RESEARCH ARTICLE

Is hypothyroidism rare in multidrug resistance tuberculosis patients on treatment? A systematic review and meta-analysis

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Abstract

Background

Hypothyroidism is one of the adverse drug reactions that associated with Multidrug Resistant Tuberculosis (MDR-TB) medications. Extremely variable magnitude of hypothyroidism in MDR-TB patients has been reported from different parts of the world. However, there is no evidence that tried to estimate the pooled prevalence of hypothyroidism to confirm the rareness of hypothyroidism in MDR-TB patients on treatment. Therefore, we did a systematic review and meta-analysis to estimate the prevalence of hypothyroidism in MDR-TB patients on treatment, and to summarize the demographic and clinical characteristics of the patients.

Methods

We conducted a systematic review and meta-analysis on studies reported around the world on the prevalence of hypothyroidism in MDR-TB patients on treatment. We searched electronic databases: PubMed/MDline, EMBASE, CINAHL, Science Direct, Academic Search Complete and Google scholar for English language articles without limiting publication year. We also reviewed the bibliographies of relevant studies and conducted an electronic search for relevant conference abstracts. Eligible studies were cross-sectional and cohort studies that included at least five participants. We used a random-effects model to estimate the pooled prevalence of hypothyroidism. The registration number of this review study protocol is CRD42018109237.

Results

We included 30 studies and pooled data on a total of 6,241 MDR-TB patients. The crude prevalence of hypothyroidism was extremely heterogeneous. The pooled prevalence of hypothyroidism in MDR-TB patients on treatment was 17.0% (95% CI: 13.0–20.0). Ethionamide and para-aminosalicylic acid (PAS) were the most frequently reported drugs that associated with the occurrence of hypothyroidism.
Conclusion
This review revealed that hypothyroidism is not a rare adverse drug reaction in MDR-TB patients on treatment. Ethionamide and PAS were the most frequently reported drugs that associated with the occurrence of hypothyroidism. Screening of hypothyroidism in MDR-TB patients on treatment is important while targeting patients on Ethionamide and PAS based treatment regimen.

Background
Multidrug Resistance (MDR) and Extensively Drug Resistance (XDR) Tuberculosis (TB) are the most threat to human health across the world. MDR-TB is defined as a *Mycobacterium tuberculosis* strain resistance to the two powerful anti-tuberculosis isoniazid and rifampicin [1,2]. XDR-TB on the other hand refers to *Mycobacterium tuberculosis* strain resistance to isoniazid and rifampicin, any of the fluoroquinolones and at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin) [1,2]. In 2017 alone, an estimated 3.5% of new cases and 18% of previously treated cases of MDR-TB have occurred globally [3]. The control of MDR-TB is much more difficult than drug-susceptible TB [4–7] which leads to further spread of resistant strains of the bacilli in several populations.

One of the most challenges in MDR-TB treatment is the severe adverse drug reactions associated with its medications [5,8–10]. The medication used for the treatment of MDR-TB is also considered as the most complicated because of its long duration, toxicity and economic burden it imposes [5,8–10]. In addition, MDR-TB drugs are known to cause multiple and severe adverse drug reactions that affect treatment outcome and quality of life of the patients [11–13]. Adverse drug reactions of MDR-TB drugs also leads to treatment interruption [14], which is the most important determinant of poor treatment outcomes such as prolonged morbidity, extensively or complete drug-resistance development, treatment failure and mortality [15]. The most frequently reported adverse drug reactions associated with MDR-TB drugs are skin rash, gastrointestinal symptoms, ototoxicity, electrolyte derangement, hepatotoxicity, nephrotoxicity, arthralgia, psychosis, suicidal tendencies, depression and hypothyroidism [1,2,12,16].

