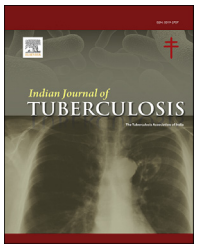
Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.journals.elsevier.com/indian-journal-of-tuberculosis/



Review article

Metformin: A review of its potential as enhancer for anti tuberculosis efficacy in diabetes mellitus-tuberculosis coinfection patients

Bernadette Dian Novita

Department of Pharmacology and Therapy, Faculty of Medicine Widya Mandala Catholic University Surabaya, Indonesia

ARTICLE INFO

Article history:
Received 18 October 2018
Accepted 28 February 2019
Available online 8 March 2019

Keywords:
Metformin
Diabetes mellitus-tuberculosis coinfection
Anti tuberculosis efficacy

ABSTRACT

Metformin is the most commonly prescribed drug for type 2 diabetes mellitus. Nowadays metformin is also use for efficacy in diabetes mellitus-tuberculosis coinfection patients through several mechanisms, such increasing superoxide production therefore activation isoniazid is increasing; inducing adeno-monophosphate kinase (AMPK) associated autophagy process; and regulating inflammation cytokines. This article will review the mechanism of action of Metformin as enhancer for anti tuberculosis efficacy.

© 2019 Tuberculosis Association of India. Published by Elsevier B.V. All rights reserved.

1. Tuberculosis and its problems

Tuberculosis (TB), the infection caused by *Mycobacterium tuberculosis* (M.tb), remains a problem to overcome in Indonesia. In East Java Provence Indonesia 2015, the incidence of new tuberculosis (TB) cases reached 647 from 100,000 population. This increased nearly 2 times from the previous year incident, in 2014, that only 399 new TB cases from 100,000 population.[1,2] This phenomena was similar to TB incidence in the world. According to the World Health Organization (WHO) data in 2013, it states that the incidence of new TB cases in the world has increased 50%, and therefore WHO has declared for TB as a "global health emergency".[3,4]

Diabetes mellitus (DM) is one of the risk factors for TB infection. The risk ratio (RR) of TB infection in DM was increased 2.39 times and the risk of failure in TB treatment was also increased 1.69 times.[5–7] Hyperglycemia condition in DM patient could interfere the human's immune response due to decrease of 1) microvascular response to inflammatory mediators such histamine and bradykinin release; 2) mast cell degranulation; 3) interaction of leukocyte and other endothelial cells; 4) release tumor necrosis factor (TNF)-α, interleukin (IL)-1β dan prostaglandin (PG)-E2[8].

M. tuberculosis has ability to manipulate both innate and adaptive immune response, and called TB's escape mechanism. In this mechanism M.tb has high ability to avoid intracellular killing process and macrophage phagocytosis.[9] Hyperglycemia condition increases its ability in escape mechanism.[10] Therefore failure of TB treatment in DM has increased.[5–7]

E-mail address: novita@ukwms.ac.id.
https://doi.org/10.1016/j.ijtb.2019.02.013
0019-5707/© 2019 Tuberculosis Association of India. Published by Elsevier B.V. All rights reserved.

The aim of TB treatment is to cure patients, to prevent death, to prevent TB infection recurrence, to break the chain of transmission, and to prevent the occurrence anti tuberculosis resistance. However, M. tb is an acid-resistant, with its ability to growth very slow but resistance emerges very quickly when M.tb exposed only to one drug, therefore TB treatment was drugs combination of several mechanism.[11,12] The aims of drugs combination as anti tuberculosis were 1) increasing bactericidal activity since the beginning of TB therapy; 2) preventing drug resistance; and 3) improving the elimination process of M. tb in infected areas.

