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Case Report Open Access

Metformin Associated Interleukin-10 Affected Insulin Sensitivity and Anti-Tuberculosis Result in Type 2 Diabetes with Tuberculosis Co-infection: A Case Report

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Abstract

Insulin is one of drug of choice in lowering blood glucose in diabetes patients with or without infection. Interleukin (IL)-10 an anti-inflammatory cytokine, plays a protective role in diabetes. The lack of IL-10 associated to development and progression of insulin resistance. On the other hands, Interferon (IFN)-γ elevation is one of the indicators of successful treatment in active TB infection and IL-10 inhibits IFN-γ secretion. Metformin has ability in increasing insulin response and also has protective effect against TB in DM patients. However the relationship between metformin and insulin induced IL-10 and metformin enhanced anti tuberculosis remains unclear.

Keywords: Insulin; Type 2 diabetes; Tuberculosis

Introduction

Tuberculosis (TB) nowadays is one of "global health emergency" diseases [1]. Diabetes mellitus (DM), a dysfunction metabolic disease affecting immune response carries a two to threefold increased risk for TB in these patients over patients without DM [2-4]. High interferon (IFN)-γ is an indicator of anti-tuberculosis (TB) successful TB eradication due to its ability in modulating the production or activities of several cytokines and chemokines [5-8]. Low IL-10 plays a critical role in the development and progression of insulin resistance [9,10]. However, IL-10 reduces the function of macrophages and dendritic cells by inhibiting IFN-γ [6,11].

Metformin hydrochloride (MET), biguanide, use in type 2 diabetes mellitus by several mechanisms of action (1) inhibiting gluconeogenesis or hepatic glucose production; (2) reducing intestinal glucose absorption; and (3) improving glucose uptake and utilization [12-15]. MET also has protective effect in TB patients and recently, by a comprehensive in silico study, MET known has possibilities of controlling the growth of drug-resistant *M.tuberculosis* strains via production of mitochondrial reactive oxygen species and facilitates phagosome-lysosome fusion [16] and its immunomodulation effect [17,18].

Materials and Methods

Study design

This involved type 2 DM–TB co-infection patients of observational clinical study within two groups, observation group, and the comparison group. The observation group (MET group) was the group receiving metformin therapy 1000 mg to 1500 mg along with insulin and anti-TB during the intensive periods, while the comparison group (non-MET group) received insulin and anti-TB therapy. Patients were carried out at outpatient ward of Surabaya Paru Hospital, with criterias: (1) patient DM with a new case of TB co-infection, who were given insulin and anti-TB regimens; (2) positive AFB in sputum smear (three times assessments); (3) Patient's age was 25 to 60 years old; (4) has normal liver function and renal function; (5) not in hypoxia condition, presenting by peripheral oxygen saturation level must be higher than 92%. The levels of IL-10 were measured before and after this observation period and as a clinical result, we also evaluated the smear reversion (two times smear assessments after the intensive phase of anti-TB therapy) in DM-TB co-infection patients in both of groups.

Diagnosis and management therapy

The diagnosis of TB was established by (1) clinical symptoms and signs of TB, such: chronic productive cough, unintentional weight loss; (2) positive sputum smear of acid-fast bacilli (AFB) by microscopic Ziehl-Neelsen-stained sputum slides (three times assessment and chose the highest levels of AFB); and (3) chest radiographs with suggestive features of TB.

Patients diagnosed with TB were registered and treated with anti-TB for a period of 6 months in accordance to WHO guidelines [19,20]. Management therapy for achieving good glycaemic control was insulin therapy. These following drugs were used: MET (Metformin(R)), insulin (Humulin (R)), rifampicin (RIF), isoniazid (INH), pyrazinamide (PYR), ethambutol (ETH). MET were given 1000-1500 mg in the divided daily dose for at least two months or during the intensive phase of TB treatment, accompanying insulin and anti-TB.

Acid Fast Bacilli smears (AFB)

Sputum smears were stained by the Ziehl-Nielsen technique and examined by light microscopy for AFB. Sputum was collected two times: (1) before treatment in order to diagnose (three times assessment and chose the highest levels of AFB) and (2) after the intensive phase of anti-TB treatment in order to do evaluation (two times assessment and chose the highest levels of AFB).

