access the differences in health beliefs of osteoporosis among TB patients.

1.10 Thesis overview

Chapter 2 presents the literature reviews of the study objectives and offers a conceptual framework in the following thesis. A systematic literature review relevant to the study, based on the potential correlation between osteoporosis and TB, delayed sputum conversion and risk factors, TB treatment outcome with its predicting characteristics. The chapter continues with a description of the practical application of knowledge of osteoporosis and health beliefs in published studies.

Chapter 3 illustrates in detail methodologies for assessing the prevalence rate of LBMD using QUS, comprehensive method of data collection of TB and knowledge of TB osteoporosis knowledge test, and health beliefs scale.

Chapter 4 describes the detailed findings, the analysis of all objectives, the correlation between the bone density T-score and QUS parameters related to demographics, the QUS parameters differences stratified by age and gender, and TB-related data results. The evaluation of TB knowledge, attitude and practices, osteoporosis knowledge and health beliefs and their effect on management of the disease.

Chapter 5 includes a detailed discussion on study findings related to TB and osteoporosis.

Chapter 6, in the final chapter, the conclusion, and limitations of this project were discussed. A description of the study concluded and a set of recommendations for further work.

CHAPTER 2

LITERATURE REVIEW

Recent data for the global burden of disease reflect major demographic and lifestyle changes, leading to a rise in non-communicable diseases. Most countries with high levels of TB face a large comorbidity burden from both non-communicable and communicable diseases (Marais et al., 2013). Traditional disease-specific approaches typically fail to recognize common features and potential synergies in the integration of care, management, and control of non-communicable and communicable diseases (Marais et al., 2013). In resource-limited countries, the need to tackle a broader range of overlapping comorbid diseases is growing. TB and HIV persist as global emergencies as communicable diseases while in the case of non-communicable recent studies published on incidence of osteoporosis in TB patients (Chen et al., 2017; Yeh et al., 2016).

2.1 Prevalence and incidence of osteoporosis among TB patients

According to National Institute of Mental Health, “Prevalence” is the proportion of a population who have a specific illness, a condition, or a risk factor in a given period, usually expressed as a percentage or as the number of cases per 10,000 or 100,000 populations while “Incidence” is a measure of the number of new cases of an illness, a condition or a risk factor that occurs in a population over a given period. Prevalence studies are done to evaluate the burden of disease in a population, to compare the frequency of disease in different populations, and to study the trends of the severity of disease over time (NIH, 2017).

Osteoporosis is a skeletal disorder characterized by compromised bone strength, which predisposes the individual to an increased risk of fractures of the hip, spine, and other skeletal sites. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density also called bone mineral density (BMD) is expressed as a relationship between two norms: the T-score and the Z-score (the expected BMD for the individual's age and sex) (Cosman et al., 2014). This criterion of bone density is used conventionally as a proxy for overall bone strength and is expressed as grams of mineral per square centimeter or grams per cubic centimeter (Compston, 1995). Ultrasound is now a clinically accepted modality in the management of osteoporosis. The most common commercial clinical devices assess fracture risk from measurements of attenuation and sound speed in calcaneus bone (Wear, 2020).

Osteoporosis is predominantly a woman's disease, particularly in postmenopausal women. It has been estimated that 30% of women are osteoporotic in both Europe and the United States, and 40% post-menopausal women and 30% of men will experience an osteoporotic fracture for the rest of their lives (Reginster & Burlet, 2006; Watts et al., 2010).

In reinforcement of our study, TB-related systemic inflammation, vitamin D deficiency, and the use of systemic corticosteroids enhance ongoing bone destruction. Osteoporosis, in turn, may cause fragility fractures, which further impair mobility and increase morbidity and mortality. TB with comorbidities may perform their role in reduced quality of life impaired other functions and enhance the risk of mortality. Of these, osteoporosis progressively considers an intention and being appreciated for therapeutic intervention (Lehouck et al., 2011).

In general, Asian countries have a higher incidence of osteoporosis than western countries, attributed to the fact, that the Asian population has a lower body mass index, weight and, short height (Babbar et al., 2006). BMD was measured in diabetes mellitus (DM) patients in Penang, Malaysia. The osteoporosis prevalence rate is predicted to increase because of the rapidly growing age population of Malaysia. The reported prevalence of normal BMD (23.3%), osteopenia (53.7%), and osteoporosis (23.0%) were measured by QUS among diabetic patients in Malaysia (Abdulameer et al., 2017).