Anti tuberculosis is classified into two lines, first and second lines. The first line of anti tuberculosis are rifampicin, isoniazid, pyrazinamid, ethambutol and streptomycin. This first line group shows high effectiveness with acceptable toxicity and are given for at least 6 months.[11,12] However drug induced hepatitis (DIH) often occurs during the first line of TB therapy, and also other complications such gastrointestinal intolerance, rash, and renal failure.[11–13] The second-line of TB treatment such fluoroquinolones, aminoglycoside and others are given for multi-drugs resistances (MDR) for 18–20 months.[11,12,14] In this review, the focus is for first line of anti tuberculosis efficacy. Isoniazid (INH) is the highest inhibition activity, due to its bacteriostatic mechanism, at the beginning of TB treatment. INH inhibits M.tb (in vitro) at concentrations of 0.025–0.05mg/L, and it become more effective when combined with ethambutol, rifampicin, pyrazinamide and streptomycin.[11,12] Rifampicin (RIF) has the highest ability in M.tb elimination at the concentrations of 0.06–0.25 mg/L. However, both of INH and RIF prevalence of drug resistance are high.[11,12,14–16] The prevalence of RIF resistance occurs at 1 in each 10^7–10^8 CFU M.tb, and INH occurs at 1 in each10^6 CFU M.tb.[11] The M.tb resistance occurs through several mechanisms, such:1) The inability of anti tuberculosis to penetrate into M.tb cell walls due to its contain a lot of lipopolysaccharide and mannose[11,17]; 2) Anaerobic conditions cause M.tb to become dormant so that anti tuberculosis, such RIF unable to inhibit the metabolic process efficiently; 3) Changes in enzymes responsible for activating pro-drugs, such pyrazinamide (PYR) and INH; 4) Gene Mutase, such single point mutations of *pncA* gene in PYR, and *embB* gene in Ethambutol.[11]

TB drug-resistant becomes a major bottleneck problem in TB infection control and eradication. It was estimated 480 000 new cases of MDR TB, and 210 000 deaths in 2013.[14,18] Extensively drug-resistant TB (XDR TB) has been reported from several countries and an estimated 9.6% of MDR TB patients are characterized as XDR TB that suffers from poor treatment outcomes.[14,19]

2. Host-directed therapy for TB patients

To develop an optimal therapeutic strategies, it needs proper understanding of TB infection pathogenesis, host-immune response, and escape mechanism. Uncontrolled chronic hyperglycemia condition in DM patients increase the risk of TB treatment failure, relapse of TB infection, and associated with death from TB infection.[20,21] The aim of new host-directed therapies identification, as WHO priority, is improving the clinical outcomes of TB patients.[22,23] Therefore, it could use to 1) shorten the duration of TB treatment; 2) prevent resistance and reduce lung tissue damage, through increased autophagia and other antimicrobial peptide production; 3) changes in macrophage effector mechanisms and modification of specific mechanisms, then preventing lung inflammation and matrix destruction; and 4) act on immunity regulation.[23] One of those drugs that has been known as host directed therapy is metformin (MET).

3. Mechanism of action of metformin as candidate for host-directed therapy in patients with diabetes mellitus – tuberculosis coinfection (Fig. 1)

Metformin(MET) is the most commonly prescribed drug for type 2 diabetes mellitus. MET through in silico studies, in vitro studies and in vivo studies using animal models, expressed as important role for anti tuberculosis through immunomodulatory mechanism,[24–26] as it is seen in Fig. 1

4. Metformin dan Superoxide Dismutase (SOD)

Superoxide Dismutase (SOD) is an enzyme produced in the host's antioxidant defense system.[27,28] TB infection increases reactive oxygen species (ROS) as respiratory burst result in macrophage phagocytosis process against M.tb. Excessive production of ROS associated with Th1 overactivation. Inhibits macrophage activity, and increasea tissue damage due to. Hyperglycemia condition could increase ROS production, therefore SOD levels could also increase also in DM patients.[29] KatG gene activates INH from prodrug to active drug. Apparently, SOD contributes during this mechanism, higher SOD related to better of INH's in inhibiting M.tb.[30] MET has ability in improving SODlevel during inflammation.[31,32] Based on this, the addition of MET provides synergism effects to increase the effectiveness of INH. MET has also a synergistic effect with RIF through increasing the expression of organic cation transporter (OCT) –1. The OCT-1 expression plays a role in inhibiting transcription M.tb.[25,33] Moreover, target of glycemic level for DM-TB patients is also need to be adjusted, therefore synchronized with SOD production.[34]