Cells culture and ELISA

Cells and ELISA: PBMC was obtained from patients' whole blood and 1×10^6 were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum, 0.1 µg mantoux and 0.7 µg penicilline. Supernatant were harvested after 72 hours and prepare for ELISA methods in order to measure the levels of IFN-γ and IL-10. ELISA. IL-10 (RnD P113058) was used as measurement kits.

Result

Characteristic of patients

This study's ethical clearance was approved by ethical committee of Surabaya Paru Hospital with no. 09.01/KERS/102.6/2016 and written informed consent obtained from all participants after information for consent was given by the investigators. During this study period, there were 476 cases of new TB infection and 156 cases (~30%) of that was type 2 DM-TB co-infection. 42 patients were eligible participated in these observational studies. All the basic conditions in both groups were homogeneous (p>0.05) (Table 1). In order to prevent MET associated lacto acidosis (MALA) during MET therapy in this study, all patients 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, Creatinine serum) (Table 1). Moreover, there was no incidence of lactic acidosis event during this observation period [21]. 100% of MET group has AFB reversion while only 75% of control group has (Table 2).

Interleukin -10

IL-10 has ability to inhibit the T lymphocyte production of cytokines, including IFN-γ [11,22,23]. Using Wilcoxon-Mann Whitney, nonparametric statistical test, Figure 1 shows that IL-10 level before treatment between MET group and non-MET group were alike (p>0.005), thus it shows that patients in both groups, before treatment, were in the similar stage of IL-10. Although IL-10 level was increased, the differences before and after observation period was not significant between MET and non-group (p>0.005). Difference of interleukin-10 level pre and post observation in MET group was not significantly different from non-MET group.

Parameters	MET group	Non MET group	P (difference)
Ages (years old)	44.59 ± 8.64	48.40 ± 8.17	0.863
HbA1c (%)	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	0.98
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 1: Characteristic of type 2 DM-TB co-infection during observation period of study; [Participants characteristic condition before observation periods. HbA1c was measured after 2 months observation period].

AFB Result	MET group		Non MET group	
	Before (%)	After (%)	Before (%)	After (%)
Negative	0	100	0	75
Scanty/+1	40.9	0	30	25
2	18.2	0	35	0
3	40.9	0	35	0
Total	100	100	100	100
Interpretation	100% AFB Reversion		75% AFB Reversion	

Table 2: Acid Fast Bacilli smears result of type 2 DM-TB patients before and after observation period.

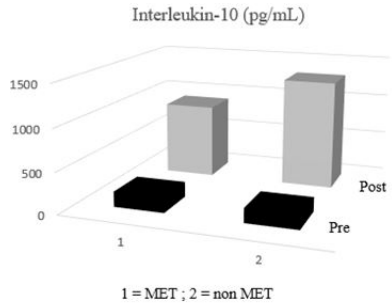

Figure 1: Interleukin (IL)-10 level of type 2 DM-TB patient before and after observation period.

Discussion

IL-10 a major anti-inflammatory cytokines plays important role in metabolic disorder such diabetes due its affect to insulin sensitivity [10]. It suppresses macrophage function and inhibits proinflammatory cytokines such IFN-γ, TNF-α and IL-1β. The increase in IL-10 levels appears to support the mycobacterial survival in the host [22] due to the inhibition of autophagy targeting signals through IL-10 activated SOCS3, and then, SOCS3 inhibits the Janus kinase-2 (Jak2)/signal transducer and activator of transcription (Stat) pathway in activating macrophage autophagy [24,25]. In this study, the increasing of IL-10 may happen not only due to macrophage related Th-2 activation but also due to insulin attenuated anti-inflammation regulatory [10,26-28]. Based on this result, MET therapy may consider as new strategy in enhancing anti TB efficacy due to its two main ability:

- MET controlled IL-10 secretion thus alter host immune response against TB infection; and
- MET also affects in Insulin sensitivity.

However, the further study requires in supporting this result in a larger population's number of DM-TB co-infection patients.

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