Hypothyroidism is one of the adverse drug reactions that cause life threatening side effect related to MDR-TB drugs [11,17,18]. The most likely MDR-TB drugs to cause hypothyroidism are Ethionamide (Eto), Thioamides (TA), Prothionamide (Pto) and Para-aminosalicylic acid (PAS) [11,19,20]. Although the effect of MDR-TB drugs on thyroid function is well cited in the literature [21–24], little is known about the exact mechanism through which these drugs influence thyroid function. Hypothyroidism is an uncommon adverse drug reaction which has vague and non-specific symptoms that can be easily missed by physicians [25]. Patients that developed hypothyroidism could manifest several symptoms which includes slow growth, puffy face, lethargy, hair loss, constipation, dry skin, enlarged thyroid gland, increased cholesterol level, irregular uterine bleeding, irritability, sensitivity to cold, sexual dysfunction, slow heart rate, weight gain, muscle weakness and stiffness or tenderness [26]. For these reasons, the World Health Organization (WHO) recommends screening of hypothyroidism at least per three or six months in MDR-TB patients on treatment [27]. However, laboratory supplies and techniques used to conduct thyroid function test are relatively rare and expensive than ordinary routine laboratory diagnosis [28,29]. In addition, access to quality assured laboratory diagnosis for such advanced test is a serious problem in low-income countries where the
burden of MDR-TB is high [30,31]. Thus, screening and repeating the test per three or six months during the follow-up period could be impractical in low-income countries.

Available studies have reported an extremely variable prevalence of hypothyroidism among MDR-TB patients on treatment and have recommended screening of hypothyroidism during follow-up period [32–61]. However, there is no review that attempt to summarize the available literature to identify evidence that support recommendation on the screening of hypothyroidism in MDR-TB patients on treatment. Therefore, we did a systematic review and meta-analysis to estimate the pooled prevalence of hypothyroidism in MDR-TB patients on treatment, and to summarize the demographic and clinical characteristics of the patients.

Methods

Search strategy

We conducted a systematic review and meta-analysis of published articles to estimate the pooled prevalence of hypothyroidism and to summarize the demographic and clinical characteristics of the patients in MDR-TB patients on treatment following PRISMA standards (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) ([62] and S1 Checklist). We systematically searched electronic databases: PubMed/Medline, Excerpta Medica Data Base from Elsevier (EMBASE), Cumulative Index to Nursing and Allied Health (CINAHL), Science Direct, Academic Search Complete and Google scholar for English language articles without limiting publication year. The electronic databases search was conducted from September 20, 2018 to November 10, 2018. We also reviewed the bibliographies of relevant studies, and conducted electronic search for conference abstracts. We used a search strategy by combining a key terms: "hypothyroidism", "thyroid disorder", "thyroid function", "symptomatic hypothyroidism", "drug-induced hypothyroidism", "goitrous hypothyroidism", "abnormal thyroid function", "adverse drug reaction", "drug side effect", "tuberculosis", "drug resistance", "multidrug resistance", "MDR-TB", "Rifampicin resistance" and "treatment" both in Medical Subject Heading (MeSH) and free text terms. When necessary, we communicated with the included studies’ authors for clarification and additional information. Two authors (HHT and TL) independently reviewed the titles, abstracts and full articles of retrieved studies.

Study inclusion and exclusion criteria

We included a cohort studies that reported the prevalence of hypothyroidism at least on five MDR-TB patients on treatment and conducted in different parts of the world. We excluded studies that were conducted on single drug, latent TB treatment, on drug-susceptible TB and results not reported on key variables. We also excluded studies that were conducted before starting MDR-TB treatment, MDR-TB contacts as prophylaxis and data overlap (Fig 1 or S1 Diagram).

Study quality assessment

We assessed the quality of the included studies by modified version of the Newcastle–Ottawa Scale (NOS) [63]. The scale assesses three key points (domains) of a given study: selection of participants; comparability of the groups; and outcome(s) assessment. We assigned stars for each point of the scale to categorize the studies into good, fair and poor quality based on the NOS [63]. A good quality study was scored 3 or 4 stars in participant selection, 1 or 2 stars in comparability of groups, and 2 or 3 stars in outcome(s) assessment. A fair quality study was scored 2 stars in participant selection, 1 or 2 stars in comparability of the groups, and 2 or 3 stars in outcome(s) assessment. A poor quality study was scored 0 or 1 star in participant...
selection, 0 stars in comparability of the groups and 0 or 1 star in outcome(s) assessment. In case of disparity between the two authors (HHT and TL) during study selection process, the disparities were resolved by the decision of the second author (KH).

**Data extraction**

We extracted data from the included studies in to two databases separately. Our primary outcome was hypothyroidism that is measured by Thyroid Stimulated Hormone (TSH). Hypothyroidism is defined as abnormally below normal level of thyroid hormones in blood circulation [21]. In this review, we considered the presence of hypothyroidism if the authors of the
included studies reported the prevalence in their results. We extracted information on characteristics of participants such as age range, mean of age, sex, HIV sero-status, treatment regimen, TB type (pulmonary versus extra pulmonary). We also extracted study’s characteristics such as first authors, publication year, study year, study setting, study duration, study design, study population, countries where the study was conducted, sample size and prevalence of hypothyroidism.