5. Metformin induced autophagy

M.tb has an escape mechanism through inhibition of host macrophage cells' autophagy.[9,17,35] Improving the autophagia process will improve anti tuberculosis in eliminating M.tb. MET activates Adeno Monophosphate Kinase (AMPK) and subsequent phosphorylation of unc-51-like kinase 1 (ULK1),[36] then AMPK works as mTOR inhibitor and enhances autophagy.[23,24,26,37] Therefore, MET from

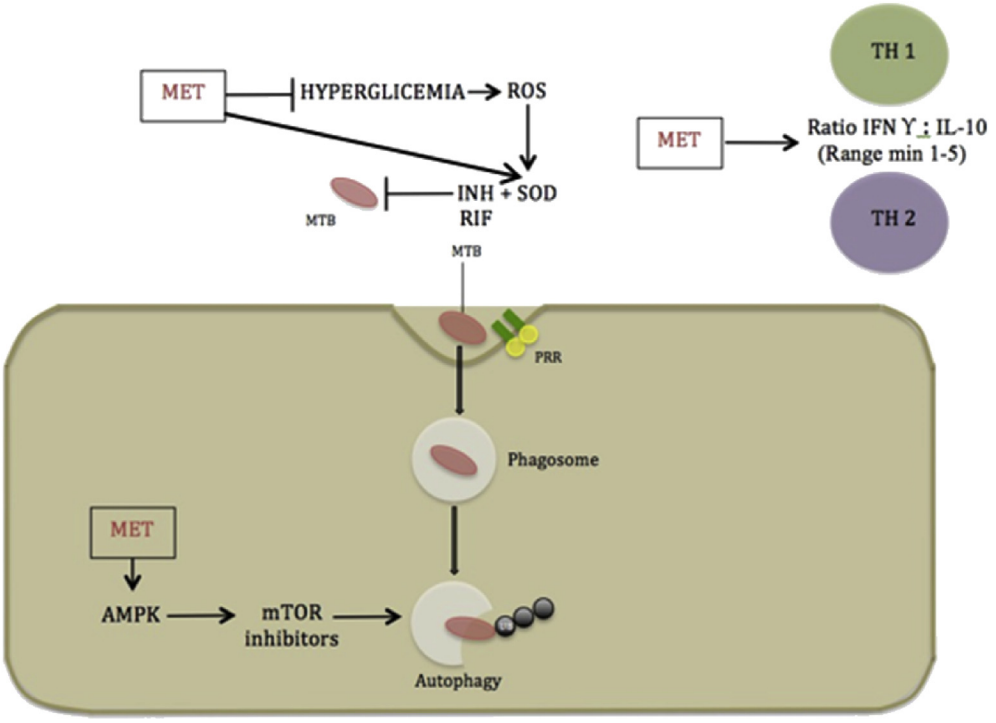


Fig. 1 – Mechanism of Action Metformin as Adjuvant therapy for DM-TB coinfection patients.

pharmacodynamics aspect has no effect to M.tb but works on host immune regulation.[34,38]

6. Metformin, interferon gamma (IFN-γ), interleukin (IL)-10 and its ratio

IFN-γ increases in chronic TB infection as the body's cellular immune response. Currently, IFN-release assay (IGRA) is used as a diagnostic tool for latent TB infection and as an indicator of therapeutic success in active TB infectionf.[39–41] IL-10 is a negative feedback regulator on the immune response produced by Th2 to inhibit excessive production of pro-inflammatory cytokines. IL-10 barriers the macrophage function, due to suppression of MHC class II molecules and reduces co-stimulator expression.[42–44]

MET associated AMPK activation, through thioredoxin-interacting protein (TXNIP) decreases activation of inflammatory mediators and transcription factors, including NF kappa B which encodes proinflammatory mediators45,46. In addition, in intracellular infections such TB MET through AMPK is also stimulated macrophage autophagy34,36, therefore MET accelerates M.tb elimination process without excessive inflammatory processes that can damage the tissue47.

