**Diabetes characteristics and long-term management needs in diabetic tuberculosis patients in Indonesia**

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**SUMMARY**

*Background:*Diabetes mellitus (DM) is common among tuberculosis (TB) patients. We assessed DM characteristics and long-term needs of DM-TB patients after completing TB therapy.

*Methods:*Newly diagnosed TB patients with DM were recruited as part of screening for a randomised clinical trial evaluating a simple algorithm to improve glycemic control during TB treatment. DM characteristics, lifestyle, and medication were compared before and after TB treatment and six months later. Cardiovascular disease (CVD) risk, albuminuria, and neuropathy were assessed after TB therapy.

*Results:*Of 218 TB-DM patients identified, 170 (78%) were followed up. Half were males, mean age of 53 years, 26.5% newly diagnosed DM. High HbA1c at TB diagnosis (median 11.2%) decreased during TB treatment (to 7.4% with intensified management and 8.4% with standard care), but this effect was lost six months later (9.3%). Hypertension and dyslipidemia contributed to a high 10-year CVD risk (32.9% at month 6 and 35.5% at month 12). Neuropathy (33.8%) and albuminuria (61.3%) were common. After TB therapy, few patients used CVD-mitigating drugs.

*Conclusion:*DM in TB-DM patients is characterised by poor glycemic control, high CVD risk and nephropathy. TB therapy provides opportunities for better DM management, but effort is needed to improve long-term care.

*Keywords:* urban setting, glycaemic control, cardiovascular risk, nephropathy

**INTRODUCTION**

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by elevated blood glucose levels and increased cardiovascular and other complications risk.1 DM requires ongoing management comprising counselling, diet, exercise, monitoring, and treatment. People living with DM are also at a higher risk of acquiring severe infections, one of which is tuberculosis (TB).2

Patients with combined DM and TB face challenges controlling their blood glucose levels. Active TB leads to inflammation-induced hyperglycaemia. Moreover, drug interactions, diet changes, reduced physical activity during illness, and lack of integrated TB and DM health services potentially hamper good glycemic control.3 TB-DM patients often present very high HbA1c levels that decline during TB treatment.4 In a previous randomised clinical trial (RCT) of patients with TB-DM in Indonesia, we have shown that a simple algorithm with frequent monitoring and DM treatment adjustments leads to better glycemic control.5

The first global guidebook on combined DM and TB has recommended continuing DM care and managing DM-associated cardiovascular disease (CVD) risk once TB treatment is completed.6 However, little is known about DM treatment needs for patients with combined TB-DM once TB treatment is completed. Therefore, by following patients screened for our previous RCT for another six months, we aimed to describe patients’ characteristics and long-term needs for glycemic control and CVD risk management.

**METHODS**

*Study design and settings*

Patients were recruited from 44 community health centres (CHC), a TB clinic in a district hospital, and TB and endocrine clinics in a tertiary hospital in Bandung City, Indonesia, between 2014 to 2017. TB patients underwent screening for DM using history taking and repeated laboratory-measured glycated haemoglobin (HbA1c) test,7 while DM patients were screened for pulmonary TB using symptom screening, chest X-rays, and sputum examination.8 Patients eligible for the RCT were aged ≥18 years with newly diagnosed pulmonary TB who had a previous diagnosis of DM or had a laboratory HbA1c ≥7%.5 We used a higher HbA1c cut-off compared to standard DM diagnosis1 to avoid misclassification due to TB-associated hyperglycaemia.9 All patients provided informed consent before enrolment. The study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia (No. 5/UN6.C2.1.2/KEPK/PN/2014) and the Research Ethics Committee, London School of Hygiene & Tropical Medicine, London, UK (LSHTM ethics ref: 6449, LSHTM amendment no. A472).

