A case risk study of lactic acidosis risk by metformin use in type 2 diabetes mellitus tuberculosis coinfection patients

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Original Article

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ABSTRACT

Metformin (MET) has possibilities to be utilized as an adjunct of tuberculosis (TB) therapy for controlling the growth of *Mycobacterium tuberculosis* (*M. tuberculosis*). MET enhances the production of mitochondrial reactive oxygen species and facilitates phagosome–lysosome fusion; those mechanism are important in *M. tuberculosis* elimination. Moreover, MET-associated lactic acidosis (MALA) needs to be considered and the incidence of MALA in patients with type 2 DM–TB coinfection remains unknown. This result contributes much to our understanding about the clinical effect of MET use in type 2 DM–TB coinfection.

For the purpose of understanding the MET effect as an adjuvant therapy in TB therapy and insulin simultaneous therapy, an observational clinical study was done in type 2 DM newly TB coinfection outpatients at Surabaya Paru Hospital. Patients were divided into two groups. First group was MET group, in which the patients were given MET accompanying insulin and TB treatment regimens, the golden standard therapy of DM–TB coinfection. MET therapy was given for at least 2 months. Second group was non-MET group, in which the patients were given insulin and TB treatment regimens. The lactate levels in both groups were measured after 2 months.

Among 42 participants, there was no case of lactic acidosis during this study period. Data were normally distributed; thus, we continued analysis of the difference using paired *T*-test with 95% confidence. There was no difference in lactate levels ($p = 0.396$) after MET therapy compared to non-MET group.

In this study involving patients with TB pulmonary diseases, there is neither evidence that MET therapy induced lactic acidosis event nor that it increased lactate blood level. Thus, we concluded that MET use in type 2 DM–TB coinfection did not induce lactic acidosis.

1. Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality throughout the world; one-third of the world's population is estimated to be infected with *M. tuberculosis* whereby approximately nine million people develop the disease each year, and almost two million die annually as a result.[1] DM–TB coinfection is associated with poor glycemic control in DM patients, and thus elevated proinflammatory state.[2–4] People with DM had approximately three times the risk of developing TB disease as people without.[2,5–10]

Metformin hydrochloride (MET) MET, the biguanide, have been used for treating type 2 diabetes mellitus for more than 60 years. MET works by inhibiting the production of hepatic glucose, reducing intestinal glucose absorption, and improving glucose uptake and utilization.[11–14] Recently, by a comprehensive in silico study, MET was known to have possibilities of being utilized as a combination drug with existing antibiotics for TB therapy,[15] and by an extensive in vitro study, MET was reported to control the growth of drug-resistant *M. tuberculosis*

strains via production of mitochondrial reactive oxygen species and facilitating phagosome–lysosome fusion.[16,17]

MET is not metabolized by P450 enzymes[12,13,18]; thus, it has no interaction with rifampicin (RIF) that could decrease therapy efficacy. However, interaction between MET and RIF increases the expression of organic cation transporter (OCT1) and hepatic uptake of MET, leading to enhanced lowering of glucose levels.[19,20]

In our previous study, MET was given to type 2 DM newly TB coinfection patients, which improved the superoxide dismutase (SOD) level (unpublished). SOD improvement after MET therapy is predicted to enhance antituberculosis efficacy and is considered to reduce the intracellular growth of *M. tuberculosis*. Collectively, these data indicate that MET is a promising candidate for host-adjunctive therapy for enhancing the effective treatment of TB.[15,21]

Although MET has several advantages in improving treatment of TB, MET use is still considered to be contraindication in many chronic conditions that may increase the risk of tissue anoxia, the development of MALA, a fatal metabolic condition, and especially pulmonary diseases due to the existence of potential hypoxia.[17,22,23]

Lactic acidosis is characterized by an elevated blood lactate concentration (>45.0 mg/dL or >5.0 mmol/L), decreased blood pH (<7.35), and electrolyte disturbances with increased anion gap[17,23–30]; it also has signs and symptoms of inadequate oxygen (hypoxia) such as shortness of breath, rapid breathing, paleness, sweating, nausea, muscle weakness, abdominal pain, and coma.[22,26,31]

The objective of this study is to assess the risk of lactic acidosis associated with MET use in patients with type 2 DM newly TB coinfection, as well as combination of MET with golden standard therapies, insulin, and TB treatment regimens. Another objective is to evaluate levels of blood lactate, measured at during treatment.

2. Materials and methods

2.1. Study design

The objective of this study was to identify clinical effect of MET to modulate host immune system and its ability to control the growth of intracellular *M. tuberculosis*. Thus, an observational clinical study was done and carried out at outpatient ward of Surabaya Paru Hospital. Patient's inclusion criteria were the following: (1) patients with DM with new case of TB coinfection, who were given insulin and TB treatment regimens; (2) positive *M. tuberculosis* in sputum smear; (3) age of 25–60 years; (4) has normal liver function and renal function; (5) not in hypoxia condition, and on presentation, peripheral oxygen saturation level must be higher than 92%.