### Statistical analysis

We estimated the pooled prevalence of hypothyroidism with its 95% Confidence Interval (CI) using random effects meta-analysis model assuming the true effect size varies between studies [64]. We expressed the pooled prevalence of hypothyroidism as the ratio of numbers of patients that developed hypothyroidism to the total sample size, and the data was presented on forest plot. We also assessed the effect of sex on the thyroid hormone and estimated the pooled odds ratio with its 95% CI using random effect models. We assessed the heterogeneity in the prevalence of the different studies using Chi-square based Q test with significant level of p-value < 0.1 and $I^2$ statistic with values above 75% as significant heterogeneity [65]. We also assessed potential publication bias with both funnel plot and Egger’s test (p-value < 0.1 as significant level). In addition, we assessed the effects of the potential source of heterogeneity in the prevalence of hypothyroidism by subgroup analysis and moment based meta-regression models. We qualitatively summarized the drugs associated with hypothyroidism and carried out all data analysis by STATA version 14.

### Ethical consideration

Ethical clearance was not sought, as this review was based on previously published articles. However, the protocol of this study was pre-registered on PROSPERO (International prospective register of systematic reviews) University of York, Centre for Reviews and Dissemination with registration number CRD42018109237.

### Results

#### Studies characteristics

We included 26 full articles, one letter to the editor [32] and three abstracts [33–35] that provided prevalence of hypothyroidism in MDR-TB patients on treatment [Fig 1, Table 1]. Studies included in this review were reported from 19 countries which cover three continents (Africa, Asia and Europe) [Table 1]. Seventeen studies were reported from Asian [32,34–40,42–44,46,48,53,54,60,61], eight from African [41,45,47,49,50,55,57,58] and five from European [33,48,52,56,59] countries. We categorized Russia, Turkey and Ukraine under European countries category. The majority of studies were reported from India (ten studies) [32,34–37,43,46,51,53,54,57,58]. Twenty four studies were based on health facility (hospital, TB clinic, research center and MDR-TB treatment center), while six were community based [Table 1]. In terms of study design, 15 were retrospective cohort study, 13 prospective cohort study, one ambispective cohort study [61] and one study [48] has not reported the study design [Table 1].

Fig 2 depicts the number of studies identified by year of publication. The publication year of the articles ranged from 2004 to 2018, and majority of the studies were published after 2010 [Fig 2, Table 1]. The study duration ranges from one month to 12 years [Table 1]. The minimum sample size used by the included studies was five participants [33] and the maximum...
Table 1. Characteristics of included studies.