Full details of the trial have previously been described.5 In brief, patients were randomised into two arms; patients in the intervention arm received a package of structured counselling, clinical monitoring, and algorithm-based DM treatment adjustments in a TB research clinic, while patients in the control arm received standard TB and DM care per routine practice. After 6-months, patients in the intervention arm were referred back to their original health providers (CHC or a hospital outpatient clinic) to continue DM treatment. Patients in the control arm no longer had to come regularly to their clinics for TB treatment, only for their DM treatment.

Patients in both arms were followed-up at months 6 and 12 after enrolment. Patients who refused randomisation but were willing to be followed up, or did not fulfill the RCT inclusion criteria of HbA1c >7% have been included in the analysis of this study in the control group.

*Data collection*

We collected sociodemographic data and interviewed patients about their history of diabetes and complications at enrolment (hereafter referred to as baseline). Complications were self-reported only by known-DM patients. Height was measured only at baseline, while weight was measured at baseline and months 6 and 12. Data on blood pressure, HbA1c, the use of diabetes and CVD medication (antihypertensive, statins, aspirin), smoking, and exercise were collected at baseline, month 6, and month 12. Blood creatinine and lipids: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, and urine albumin creatinine ratio (ACR) were measured at months 6 and 12. Patients were also asked about symptoms of neuropathy at month 6.

Interviews and procedures were undertaken by trained research doctors and nurses using standard operating procedures. Data were entered into an electronic database (REDCap).10 Data quality was checked for accuracy and completeness monthly during the study, and a final check was done after the completion of the study.

*Data analysis*

Patients’ body mass index (BMI) were classified according to the Asia Pacific criteria: underweight (<18.5 kg/m2); normal (18.5-22.9 kg/m2); overweight (23.0-24.9 kg/m2); and obese (≥25.0 kg/m2).11 Blood pressure was categorised based on the JNC VII: normal (systolic and diastolic <120/80 mmHg); pre-hypertension (systolic 120-139 or diastolic 80-89 mmHg); stage I hypertension (systolic 140-159 or diastolic 90-99 mmHg); stage II hypertension (systolic ≥160 mmHg or diastolic ≥100 mmHg).12 Total cholesterol were categorised according to the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.13 Ten-years cardiovascular risk was calculated using World Health Organization (WHO) CVD risk calculator (including laboratory results).14 We calculated estimated glomerular filtration rate (eGFR) according to the CKD-EPI creatinine equation 2009.15 Kidney function was then categorized as: Stage 1 (eGFR ≥90), Stage 2 (eGFR 60-89), Stage 3 (eGFR 30-59), Stage 4 (eGFR 15-29), Stage 5 (eGFR <15).16

The 15-item Michigan Neuropathy Screening Instrument (MNSI) was administered to all participants. Responses were added to obtain a total symptom score: ‘yes’ to questions 1-3, 5-6, 8-9, 11-12, 14-15, and ‘no’ to questions 7 and 13 were each counted as one point. Questions 4 and 10 were excluded from the published scoring algorithm.17 A score of ≥7 was considered abnormal in the original algorithm.17 However, a recent study suggested that ≥4 cut-off improves the instrument’s performance.18 Therefore, the MNSI score in this study is categorised into 0, 1-3, 4-6, and ≥7.

Clinical characteristics of the patients are described as number and percentage for categorical variables and mean and standard deviations (SD) or median and interquartile range (IQR) for numerical variables. The proportion of patients who achieved treatment targets defined by the Indonesian Endocrinologist Association19: BMI <23 kg/m2, systolic blood pressure <140 mmHg, diastolic blood pressure <90, HbA1c <7%, LDL cholesterol <100 mg/dL, HDL cholesterol >40 mg/dL (male) or >50 mg/dL (female), and triglycerides <150 mg/dL are illustrated in a bar graph at each time point.

As a secondary analysis, we compared the mean HbA1c and 95% confidence interval (CI) between randomisation arms of patients with complete HbA1c measurements at baseline, months 6 and 12 using ANOVA repeated measures.