During this clinical study, type 2 DM newly TB coinfection patients were divided into two groups. First group was MET group, in which the patients were given MET accompanying insulin and TB treatment regimens, the golden standard therapy of DM–TB coinfection. MET therapy was given for at least 2 months. Second group, a comparison group, was non-MET group, in which the patients were given insulin and TB treatment regimens.

We evaluated MET combined with insulin and TB treatment regimens. MET therapy was given for at least 2 months. During MET therapy, as a follow-up program, patients were physical examined weekly; thus, signs and symptoms for lactic acidosis were monitored. Lactate level was measured after 2-month MET therapy for MET group. For comparison, patients belonging to non-MET group, who were given insulin and TB treatment regimens, were also physical examined weekly and lactate level was measured after 2-month insulin and anti-TB therapy.

2.2. Diagnosis and management therapy

The diagnosis of TB was established by (1) clinical symptoms and signs of TB, such as chronic productive cough, unintentional weight loss; (2) positive sputum smear of acid-fast bacteria by microscopic Ziehl–Neelsen-stained sputum slides; and (3) chest radiographs with suggestive features of TB. Diagnosis of DM was established by fasting and 2 h after meal blood glucose levels. HbA1c was measured after 2 months of MET therapy, as evaluation.

Patients diagnosed with TB were registered and treated with TB treatment regimens for a period of 6 months in accordance to WHO guidelines.[32–34] Management therapy for achieving good glycemic control was insulin therapy.

These following drugs were used: MET (Metformin®), insulin (Humulin®), RIF, isoniazid (INH), pyrazinamide (PYR), and ethambutol (ETH). MET was given 1000–1500 mg in divided daily dose for at least two months or during intensive phase of TB treatment, accompanying insulin therapy and TB treatment regimens.

2.3. Lactate blood measurement

After at least 2 months therapy, whole blood samples, in both groups, were measured by using Biosen C-line glucose and lactate analyzer® to test lactate blood levels.[26]

3. Results

3.1. Characteristics of patients

During this study period, there were 476 cases of new TB infection and 156 cases (~30%) of what were type 2 DM newly TB coinfection. 42 patients, with equal number of males and females, were eligible and participated in this observational study (Table 1). The condition in both groups was homogenous ($p = 0.17$; $p > 0.05$) using *Saphiro Wilk test*. The youngest patient's age was 26 years.

Table 1 – Characteristics of patients' sex and ages.

Sex	MET group		Non-MET group	
	N	Age ($\bar{X}\pm SD$)	N	Age ($\bar{X}\pm SD$)
Male	11	44.29 ± 9.76	12	43.00 ± 9.14
Female	11	43.45 ± 9.10	8	49.63 ± 6.44
Total	22	43.78 ± 9.08	20	47.53 ± 7.53

Table 2 – Distribution of patient's eligibility criteria.

Parameters	MET group	Non-MET group	*p* (difference)
HbA1c (g/dL)	8.82 ± 1.91	9.52 ± 2.02	0.379
Oxygen saturation (SpO_2) (%)	98.06 ± 0.73	97.47 ± 0.83	0.308
BUN (mg/dL)	0.95 ± 0.16	0.93 ± 0.13	0.980
Creatinine serum (U/L)	23.92 ± 11.92	27.3 ± 12.01	0.103
SGOT (U/L)	17.63 ± 6.16	14.44 ± 6.48	0.354
SGPT (U/L)	19.22 ± 8.73	16.09 ± 7.56	0.509

Table 3 – Lactate blood level.

MET group (mmol/L)	Non-MET group (mmol/L)	*p* (difference)
1.77 ± 0.60	1.71 ± 0.54	0.240

Distribution of patient's eligibility criteria such as HbA1c, oxygen saturation, renal function (BUN and creatinine serum), and liver function (SGOT, SGPT) are shown in Table 2. All data were normally distributed using *Saphiro Wilk* test; thus, we continued analysis of the data for the difference using paired *T*-test statistics with 95% confidence.

Blood glucose condition for both groups was similar ($p = 0.26$); thus, we dismissed the influence of hyperglycemia condition on lactate blood level.[26,35]

3.2. *Lactate blood level*

After observational of MET therapy, on divided daily dose of 1000–1500 mg for at least 2 months accompanying insulin therapy and TB treatment regimens. Lactate blood levels were measured after 2 months of MET therapy.

There was no incidence of lactic acidosis event during this period. Additionally, other side effects of MET therapy such as gastrointestinal intolerance were also reported. Only two cases of mild gastrointestinal disturbance, such as mild frequent diarrhea and nausea/vomiting, were reported.

Lactate blood level in both groups was normally distributed using *Saphiro Wilk test* ($p = 0.24$; $p > 0.05$); then, we analyzed the difference between both groups using paired *T*-test (Table 3 and Fig. 1).