| First author, (publication year) | Study duration | Study setting | Study location | Study design | Sample size | Hypothyroidism n (%) | Hypothyroidism definition |
|----------------------------------|----------------|---------------|---------------|-------------|-------------|-----------------------|---------------------------|
| Akshata et al (2015) [36]        | 2011–2014      | Health facility | India         | Retrospective cohort | 484         | 19(3.9)               | TSH value > 10 microIU/ml  |
| Andries et al (2013) [37]        | 2006–2013      | Health facility | India         | Prospective cohort | 69          | 37(54.0)              | TSH value > 10 mIU/L after 3 months of treatment |
| Baghaei et al (2011) [38]        | 2006–2009      | Health facility | Iran          | Retrospective cohort | 80          | 1(1.3)                | ——-                        |
| Bares et al (2016) [39]          | 2011–2012      | Health facility | Pakistan      | Prospective cohort | 50          | 39(78.0)              | Adverse effect of certain anti-tuberculosis drugs |
| Bhatt et al (2017) [40]          | Jul-Nov, 2012  | Health facility | Nepal         | Prospective cohort | 101         | 6(6.4)                | ——-                        |
| Brust et al (2013) [41]          | 2008–2011      | Health facility | South Africa  | Retrospective cohort | 73          | 26(36.0)              | TSH level > 8 mIU/L         |
| Cheung et al (2018) [42]         | 1999–2017      | Health facility | Australia     | Retrospective cohort | 29          | 9(31.0)               | TSH above upper limit      |
| Chhabra et al (2011) [32]        | 2005–2011      | Health facility | India         | Prospective cohort | 54          | 6(11.0)               | ——-                        |
| Gupta et al (2011) [33]          | ——-            | Health facility | United Kingdom | Prospective cohort | 5           | 4(80.0)               | ——-                        |
| Hire et al (2014) [43]           | Jan-Dec, 2012  | Health facility | India         | Prospective cohort | 110         | 1(0.9)                | ——-                        |
| Hoa et al (2015) [44]            | 2010–2012      | Health facility | Vietnam       | Prospective cohort | 282         | 3(1.3)                | ——-                        |
| Huerga et al (2017) [45]         | 2006–2012      | Health facility | Kenya         | Retrospective cohort | 169         | 31(18.0)              | TSH > 10 mIU/l              |
| Isaakidis et al (2012) [46]      | 2007–2011      | Community      | India         | Prospective cohort | 67          | 21(31.0)              | TSH > 10 mIU/L              |
| Jacobs et al (2014) [47]         | 2010–2011      | Health facility | South Africa  | Retrospective cohort | 350         | 29(8.3)               | ——-                        |
| Kala et al (2008) [34]           | ——-            | Health facility | India         | Retrospective cohort | 110         | 12(12.9)              | ——-                        |
| Matveyeva et al (2017) [48]      | ——-            | Health facility | Ukraine       | ——-          | 30          | 5(16.7)               | Increased TSH value and decline in T4 levels  |
| Meressa et al (2015) [49]        | 2009–2014      | Health facility | Ethiopia      | Retrospective cohort | 612         | 105(17.2)             | ——-                        |
| Modongo et al (2012) [50]        | 1–30/Jan/2007  | Community      | Botswana      | Prospective cohort | 213         | 73(34.3)              | TSH > 10.0 μIU/l           |
| Munivenkatappa et al (2016) [51] | 2014–2015      | Community      | India         | Prospective cohort | 188         | 43(23.0)              | TSH value ≥ 10 mIU/ml      |
| Nathanson et al (2004) [52]      | 1998–2002      | Community      | Estonia, Latvia | Retrospective cohort | 818         | 29(3.5)               | TSH > 10 mU/L              |
| Prasad et al (2016) [53]         | 2009–2010      | Health facility | India         | Prospective cohort | 98          | 10(0.8)               | TSH > 10.0 IU/ml           |
| Prasad et al (2013) [35]         | 2009–2012      | Health facility | India         | Prospective cohort | 98          | 3(3.1)                | ——-                        |
| Saharia et al (2015) [54]        | 2012–2013      | Health facility | India         | Prospective cohort | 99          | 5(5.1)                | TSH >10 mIU/mL             |
| Satti et al (2012) [55]          | 2007–2009      | Community      | Lesotho       | Retrospective cohort | 186         | 129(69.0)             | TSH value > 10.0 mIU       |
| Shin et al (2007) [56]           | 2000–2002      | Community      | Russia        | Retrospective cohort | 244         | 42(17.2)              | TSH >10.0 IU/ml            |
| Tag El Din et al (2015) [57]     | 2009–2012      | Health facility | Egypt         | Retrospective cohort | 107         | 11(10.3)              | ——-                        |

(Continued)
Table 1. Twenty studies were clearly defined hypothyroidism, but eleven studies did not provide the definition of hypothyroidism [Table 1]. Majority of the studies used TSH concentration level to assess the presence of hypothyroidism [Table 1].

Six studies [32,36,37,39,51,54] used immunoassay based techniques as the method to measure TSH concentration, while 14 studies [38,41,42,44,46,47,49,55–61] retrieved the value of TSH concentration from record (treatment card or laboratory report). However, ten studies [33–35,40,43,45,48,50,52,53] did not report how TSH concentration was measured, and from where data on TSH concentration was collected.

Seventeen studies did not provide age ranges of their participants, and the remainder covered adult participants [Table 2]. In addition, eight studies did not provide either mean or median of age, but 22 studies provided either mean or median of age [Table 2]. Thirteen studies reported HIV sero-reactive status of the participants with the pooled prevalence of HIV co-infection with MDR-TB was 30.0% (95% CI: 21.0–40.0). Analysis from six studies shown that the pooled prevalence of pulmonary TB was 89.0% (95% CI: 84.0–93.0)[37,38,42,46,49,61], while the pooled prevalence of extra-pulmonary TB as estimated from the same six studies was 12.0% (95% CI: 7.0–17.0).