*Results*

From February 2014 to January 2016, we screened 748 TB patients aged ≥18 years and found 128 (17.1%) with DM (non-selective screening). Following this, an additional 160 TB patients with known DM or aged ≥35 with elevated random blood glucose (≥110 mg/dL) or point-of-care HbA1c tests (≥6.5%) were screened for the aforementioned clinical trial,5 bringing the total of TB-DM patients to 218 (Figure 1).

From 218 TB-DM patients identified, 170 were willing to participate. One hundred and fifty were randomised to the intervention (n=76) and control arm (n=74).5 Twenty patients were not randomised: six patients had HbA1c <7%, five were hospitalised, four had started TB treatment before randomisation, four refused randomisation, and one was recruited before the trial began. These 20 patients had a lower median HbA1c (8.9%, IQR 6.2-12.5) than those in the control arm (11.6, IQR 7.8-15.9), and fewer were newly diagnosed DM (15.0% vs 35.1%), while sociodemographic and other clinical characteristics did not differ from the control arm (data not shown). Since these 20 non-RCT patients received no intervention, we added them to the control arm for follow-up analysis, giving a total number of 94 people in the control arm (Figure 1). There were no differences in the results when we removed those patients from the sensitivity analyses.

TB-DM patients had a mean age of 53 years, half were males, and 73.5% had previously been diagnosed with DM (Table 1). Some patients reported a history of heart problems or surgery (4.8%), stroke (3.2%), and angina or heart failure (4.0%). In addition, many patients reported cataracts or eye surgery (10.4%) and visual loss (35.2%) (data not shown).

A total of 148 (87.0%) patients attended follow-up at month 6 and 125 (73.5%) patients at month 12 (Table 1). All patients who attended follow-up visits had their HbA1c measured. At baseline, HbA1c values were very high and one fifth were obese. A minority (14%) were current smokers, half reported regular exercise, and about a quarter had hypertension. Half were taking metformin, 24% were on other oral diabetes medication, and only seven (4.1%) were on insulin. Very few were on antihypertensive medication, antiplatelet or lipid-lowering drugs. About one third of the patients had mild to severe kidney function loss (eGFR Stage 2 – 4 categories).

At month 6, after completion of TB treatment, TB-DM patients showed suboptimal glucose control, signs of diabetic nephropathy and unmet needs in terms of CVD risk. Almost all patients had proteinuria, predominantly clinical albuminuria. Also, most patients had neuropathy (primarily mild or moderate). Obesity (20% baseline, 34% month 6, 40% month 12), hypertension (26% baseline, 41% month 6, 46% month 12), and smoking (14% baseline, 17% month 6, 23% month 12) increased over time (Table 1).

HbA1c had decreased, especially among those randomised to the intervention arm for the duration of TB treatment, but this effect mainly disappeared six months later. The number of patients with complete HbA1c measurement at all time points was 123, with 59 patients in the intervention arm and 64 in the control arm. At baseline, mean HbA1c were 11.1% (95% CI 10.4-11.8) and 11.2% (10.6-11.9) in the intervention arm and control arm, respectively. At month 6, the mean HbA1c in the intervention arm (7.5%, 95% CI 6.9-8.2) was lower compared to the control arm (9.6%, 95% CI 9.0-10.2). The mean HbA1c increased in both arms at month 12; 9.4% (95% CI 8.7-10.1) in the intervention arm and 10.0% (95% CI 9.4-10.6) in the control arm. There was a significant difference of mean HbA1c between intervention arms over time (P = 0.0003) (Figure 2).

At month 12, only 15% achieved an HbA1c <7%, including those who had HbA1c <7% at baseline. Six per cent were underweight (<18.5% kg/m2) and 41% had normal BMI (18.5-22.9 kg/m2) (Table 1), 57% achieved systolic blood pressure <140 mmHg, and 9% achieved LDL <100 mg/dL (Figure 3). Approximately one third (35.5%) of patients had a 10-year CVD risk ≥30% (Table 1). According to national guidelines, many who qualified for insulin (48.2%), antihypertensives (43.2%), and statins (91.1%) did not receive this medication (Figure 4).