In the case of TB, a link between RT and bone fracture with or without comorbidities was discovered in the literature. We conduct a review of recent research based on these cues. The first leading reason is the existence of hazardous associated factors of TB and osteoporosis, which were not noticed eminently. Secondly, limited studies on TB and osteoporosis coexistence were published recently after 2015. Consequently, a coordinated effort to determine the rate of the prevalence and linked risk factors of the two comorbid conditions would be required for the evolution of TB and osteoporosis assimilated features and devising the educational interventions for patient health improvement.

A retrospective study was performed by using the National Health Insurance Research Database of Taiwan to classify 6612 newly diagnosed patients with RT and 13220 patients without RT from 1999 to 2005. The incidence of fragility fracture and osteoporosis/fragility fracture were followed up until the end of 2011. and was found as 1.69 (95% CI = 1.26–2.2) for RT and 1.42 (95% CI = 1.25–1.61) for non-RT

The current research focused to determine the existence of incident osteoporosis in patients who completed ATT. Chronic inflammatory disorders are related to an increased risk of osteoporosis. While TB is an infectious disease characterized by systemic inflammatory responses, there is no clear pathogenesis impact of active TB on incident osteoporosis. Moreover, inflammatory cytokines such as IL 6 and TNF-α are also produced during infection that may improve bone turnover by activation of osteoclastogenesis. Chen et al., (2017) reported the occurrence of osteoporosis with chronic TB infection. In this nationwide retrospective study, a total of 3,725 active TB patients and 14,900 age and sex-matched controls were included from the National Health Insurance Research Database in Taiwan during 2000-2012. Significantly higher incidence rates of osteoporosis 4.31 per 1000 person-years in TB cohort and 1.80 in non TB matched control cohort was observed. This indicates that osteoporosis screening should be considered in TB patients' follow-up programs. The osteoporosis incidence was observed as 2.2% in TB patients and 1.1% matched controls. In COX regression analysis, TB has reported an independent risk factor for osteoporosis.

Choi et al. (2017) elaborated on the risk of sarcopenia and osteoporosis among Korean male TB survivors. Korea National Health and Nutrition Examination Survey (KNHANES) (2008–2011) database were analyzed, 3,228 males of ≥ 50 years age, with radiological pieces of evidence of TB and dual-energy x-ray absorptiometry (DEXA), were recruited. The patients with both TB scars on CXR and medical history had a high risk of osteoporosis (OR 1.75, 95% CI 1.04–2.95). Medical history of TB with TB scars on CXR is an independent risk factor for sarcopenia and osteoporosis (Choi et al., 2017).

Holloway et al. (2011) conducted a meta-analysis was on 531 palaeopathological TB cases from 221 sites of all continents to test any change in frequency of bone lesions over time and to observe any change in the distribution of bone lesions in the skeleton over time and concluded that bone lesions occur in 3-5% of active TB cases and can be used to diagnose the disease in ancient skeletal remains. These findings are an important addition to the current co-existence of LBMD and *MTB* association (Holloway et al., 2011). Another study supports the presence of skeletal lesions in TB cases (Holloway et al., 2013).

2.2 Sputum conversion among TB with Osteoporosis patients

Many studies have suggested that sputum smear conversion after 2 months of ATT treatment is an important determinant of treatment success and can be a predictor for TB success rate. Smear-positive PTB becomes the main source in transmitting the infection, in which one untreated patient can infect another 10 to 15 persons annually (Gunda et al., 2017; WHO, 2020). Therefore, delayed sputum smear conversion is an important clinical indicator for ATT treatment. Apart from a possible continuity of infectiousness, prior studies have indicated that delayed smear conversion is a risk factor for TB treatment failure, the emergence of drug-resistant TB, and the potential increase in TB mortality (Gunda et al., 2017).

The sputum conversion rate (SCR) is the percentage of smear-positive PTB cases converted to smear-negative after 2 months of treatment (Kayigamba et al., 2013). Patients are considered non-infectious once the sputum smear turned into negative. The intensive phase is prolonged to an additional one month for the patient who remains smear-positive at the end of 2nd month of treatment (Horne et al., 2010). If smear-positive PTB patients do not become negative at the end of the 5th month of

ATT, treatment failure is declared in these patients (Azarkar et al., 2016). It is estimated that 80 to 90% of smear-positive PTB patients experience smear conversion in 2 to 3 months of treatment (Gunda et al., 2017). Negative smears during and at the end of treatment are required to state a patient cured of TB. Consistent sputum smear at the end of the intensive phase of treatment is likely to be associated with unfavorable outcomes, definitely with failure, default, and drug resistance TB (Djouma et al., 2015). Below are given the findings of studies estimating sputum conversion rate and predictors of delayed sputum smear conversion and its effect on treatment outcomes among TB adults.