Twelve studies did not report the regimen used for the treatment of MDR-TB patients [Table 2]. However, 11 studies reported standardized regimen, while seven studies reported individualized regimen [Table 2]. The majority of studies (eighteen) reported the drugs that are associated with hypothyroidism [Table 2], including Ethionamide, PAS, Kanamycin, Thioamide and Prothionamide [Table 2]. Ethionamide and PAS were the most frequently reported drugs that are associated with hypothyroidism [Table 2]. Four studies [37,42,50,51] reported the proportion of hypothyroidism by sex, and we pooled the odds ratio of these four studies to assess the effect of sex on the thyroid hormone in MDR-TB patients on treatment. As a result, the pooled odds ratio between female and male was 0.534 (95% CI 0.262–1.09) by considering female as risk category.

Pooled prevalence of hypothyroidism

We pooled data on 6,241 MDR-TB patients on treatment to estimate the pooled prevalence of hypothyroidism in this meta-analysis. We used random effects model because the results of overall Chi-square based Q test and I² statistic (variation in effect sizes attributable to heterogeneity) shown high heterogeneity between the results of the studies (Q = 1154.00, df = 29, p-value < 0.001 and I² = 97.49%) for hypothyroidism prevalence estimation.

Fig 3 shows a forest plot with effect size (ES-prevalence) and 95% confidence interval. The crude prevalence of hypothyroidism ranges from 1.0% to 80.0% [Fig 3]. The overall pooled
hypothyroidism prevalence was 17.0% (95% CI: 13.0–20.0) [Fig 3]. The pooled prevalence of hypothyroidism in Africa was 25.0% (95% CI: 14.0–37.0) which was significantly higher than Asian prevalence of 13.0% (95% CI: 10.0–17.0), and European prevalence of 9.0% (95% CI: 4.0–15.0) [Fig 3].

Subgroup analysis

Table 3 depicts subgroup analysis results based on study setting, study design, treatment regimen and continent from where the study was reported. The results of all subgroup analysis have shown significant heterogeneity between groups and within the group [Table 3].

Meta-regression analysis

We assessed the effects of year of study and sample size of each study on heterogeneity between studies using meta-regression model [Table 4]. Sample size (p = 0.002) was significantly predicted prevalence of hypothyroidism heterogeneity across the studies [Table 4]. However, study year (p = 0.300) was not significantly predicted prevalence of hypothyroidism heterogeneity [Table 4].

Publication bias

The funnel plot (Fig 4) was asymmetrical, which suggested the possibility of publication bias. An Egger’s test result (p = 0.01) was also confirmed the presence of publication bias in the included studies in estimated prevalence of hypothyroidism.
Table 2. Characteristics of study participants.