7. Side effects of metformin that might occur

Gastrointestinal disorders (anorexia, nausea, vomiting and diarrhea) is one of the most common MET's side effect. Impaired absorption of vitamin B_{12}, impaired liver and orkidney function or in elderly people.[11,12] Increased levels of lactate or known as Metformin-associated lactoacidosis (MALA) although the occurrence is low, must still be prevented. MALA is a life-threatening event.[45] However, in Diabetes Tuberculosis coinfection patients, MALA could be prevented by determining patients criterias, including: 1) has minimal - moderate advanced pulmonary lesions in X-ray chest examination; 2) has oxygen saturation has at least above 92%; 3) has normal liver function (SGOT, SGPT) and normal kidney function (BUN, SK). Providing consultation, information and education related to the symptoms of lacto-acidosis is also needed during MET additional therapy. MET may increases lactate but rarely increase the risk of DM-TB coinfection patients experience MALA.[46,47] Therefore, MET is relatively safe to use for DM-TB coinfection patients.

8. What we will do in the future?

Developing new drug in host directed therapy that has similar function to MET is a prospective project. Enhancing anti tuberculosis efficacy through host immune response is future approach in TB elimination. MET has several potential effect in enhance anti TB, its side effect remains unpleasant.

Conflicts of interest

The author has none to declare.

Acknowledgement

This project was funded by Widya Mandala Catholic University Surabaya for Doctoral Research. Special thank to Gerardo who provide such good illustration for this paper.