2.2.1 Predicting factors of delayed sputum conversion

There is a lack of literature on the impact of osteoporosis on sputum conversion and factors that affecting the rate of delayed sputum. Owing to the limited information on sputum delayed conversion among osteoporotic TB patients, we are unable to discuss the delayed sputum conversion in the presence of osteoporosis among TB patients.

Tok et al. (2016) conducted a retrospective cohort study among new smear-positive PTB patients for the year 2014 in Johor Bahru, a Malaysian state, to investigate the sputum smear conversion at the end of two months of treatment and the impact of DM on treatment outcomes. Sputum smear examination results were available for 367 patients and 260 patients successfully converted their sputum from smear-positive to smear-negative at the end of two months of treatment. The sputum conversion rate was 70.8% and DM was not found to be an associated risk factor with sputum conversion (Tok et al., 2016).

Shariff and Safian, (2015) conducted a case-control study among smear-positive PTB patients registered in the Institute of Respiratory Medicine, Kuala Lumpur, Malaysia. A total of 75 cases and 75 controls were interviewed, and their medical records were retrieved to extract the information needed. Multivariable analysis identified DM (OR = 4.01, 95% CI 1.61–9.96) as being independently associated with the risk of delayed sputum smear conversion after two months of treatment (Shariff & Safian, 2015).

Azarkar et al., 2016 prospectively evaluated the time of sputum conversion after treatment in 85 smears positive PTB patients and factors affecting the sputum conversion. The mean time to sputum conversion after starting ATT was 1.99 ± 1.06 months. At the end of the 2nd month, around 64.7% of patients presented smear conversion, and the number reached 91.8% and 98.8% at the end of the 3rd and 4th month, respectively. It was revealed that earlier illness, the high number of bacilli in smear at baseline, and cavitation in the lung on radiography seemed to be associated with delay in sputum smear conversion.

A systematic review was designed to analyze the factors in delaying sputum conversion among smear-positive PTB patients by using electronic databases of PubMed, ScienceDirect, Google Scholar from 19th to 25th February 2018. Subsequently, more articles and reports were identified by combing through the references from the relevant literature. Finally, 20 articles were recruited for comprehensive analysis. From previous studies, male gender, older age, unemployment, low BMI, having DM, HIV, smoker, alcohol consumption, high AFB load, advanced or cavitation in CXR, prolonged symptoms, and non-adherence to TB treatment were significant factors in delaying sputum conversion (Mohd Anwar et al., 2018).

Another prospective study was carried out by Musteikienė et al., (2017), to know which factors are associated with early sputum culture conversion in cases of PTB after 1 month of TB treatment. A sample of 52 patients with new cases of bacteriologically evident drug-susceptible PTB was included. Culture conversion after one month was found in 20 (38.5%) cases. Patients who smoked for more than 20 pack-years were reported as having a higher risk of not converting. The most important factor with a higher risk for non-conversion was a sputum smear grade of 2+ or more at the beginning of treatment (Musteikienė et al., 2017).

Another prospective study was designed to identify medico-social factors of delayed sputum smear conversion at the end of an intensive phase and to find the influence of sputum smear conversion on treatment outcome. Study participants were 216 newly diagnosed smears positive PTB patients aged ≥15 years, registered under the Revised National TB Control Program. The overall sputum conversion rate was 85.8%. In multivariate analysis, tobacco smoking, DM, and higher pre-treatment smear grading of 3+ emerged as independent predictors of delayed sputum smear conversion. Delayed sputum smear conversion was also found to be significantly linked with unfavorable treatment outcomes (Rate, 2017).

Kigozi et al. (2014) retrospectively evaluated the non-conversion of sputum smear at the end of the intensive phase in South Africa. A total of 54164 records were extracted, 2-month sputum smear results were available only in 73.8% of cases. In the regression model, factors linked with non-conversion were age, baseline sputum grading, TB type, and HIV co-infection (Kigozi et al., 2014).