| First author (publication year) | Age range (in year) | Mean age (in year) | Treatment regimen | Drug associated | Drugs used for MDR-TB treatment |
|---------------------------------|---------------------|--------------------|-------------------|-----------------|--------------------------------|
| Akshata et al (2015) [36]       | 14–55               | 31.7               | Standardized      |                 | Levofoxacin, Ethionamide, Ethambutol, Cycloserine, PAS |
| Andries et al (2013) [37]       |                     |                    | Individualized    | Ethionamide and PAS | Pyrazinamide, Capreomycin, Ethionamide, Cycloserine, PAS |
| Baghæi et al.(2011) [38]        | 14–81               | 40.64              | Standardized      |                 | Amikacin, Cycloserine, Prothionamide, Ofloxacin, Ethambutol, Pyrazinamide |
| Bares et al (2016) [39]         | 14–50               | 25.5               | Individualized    |                 | Isoniazid, Rifampicin, ethambutol, pyrazinamide, streptomycin, PAS |
| Bhatt CP et al (2017) [40]      |                     |                    |                   |                 |                                |
| Brust et al (2013) [41]         |                     | 34                 | Standardized      | Ethionamide and PAS | Kanamycin, Ofloxacin, Cycloserine, Ethionamide, Pyrazinamide, Ethambutol |
| Cheung et al (2018) [42]        | 22–47               | 35                 |                   | Prothionamide and PAS | Prothionamide and PAS |
| Chhabra et al.(2011) [32]       |                     | 38.57              |                   | Prothionamide and PAS | Regimens containing PAS and Prothionamide. |
| Gupta et al (2011) [33]         | 29–40               |                    |                   |                 |                                |
| Hire et al (2014) [43]          | 18–79               |                    | Ethionamide       | Kanamycin, Levofloxacin, Ethionamide,Pyrazinamide, Ethambutol, Cycloserine |
| Hoa et al.(2015) [44]           | 30–45               | 42.35              | Standardized      | Amikacin, Kanamycin, Ofloxacin, Ethionamide, Cycloserine, PAS, Ethambutol |
| Huerga et al.(2017) [45]        |                     |                    | Standardized      |                 | Kanamycin, Capreomycin, Levofloxacin, Prothionamide, Cycloserine, PAS |
| Isaakidis et al (2012) [46]     |                     |                    | Standardized      | Ethionamide and PAS | Pyrazinamide, Isonized, Rifampicin, Ethionamide, Cycloserine and PAS |
| Jacobs et al.(2014) [47]        |                     | 35.65              | Standardized      | Ethionamide      | Kanamycin, Amikacin, Ofloxacin, Ethionamide, Terizidone, Pyrazinamide |
| Kala et al (2008) [34]          |                     | 48                 | Individualized    |                 |                                |
| Matveyeva et al.(2017) [48]     |                     | 38.57              | Individualized    | Ethionamide and PAS | Ethionamide and PAS |
| Meressa et al.(2015) [49]       |                     |                    |                   |                 |                                |
| Modongo et al (2012) [50]       | 28–48               | 37                 | Ethionamide and PAS | Ethionamide and PAS |
| Munivenkatappa et al (2016) [51]|                     |                    | Ethionamide and PAS | Ethionamide and PAS |
| Nathanson et al.(2004) [52]     |                     |                    | Standardized      | Thioamides and PAS | Amikacin, Capreomycin, Cycloserine, Ethionamide, Kanamycin, PAS |
| Prasad et al (2016) [53]        | >18                 | 29.3               | Standardized      | Ethionamide      | Streptomycin, Rifampicin, Isoniazid, Ethambutol, Pyrazinamide |
| Prasad et al.(2013) [35]        |                     |                    | Ethionamide       | Kanamycin, Cycloserine, Ethionamide, Pyrazinamide |
| Saharia et al.(2015) [54]       | 31352               | 32.29              | Standardized      | Ethionamide and PAS | Ethionamide and PAS |
| Satti et al.(2012) [55]         |                     |                    | Ethionamide and PAS | Ethionamide and PAS |
| Shin et al.(2007) [56]          | 17–65               | 31.8               | Individualized    | PAS              | Ethionamide, PAS, Cycloserine, Capreomycin, Kanamycin, Streptomycin |
| Tag El Din et al (2015) [57]    | 15–67               | 37.1               | Individualized    | Kanamycin        | Kanamycin, Ethionamide, Cycloserine, PAS, Ofloxacin, Amikacin |
| Tag El-Din et al (2015) [58]    | 15–67               | 37.6               | Ethionamide and PAS | Ofloxacin, Ethionamide, Cycloserine, PAS, Kanamycin, Amikacin |
| Töprün et al.(2005) [59]        | 14–68               | 37.8               | Individualized    |                 | Isoniazid, Rifampicin, Ethambutol, Streptomycin, Prothionamide, Amikacin, Kanamycin |

(Continued)
Table 2. (Continued)

| First author (publication year) | Age range (in year) | Mean age (in year) | Treatment regimen | Drug associated | Drugs used for MDR-TB treatment |
|---------------------------------|---------------------|--------------------|-------------------|-----------------|--------------------------------|
| Yang et al (2017) [60]           | ——             | 42.1               | Individualized     | ——              | Isonized, Ethambutol, Streptomycin, Kanamycin, Ethionamide, PAS |
| Zhang Y et al (2017) [61]        | ——             | ——                | Standardized      | ——              | Pyrazinamide, Amikacin, Kanamycin, Capreomycin, Levofloxacin, PAS |