**DISCUSSION**

In this study, we found that HbA1c temporarily decreased during TB therapy, especially with a structured counselling and clinical monitoring, only to bounce back afterwards. Moreover, DM nephropathy and neuropathy were common. Despite the hyperglycemia and high estimated CVD risk, few patients used insulin and other indicated drugs according to guidelines, and even fewer met DM treatment targets after completion of TB treatment. These findings highlight the severity of DM in TB-DM patients and the unmet need for continued DM care in this setting.

TB patients with DM presented a much higher HbA1c (median 11.2%) compared to DM patients without TB included in the previous TANDEM project (median 7.8%),8 in line with earlier studies.9,20 These groups come from the same population. Another study on DM patients in Indonesia showed mean HbA1c about 8%,21 suggesting that even though routine DM care in general needs improvement, TB remains a significant factor in the increase of A1c level. Higher HbA1c in TB-DM patients are likely a result of inflammation-induced hyperglycaemia.22 Of note, a hyperglycemic environment during active TB may impact metabolism leading to more complications even after blood glucose levels return to normal after TB treatment, through epigenetic reprogramming on vascular and immune cells.23

Our study shows that CVD risk increased at month 12 compared to month 6, while the CVD medication prescribed was inadequate. This finding is consistent with a previous study of diabetes care in public health facilities.24 Improved DM management is essential to prevent DM complications and for improved TB outcomes such as reduced deaths, failures and relapse. TB can result in high mortality, morbidity, and residual disability, even in successfully treated patients.25 Compared to healthy controls, TB patients have impaired pulmonary function and lower quality of life.26 Moreover, they are at a greater risk of acute coronary syndrome (ACS), the probability of which increases in the years following TB diagnosis.27 Considering that DM is also an independent risk factor for CVD, it is essential to improve clinical management in TB-DM patients to prevent early mortality and loss of productivity from TB sequelae or DM complications.

This study was linked to an RCT which showed that we could achieve better glycaemic control during TB treatment through a simple algorithm. However, after TB treatment was finished, few people achieved treatment targets, indicating that more effort is required to sustain glycaemic control. The higher A1c rebound in the intervention group compared to the control group indicates that DM care intervention needs to be maintained for better outcomes.

Many factors may be contributing to people not achieving treatment targets. These may be at the health systems levels, for example, a limited supply of medications (especially insulin) and laboratory equipment for monitoring at the primary care level and overcrowded facilities at the secondary and tertiary levels.28 Medication uptake may also affected by factors such as irregular mealtime, the size of oral DM drug or the pain caused by insulin injection, side-effects, etc.29 More in-depth research is required to understand the different contributing factors and possible improvement methods.

Previous evidence or experience concerning CVD risk assessment and management in TB-DM patients is scarce. This study seems to be the first to observe TB-DM patients after completing TB treatment to investigate DM characteristics, its complications, and management. The international guidebook on diabetes and tuberculosis has helped set targets for the management and monitoring TB-DM.6 While assessment and management of patients’ CVD risk is essential, successful initiation of TB treatment and glucose control is of greater priority at the time of TB diagnosis.6 Therefore, the initiation of aspirin for those with established CVD disease and initial counselling for smoking cessation and diet should be prioritised. After completing the intensive phase of TB treatment, more counselling about healthy lifestyles, antihypertensive medication, and statin treatment may be started as indicated.6 After TB treatment, patients should be advised about continuing care for DM, lowering CVD risk, and further monitoring and treatment. Since DM-associated TB is associated with a higher relapse rate, patients should be advised to seek care immediately if TB symptoms re-appear.6

Our study has limitations. The sample size was relatively small, therefore, there might be uncertainties. Some patients did not finish the 12-month follow-up, which may introduce a bias. We also did not have a comparison group of DM patients with no history of TB, therefore, we cannot be certain that the CVD risk in our study population is higher than those in the general DM population.