REFERENCES

1. Depkes RI. Tuberkulosis : temukan obati sampai sembuh. *Tuberkulosis temukan obati sampai sembuh*. 2016;2–10:24442–27659.
2. Kementerian Kesehatan Republik Indonesia. *Data Dan Informasi Profil Kesehatan Indonesia Tahun*. vol. 2017. 2016:100.
3. Erkens CGM, Kamphorst M, Abubakar I, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J*. 2010;36(4):925–949. https://doi.org/10.1183/09031936.00201609.
4. WHO, World Health Organization. *Collaborative Framework for Care and Control of Tuberculosis and Diabetes*. 2011. ISBN 978 92 4 150225 2.
5. Ogbera AO, Kapur A, Abdur-Razzaq H, et al. Clinical profile of diabetes mellitus in tuberculosis. *BMJ Open Diabetes Res Care*. 2015;3(1). https://doi.org/10.1136/bmjdrc-2015-000112. e000112.
6. Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes : a systematic review. *BMC Med*. 2011;9(81):1–15. https://doi.org/10.1186/1741-7015-9-81.
7. Stevenson CR, Critchley JA, Forouhi NG, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health? *Chronic Illness*. 2007;3(3):228–245. https://doi.org/10.1177/1742395307081502.
8. Munhoz CD, Martins JO, Cerchiaro GA, et al. Neutrophil function and metabolism in individuals with diabetes mellitus. *Braz J Med Biol Res*. 2007;40:1037–1044.
9. Ernst JD. The immunological life cycle of tuberculosis. *Nat Rev Immunol*. 2012;12(8):581–591. https://doi.org/10.1038/nri3259.
10. Silva Miranda M, Breiman A, Allain S, Deknuydt F, Altare F. The tuberculous granuloma: an unsuccessful host defence mechanism providing a safety shelter for the bacteria? *Clin Dev Immunol*. 2012;2012:139127. https://doi.org/10.1155/2012/139127.
11. Brunton L, Chapner B, Knollmann B. In: Brunton L, Chapner B, eds. *The Pharmacological Basis of Therapeutics-Goodman & Gillman-*. 12th ed. San Diego, California: Mc Graw Hill Medical; 2011.
12. Katzung BG, Mastres SB, Trevor AJ. *Basic & Clinical Pharmacology*. 14th ed. Singapore: Mc Graw Hill Education (Asia); 2018.
13. Sotsuka T, Sasaki Y, Hirai S, Yamagishi F, Ueno K. Association of isoniazid-metabolizing enzyme genotypes and isoniazid-induced hepatotoxicity in tuberculosis patients. *In Vivo*. 2011;25(5):803–812. http://www.ncbi.nlm.nih.gov/pubmed/21753138.
14. Parida SK, Axelsson-Robertson R, Rao MV, et al. Totally drug-resistant tuberculosis and adjunct therapies. *J Intern Med*. 2015;277(4):388–405. https://doi.org/10.1111/joim.12264.
15. Milburn H, Ashman N, Davies P, et al. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. *Thorax*. 2010;65(6):557–570. https://doi.org/10.1136/thx.2009.133173.
16. Thee S, Seddon J a, Donald PR, et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. *Antimicrob Agents Chemother*. 2011;55(12):5560–5567. https://doi.org/10.1128/AAC.05429-11.
17. Azad AK, Sadee W, Schlesinger LS. Innate immune gene polymorphisms in tuberculosis. *Infect Immun*. 2012;80(10):3343–3359. https://doi.org/10.1128/IAI.00443-12.
18. Rayasam GV, Balganesh TS. Exploring the potential of adjunct therapy in tuberculosis. *Trends Pharmacol Sci*. 2015;36(8):506–513. https://doi.org/10.1016/j.tips.2015.05.005.
19. Koch A, Cox H, Mizrahi V. Drug-resistant tuberculosis: challenges and opportunities for diagnosis and treatment. *Curr Opin Pharmacol*. 2018;42:7–15. https://doi.org/10.1016/j.coph.2018.05.013.
20. Harries AD, Satyanarayana S, Kumar AMV, et al. Epidemiology and interaction of diabetes mellitus and tuberculosis and challenges for care : a review of diabetes mellitus. *Public Health Action*. 2013;I(May):S3–S9.
21. Riza AL, Pearson F, Ugarte-gil C, et al. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *Lancet Diabetes Endocrinol*. 2016;2(9):740–753. https://doi.org/10.1016/S2213-8587(14)70110-X.Clinical.
22. Hawn TR, Matheson AI, Maley SN. Host-directed therapeutics for Tuberculosis : can we harness the host ? *Microbiol Mol Biol Rev*. 2013;77(4):608–627. https://doi.org/10.1128/MMBR.00032-13.
23. Wallis RS, Hafner R. Advancing host-directed therapy for Tuberculosis. *Nat Rev Immunol*. 2015;15(4):255–263. https://doi.org/10.1038/nri3813.
24. Singhal A, Jie L, Kumar P, et al. Metformin as adjunct antituberculosis therapy. *Sci Transl Med*. 2014;6(263). https://doi.org/10.1126/scitranslmed.3009885, 263ra159-263ra159.
25. Vashisht R, Brahmachari SK. Metformin as a potential combination therapy with existing front-line antibiotics for Tuberculosis. *J Transl Med*. 2015;13(83):1–3. https://doi.org/10.1186/s12967-015-0443-y.
26. Restrepo BI. Metformin: candidate host-directed therapy for tuberculosis in diabetes and non-diabetes patients. *Tuberculosis*. 2016;101:S69–S72. https://doi.org/10.1016/j.tube.2016.09.008.
27. Kaminski M, Kiessling M, Süss D, Krammer PH, Gülow K. Novel role for mitochondria: protein kinase Ctheta-dependent oxidative signaling organelles in activation-induced T-cell death. *Mol Cell Biol*. 2007;27(10):3625–3639. https://doi.org/10.1128/MCB.02295-06.
28. Allen BW, Demchenko IT, Piantadosi CA. Two faces of nitric oxide: implications for cellular mechanisms of oxygen toxicity. *J Appl Physiol*. 2009;106(2):662–667. https://doi.org/10.1152/japplphysiol.91109.2008.
29. Omori K, Ohira T, Uchida Y, et al. Priming of neutrophil oxidative burst in diabetes requires preassembly of the NADPH oxidase. *J Leukoc Biol*. 2008;84(1):292–301. https://doi.org/10.1189/jlb.1207832.
30. Palanisamy N, Manian S. Protective effects of Asparagus racemosus on oxidative damage in isoniazid-induced hepatotoxic rats: an in vivo study. *Toxicol Ind Health*. 2012;28(3):238–244. https://doi.org/10.1177/0748233711410911.
31. Yilmaz B, Sucak A, Kilic S, et al. Metformin regresses endometriotic implants in rats by improving implant levels of superoxide dismutase, vascular endothelial growth factor, tissue inhibitor of metalloproteinase-2, and matrix metalloproteinase-9. *Am J Obstet Gynecol*. 2010;202(4). https://doi.org/10.1016/j.ajog.2009.10.873, 368.e1-8.
32. Hink J, Thom SR, Simonsen U, Rubin I, Jansen E. Vascular reactivity and endothelial NOS activity in rat thoracic aorta during and after hyperbaric oxygen exposure. *Am J Physiol Heart Circ Physiol*. 2006;291(4):H1988–H1998. https://doi.org/10.1152/ajpheart.00145.2006.