PAS- para-aminosalicylic acid, a-abstract, l-letter

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Discussion

Medications used to treat MDR-TB are known to cause multiple and severe adverse drug reactions that affect treatment outcome, treatment adherence and patient’s quality of life [11–13]. Hypothyroidism is one of adverse drug reactions that cause life threatening conditions in patients [11,17,18]. However, there is little evidence that attempted to summarize the available literatures to estimate the pooled prevalence, and summarize sociodemographic and clinical characteristics of patients. We included 30 studies reported from 19 countries across three continents (Africa, Asia and Europe), and pooled data on a total of 6,241 MDR-TB patients on treatment. The data reported from the included studies were mostly from small and heterogeneous single centre studies. The result of our meta-analysis revealed 17.0% of pooled prevalence of hypothyroidism in MDR-TB patients on treatment. Our review also suggested that hypothyroidism is not a rare adverse drug reaction in MDR-TB patients on treatment. The pooled prevalence of hypothyroidism in Africa (25.0%) was significantly higher than in Asia (13.0%) and Europe (9.0%). Furthermore, Ethionamide and PAS were the most frequently reported drugs that were associated with the occurrence of hypothyroidism.

The burden of hypothyroidism should not be considered as a rare adverse drug reaction in MDR-TB patients on treatment, because the pooled estimate of our review indicated high prevalence (17.0%) of the problem. This finding was consistent with the previous review report that pooled the results of three studies in which the pooled prevalence of hypothyroidism was 15.9% [17]. In contrast to our finding, a review reported by Wu et al [66] indicated low (3.6%) prevalence of hypothyroidism in MDR-TB patients on treatment. This difference might be due to differences in included studies or diagnosis upper limit used by the included studies. The treatment of MDR-TB is a difficult phenomenon that challenges patient management due to its long term treatment, expensive cost and severe adverse drug reactions [5,8–10]. The adverse drug reactions are more common and severe than the standard treatment for drug-susceptible TB, which reduce patient adherence and result to poor treatment outcomes [11,12,14,15]. Thus, it is critical for physicians to monitor the patient thyroid hormone status and provide appropriate treatment for patients parallel to the standard MDR-TB medication to support a successful treatment outcome.

There was a significant difference in the pooled prevalence of hypothyroidism within the group and between the groups during subgroup analysis. This might be due to variation in the prevalence of hypothyroidism at individual study level, and the heterogeneity due to potential confounding factors at the study level such as other drug adverse reactions and availability of hypothyroidism or chronic conditions before MDR-TB treatment started, which could aggravated by MDR-TB and its medications.

The pooled prevalence of hypothyroidism in African countries was significantly higher than in Asian and European. This probably due to the presence of autoimmune disease, infections [67], and food availability and diversity [68]. The difference in baseline thyroid hormone...
concentration level of patients in each study could also be the main reason of variation in the pooled prevalence of hypothyroidism between the groups and within the group.

Ethionamide and PAS were the most frequently reported drugs that were associated with hypothyroidism. As we did not obtain the adjusted measure of association from the included studies, further studies are needed to establish a causal relationship.
studies, we could not estimate the pooled measure of associations to know the effect size of these two drugs on the occurrence of hypothyroidism. More importantly, several studies did not report the diagnostic criteria of hypothyroidism which could help in the estimation of the burden of hypothyroidism and the level of association of these drugs. For instance, 11 studies did not report the definition of hypothyroidism which might be the potential source of heterogeneity on the estimated prevalence. All these conditions may have an impact on the accuracy of the results. However, the finding of this review highlights the need of standardized data registration and reporting forms in MDR-TB programs, which could have important implications on the international MDR-TB control program. Thus, based on this finding physicians who treat MDR-TB patients should be aware of the occurrence of hypothyroidism during the treatment of MDR-TB. In addition, our pooled estimated prevalence of hypothyroidism, summarized demographic, and clinical characteristics could help as a point of reference for the physicians to take evidence-based actions carefully in patient monitoring and management.

Table 3. Subgroup analysis based on study setting, study design, regimen type and continent from where the study reported.