Our study results underline the need for continuation of DM care in routine practice. Strengthening the integration of relevant health system components will be needed to prevent these patients from being lost to care.30 Research questions also arise from this study: how could routine CVD and TB symptom assessments be done? Can we build a programme in health care facilities to help maintain a healthy lifestyle? A cohort study of DM patients with appropriate controls would help answer these questions.

In conclusion, in our study, DM in TB-DM patients is characterised by poor glycemic control, high CVD risk and nephropathy. We found that TB therapy provides opportunities for better DM management. However, long-term care for DM and CVD assessment should be provided and improved.

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*Conflict of Interest*

None declared.

*Author Contributions*

RCK: Investigation, formal analysis, data curation, validation, visualisation, writing – original draft; SMM: Supervision, project administration, writing – review and editing; NNMS: Investigation, resources; PS: Investigation, resources; NFD: Investigation, resources; HP: Resources, supervision; RR: Supervision, project administration, funding acquisition; BA: Supervision, project administration, funding acquisition; JAC: Conceptualisation, methodology, funding acquisition, writing – review and editing; HMD: Funding acquisition, writing – review and editing; PCH: Conceptualisation, methodology, funding acquisition, writing – review and editing;RvC: Conceptualisation, methodology, funding acquisition, writing – review and editing. All authors approved the final manuscript.

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**TABLES**

*Table 1. Clinical characteristics of patients at baseline, month-6, and month-12*