33. Bachmakov I, Glaeser H, Fromm MF, König J. Interaction of oral antidiabetic drugs with hepatic uptake transporters: focus on organic anion transporting polypeptides and organic cation transporter 1. *Diabetes*. 2008;57(6):1463–1469. https://doi.org/10.2337/db07-1515.
34. Novita BD, Ali M, Pranoto A, Soediono EI, Mertaniasih NM. Metformin induced autophagy in diabetes mellitus – tuberculosis co-infection patients: a case study. *Indian J Tuberc*. 2019;66(1):64–69. https://doi.org/10.1016/j.ijtb.2018.04.003.
35. Caire-Brändli I, Papadopoulos A, Malaga W, et al. Reversible lipid accumulation and associated division arrest of Mycobacterium avium in lipoprotein-induced foamy macrophages may resemble key events during latency and reactivation of tuberculosis. *Infect Immun*. 2014;82(2):476–490. https://doi.org/10.1128/IAI.01196-13.
36. Zhuang Y, Miskimins WK. Metformin induces both caspase-dependent and poly(ADP-ribose) polymerase-dependent cell death in breast cancer cells. *Mol Canc Res*. 2011;9(5):603–615. https://doi.org/10.1158/1541-7786.MCR-10-0343.
37. Uhlin M, Andersson J, Zumla A, Maeurer M. Adjunct immunotherapies for tuberculosis. *J Infect Dis*. 2012;205(suppl 2):325–334. https://doi.org/10.1093/infdis/jis197.
38. Hur KY, Lee M-S. New mechanisms of metformin action. *J Diabetes Investig*. 2015;4. https://doi.org/10.1111/jdi.12328. n/a-n/a.
39. Lange C, Pai M, Drobniewski F, Migliori GB. Interferon-gamma release assays for the diagnosis of active tuberculosis: sensible or silly? *Eur Respir J*. 2009;33(6):1250–1253. https://doi.org/10.1183/09031936.00019709.
40. Chee CBE, KhinMar KW, Gan SH, et al. Tuberculosis treatment effect on T-cell interferon-gamma responses to Mycobacterium tuberculosis-specific antigens. *Eur Respir J*. 2010;36(2):355–361. https://doi.org/10.1183/09031936.00151309.
41. Matsushita I, Hang NT Le, Hong LT, et al. Dynamics of immune parameters during the treatment of active tuberculosis showing negative interferon gamma response at the time of diagnosis. *Int J Infect Dis*. 2015;40:39–44. https://doi.org/10.1016/j.ijid.2015.09.021.
42. Gaultier A, Arandjelovic S, Niessen S, et al. Regulation of tumor necrosis factor receptor-1 and the IKK-NF-kappaB pathway by LDL receptor-related protein explains the antiinflammatory activity of this receptor. *Blood*. 2008;111(11):5316–5325. https://doi.org/10.1182/blood-2007-12-127613.
43. Yuhas Y, Berent E, Cohen R, Ashkenazi S. Roles of NF-kappaB activation and peroxisome proliferator-activated receptor gamma inhibition in the effect of rifampin on inducible nitric oxide synthase transcription in human lung epithelial cells. *Antimicrob Agents Chemother*. 2009;53(4):1539–1545. https://doi.org/10.1128/AAC.00961-08.
44. Kresno SB. *Imunologi : Diagnosis Dan Prosedur Laboratorium*. V. Badan Penerbit Fakultas Kedokteran Universitas Indonesia; 2013.
45. Suh S. *Metformin-Associated Lactic Acidosis*. 2015:45–46.
46. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Arch Intern Med*. 2003;163:2594–2602.
47. Novita BD, Pranoto A, Wuryani, Soediono EI, Mertaniasih NM. A case risk study of lactic acidosis risk by metformin use in type 2 diabetes mellitus tuberculosis coinfection patients. *Indian J Tuberc*. 2018;65(3):252–256. https://doi.org/10.1016/j.ijtb.2017.05.008.