| Group Variable | Number of study | Hypothyroidism prevalence, %,(95% CI) | Heterogeneity tests |
|----------------|----------------|--------------------------------------|--------------------|
|                |                | X² | d.f. | p-value | I² | p-value |
| Study setting  |                |    |      |         |    |         |
| Health facility| 24             | 13.0(10.0–16.0) | 612.50 | 23 | <0.001 | 96.24 | <0.001 |
| Community      | 6              | 30.0(11.0–49.0) | 496.84 | 5  | <0.001 | 98.99 | <0.001 |
| Study design   |                |    |      |         |    |         |
| Retrospective  | 15             | 15.0(10.0–19.0) | 592.97 | 14 | <0.001 | 97.64 | <0.001 |
| Prospective    | 11             | 20.0(14.0–26.0) | 437.59 | 12 | <0.001 | 97.26 | <0.001 |
| Ambispective   | 1              | 20.0(17.0–23.0) | —      | 0  | —      | —     | —      |
| Regimen type   |                |    |      |         |    |         |
| Standardized   | 11             | 12.0(8.0–17.0) | 278.44 | 10 | <0.001 | 96.41 | <0.001 |
| Individualized | 7              | 14.0(8.0–20.0) | 131.34 | 6  | <0.001 | 95.43 | <0.001 |
| Not reported   | 12             | 25.0(16.0–33.0) | 725.00 | 11 | <0.001 | 98.48 | <0.001 |
| Continent      |                |    |      |         |    |         |
| Asia           | 16             | 13.0(10.0–17.0) | 449.71 | 15 | <0.001 | 96.66 | <0.001 |
| Africa         | 10             | 25.0(14.0–37.0) | 600.68 | 9  | <0.001 | 98.50 | <0.001 |
| Europe         | 5              | 9.0(4.0–15.0)  | 65.93  | 4  | <0.001 | 93.93 | <0.001 |
| Overall        | 31             | 16.0(13.0–20.0) | 1155.43| 30 | <0.001 | 97.40 | <0.001 |

CI: Confidence Interval; d.f.: degree of freedom

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Table 4. Meta-regression analysis for year of study and sample size as a reason of heterogeneity on the prevalence of hypothyroidism.

| Predictive Variable | Unadjusted Model | Adjusted Model |
|---------------------|-----------------|---------------|
|                     | β (95% CI)      | SE  | p-value | β (95% CI) | SE  | p-value |
| Year of study       | 0.69(-3.37–4.76)| 1.98 | 0.729 | 1.86(-1.64–5.36)| 1.70 | 0.286 |
| Sample size         | 0.10(0.040–0.16)| 0.03 | 0.002 | 0.105(0.044–0.17)| 0.30 | 0.002 |

SE-Standard error, β-regression coefficient, CI- 95% Confidence interval

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MDR-TB treatment. In addition, this difference might occur due to small amount of studies included to pool the odds ratio in this review which might under estimate the effect of female sex on the occurrence of hypothyroidism.

A major strength of this review is the inclusion of a large number of studies and the use of large sample size, which made the estimation of pooled prevalence of hypothyroidism more precise. In addition, the large sample size further facilitated rigorous subgroup analyses to investigate the potential sources of heterogeneity on the estimation of hypothyroidism prevalence. Moreover, we employed a random effects model to address heterogeneity among the studies.

The main limitation of this review was inclusion of studies published in English language only. This might induce publication bias. In addition, although individual data pooling is very important to perform subgroup analysis, statistical interaction test and refine dose-response curve, we did not use individual data pooling in this analysis. This might limited our subgroup analysis to further explore the source of heterogeneity. Moreover, there was inconsistent reporting of important participants’ characters such as prevalence of hypothyroidism by TB type (pulmonary versus extra pulmonary), HIV sero-status, antiretroviral treatment status,
treatment regimen, treatment duration and baseline TSH concentration level. These inconsistencies limited our analysis to further determine the potential source of heterogeneity on the prevalence of hypothyroidism. Particularly, the absence of baseline hypothyroidism status might induce estimation bias to the pooled prevalence of hypothyroidism. Thus, measuring and accounting for baseline hypothyroidism is very important to estimate the independent prevalence of hypothyroidism due to MDR-TB drugs. Moreover, few studies reported the drugs and other associated factors on the hypothyroidism. This limited our analysis to estimate the pooled effect size of drugs and other factors that are associated with hypothyroidism, while accounting for the potential confounders.

Conclusion

Our review indicated that hypothyroidism is not a rare drug adverse reaction in MDR-TB patients on treatment. Ethionamide and PAS were the most frequently reported drugs that were associated with the occurrence of hypothyroidism. Screening hypothyroidism among MDR-TB patients on treatment is vital, particularly targeting patients on regimen containing Ethionamide and/or PAS to treat the condition at early stage. In addition, larger scale prospective study is so important to further explore the effect of MDR-TB drugs on thyroid hormone function while controlling baseline hypothyroidism and other confounding factors.

Supporting information

S1 Checklist.
(DOC)

S1 Diagram.
(DOC)

S1 Dataset.
(XLSX)

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