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Baseline(n=170) | Month-6(n=148) | Month-12(n=125) |
| Male sex\* | 86 (50.6) | 73 (49.3) | 61 (48.8) |
| Mean age\* (SD) – year | 52.8 (9.3) | 52.5 (9.6) | 52.5 (9.3) |
| Duration of DM\* – year |  |  |  |
|  | Newly diagnosed | 45 (26.5) | 40 (27.0) | 34 (27.2) |
|  | <1 | 35 (20.5) | 29 (19.6) | 21 (16.8) |
|  | 1 – 5 | 55 (32.4) | 45 (30.4) | 43 (34.4) |
|  | 6 – 15 | 27 (15.9) | 27 (18.2) | 21 (16.8) |
|  | ≥15 | 8 (4.7) | 7 (4.7) | 6 (4.8) |
| Median HbA1c (IQR) – % | 11.2 (6.2-16.5) | 7.8 (5.7-15.3) | 9.3 (5.8-15.2) |
| BMI category – kg/m2 |  |  |  |
|  | Underweight (<18.5) | 34 (20.0) | 17 (11.5) | 7 (5.6) |
|  | Normal (18.5-22.9) | 81 (47.6) | 58 (39.2) | 51 (41.1) |
|  | Overweight (23.0-24.9) | 21 (12.4) | 22 (14.9) | 17 (13.7) |
|  | Obese (≥25.0) | 34 (20.0) | 51 (34.4) | 49 (40.0) |
| Blood pressure – mmHg |  |  |  |
|  | Normal (<120/80) | 58 (34.1) | 39 (26.4) | 24 (19.2) |
|  | Prehypertension (120-139/80-89) | 68 (40.0) | 48 (32.4) | 43 (34.4) |
|  | Hypertension I (140-159/90-99) | 31 (18.2) | 40 (27.0) | 31 (24.8) |
|  | Hypertension II (≥160/100) | 13 (7.6) | 21 (14.2) | 27 (21.6) |
| Current smoking | 24 (14.0) | 25 (17.0) | 25 (22.5) |
| Exercise regularly | 85 (50.0) | 96 (64.9) | 67 (60.4) |
| DM medication |  |  |  |
|  | Metformin | 89 (52.4) | 90 (63.4) | 80 (58.8) |
|  | Insulin | 7 (4.1) | 41 (28.9) | 14 (10.3) |
|  | Other OAD | 40 (23.5) | 21 (14.8) | 19 (20.2) |
|  | No medication | 17 (10.0) | 0 (0.0) | 0 (0.0) |
| CVD medication |  |  |  |
|  | Antihypertensives | 7 (4.1) | 33 (21.2) | 28 (18.4) |
|  | Aspirin | 1 (0.6) | 3 (1.9) | 1 (0.7) |
|  | Statins | 3 (1.8) | 5 (3.2) | 9 (5.9) |
| Total cholesterol – mg/dL |  |  |  |
|  | Desirable (<200) | ND | 50 (34.2) | 49 (39.5) |
|  | Borderline high (200-239) | ND | 49 (33.6) | 41 (33.1) |
|  | High (≥240) | ND | 47 (32.2) | 34 (27.4) |
| WHO 10-year CVD risk |  |  |  |
|  | <5% | ND | 2 (1.4) | 2 (1.6) |
|  | 5% to <10% | ND | 16 (11.0) | 17 (13.7) |
|  | 10% to <20% | ND | 42 (28.8) | 38 (30.6) |
|  | 20% to <30% | ND | 38 (26.0) | 23 (18.6) |
|  | ≥30% | ND | 48 (32.9) | 44 (35.5) |
| Estimated glomerular filtration rate |  |  |  |
|  | Stage 1 (≥90) | 116 (68.2) | 108 (74.5) | 84 (68.3) |
|  | Stage 2 (60-89) | 40 (23.5) | 29 (20.0) | 32 (26.0) |
|  | Stage 3 (30-59) | 12 (7.1) | 8 (5.5) | 5 (4.1) |
|  | Stage 4 (15-29) | 2 (1.2) | 0 (0.0) | 2 (1.6) |
| ACR – mg/mmol |  |  |  |
|  | Normal (<3) | ND | 15 (10.3) | 7 (5.6) |
|  | Microalbuminuria (3-30) | ND | 41 (28.3) | 41 (33.1) |
|  | Clinical albuminuria (>30) | ND | 89 (61.4) | 76 (61.3) |
| MNSI symptom score |  |  |  |
|  | 0 | ND | 28 (18.9) | ND |
|  | 1 – 3 | ND | 70 (47.3) | ND |
|  | 4 – 6 | ND | 44 (29.7) | ND |
|  | ≥7 | ND | 6 (4.1) | ND |

\*Data taken at baseline. Data is presented in numbers and percentages unless stated otherwise.

Abbreviations: BMI = body mass index; CVD = cardiovascular disease; DM = diabetes Mellitus; HbA1c = glycated haemoglobin; HDL = high density lipoproteins; IQR = interquartile range; LDL = low density lipoproteins; MNSI = Michigan Neuropathy Screening Instrument; ND = no data collected OAD = oral anti-diabetes.

**FIGURE LEGENDS**

*Figure 1. Flow chart of the study participants*

Abbreviations: DM=diabetes mellitus; MDR-TB: multidrug resistant tuberculosis; NDM=non-diabetes mellitus; TB=tuberculosis

*Figure 2.*

*Hba1c among TB-DM patients before (baseline) and at the end of TB treatment (Month-6) and six months later (Month-12)*

*Figure 3. The proportion of TB-DM patients achieving Indonesian Endocrinology Association targets related to DM management at baseline, Month-6 (after completion of TB treatment), and Month-12*

*Figure 4. Treatment indication and patients receiving treatment with insulin (HbA1c ≥10%), antihypertensive (systolic blood pressure ≥140 mmHg), and statins (LDL ≥100 mg/dL) at month-12 (under routine care)*

Abbreviations: HbA1c = glycated haemoglobin; LDL = low-density lipoprotein.