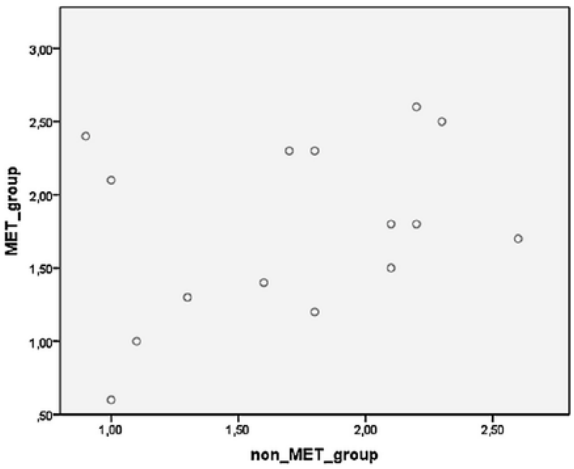

Fig. 1 – Lactate blood level (mmol/L).

Comparing MET group with non-MET group, we concluded there was no statistically significant difference of lactate blood level after at least 2 months of MET therapy ($p > 0.05$). The level of blood lactate was in the normal range (less than 2.50 mmol/L) both in MET group and also non-MET group.

4. Discussion

The optimum treatment strategy for DM–TB coinfection remained unclear to date. Uncontrollable chronic hyperglycemia in DM patients increases the incidence of TB therapy failure. Besides, DM is also associated with deaths due to TB infection and relapse of TB infection.[4,9,36–38] TB treatment for TB patients with DM is no different from treatment for patients without DM.[5] Insulin becomes the main therapy to control hyperglycemia condition. In this study, DM–TB patients got insulin and TB treatment, with TB regimen dose referring to World Health Organization (WHO).

Identification of new host-directed therapies that can improve clinical outcomes for DM–TB coinfection patients has been a priority by the WHO, leading to the study of immunomodulatory agents for adjunct treatment of TB.[21,39–41]

MET in some studies enhances *M. tuberculosis* – specific host immunity, reduces inflammation, and enhances efficacy of TB treatment. MET, which is not metabolized by P450[12,13,18] enzyme, does not decrease the efficacy of RIF. Interaction between MET and RIF increases OCT1 expression, which has its role in blocking *M. tuberculosis*[15,42] transcription. SOD is one essential factor to prevent INH resistency,[43] and MET has been known to increase SOD.[44–46] Hence, it can be concluded that MET possesses the potency to boost OAT effectiveness. MET treatment was associated with improved control of *M. tuberculosis* infection and decreased disease severity.[15,16]

The use of MET may cause side effects such as digestion problem (anorexia, nausea, vomit, and diarrhea), lactate level increase, vitamin B_{12} malabsorption, and kidney/heart function problem.[12,13] Though the incidence of MET-associated lactic acidosis (MALA) is low, it must be prevented as it threatens lives. In this study, MALA can occur in very rare situations such as (1) *drug-induced hepatitis* caused by OAT and/or MET and (2) lung damage, which becomes worse causing hypoxia.[47,48] MALA prevention in this study has been determined at the following precondition criteria: (1) minimal to moderate lung lesion; (2) oxygen saturation > 92%; (3) normal function of SGOT and SGPT, and normal kidney function (BUN and SK) (see Table 2). This study also provides consultation,

information, and education related to symptoms of *lactic acidosis*.

Lactic acidosis is also influenced by high glycemic index. To minimize the bias due to hyperglycemia, HbA1c measurement was done 2 months after the MET therapy accompanying insulin and TB treatment regimens for MET group. HbA1c, for non-MET group, was also performed after 2 months of insulin and OAT therapy, or after intensive TB therapy phase was done (see Table 2).

There were no MALA cases during this 2-month study, both for MET and non-MET groups. It was even proved that blood lactate level was in normal range (<2.50 mmol/L). The blend of MET, insulin, and TB treatment was relatively safe for DM–TB patients if some condition was controlled (see Table 3).

In this study, we also found that the participants (<5%) in MET group experienced mild gastrointestinal intolerance (nausea and vomit). This can be related to high concentrated MET or glucose metabolism change causing local irritation, fluid retention, and salt malabsorption, leading to loose stools and diarrhea.[17]

In this study, we were not yet involved TB patients non-type 2 DM, even in our knowledges MET, which has low hypoglycemic effect, could be beneficial in TB patients non-DM due to anti-inflammatory effect and increasing efficacy of TB treatment.[21,41] In future, after establishing MET clinical effect in type 2 DM–TB coinfection, we may combine MET therapy with anti-TB for TB patients with non-type 2 DM in order to evaluate the efficacy of MET therapy in immune modulation.

5. Conclusion

Lactic acidosis in MET therapy is a rare but important adverse event and clearly we need to prevent it. In this case risk study, there is no evidence of MALA. Elevation of levels of lactate, compared with placebo, also did not occur. Thus, we concluded that MET use in type 2 DM–TB coinfection did not induce lactic acidosis. Furthermore, this result, due to our limitation in number of participants involved in the study, needs to be confirmed in a cohort study.

Conflicts of interest

The authors have none to declare.

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