ORIGINAL ARTICLE

AFRICAN JOURNAL OF CLINICAL AND EXPERIMENTAL MICROBIOLOGY JULY 2016 ISBN 1595-689X VOL17 No. 3
AJCEM/1625 http://www.ajol.info/journals/ajcem
 http://dx.doi.org/10.4314/ajcem.v17i3.3
AFR. J. CLN. EXPER. MICROBIOL. 17 (3): 173-178

GLYCATED HAEMOGLOBIN LEVELS IN PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS INFECTION DURING 6 MONTHS OF TREATMENT

Akinlade KS1, Rahamon SK1, Edem VF1, Ige OM2, Arinola OG1

1Department of Chemical Pathology, College of Medicine, University of Ibadan, Nigeria; 2Department of Medicine, College of Medicine, University of Ibadan, Nigeria.

Corresponding author:Dr. KS Akinlade,Metabolic Research Unit,Department of Chemical Pathology,University College Hospital/University of Ibadan,Ibadan.E-mail: ksakinlade@yahoo.co.ukMobile: 08075010718

RUNNING TITLE: GLYCATED HAEMOGLOBIN IN PATIENTS WITH MDR-TB INFECTION

ABSTRACT

Background: There is little information on the possible impact of drugs used in the treatment of multi-drug resistant tuberculosis (MDR-TB) on glycaemic levels. This study therefore assessed changes in glycated haemoglobin levels in patients with MDR-TB.

Materials and Methods: This longitudinal study involved 21 MDR-TB patients who were followed up for 6 months. Glycated haemoglobin (HbA1c) level of each patient was determined before the commencement of MDR-TB drug regimen and at 2, 4 and 6 months post treatment as part of a study which investigated them every 2 months. Differences in means were assessed using the paired Student's t-test and statistical significance was set at $P<0.05$.

Results: A patient had undiagnosed diabetes mellitus (DM) with an HbA1c value of 6.5% and died before the second month sample collection; another patient became critically ill; therefore, 19 patients completed the study. Before the commencement of MDR-TB therapy, two patients had pre-diabetes with HbA1c values of 6.0% and 5.8% while the HbA1c values of the remaining patients were less than 5.7%. There was a significant reduction in the mean HbA1c level at 2 months post therapy compared with the baseline. However, the HbA1c levels increased slightly after the 2nd month of therapy but no significant change was observed in the HbA1c levels at 4 and 6 months of MDR-TB therapy compared with baseline.

Conclusion: Diabetes mellitus is not common among Nigerians with MDR-TB and MDR-TB drug regimen might have an acute effect on glycaemic changes in patients with MDR-TB.

Keywords: Diabetes mellitus, Glycaemic change, Glycated haemoglobin, Multidrug resistant tuberculosis therapy

L'HÉMOGLOBINE GLYQUÉE CHEZ LES PATIENTS PRÉSENTANT UNE INFECTION À LA TUBERCULOSE MULTIRÉSISTANTE AU COURS DES 6 PREMIERS MOIS DE TRAITEMENT

Akinlade KS[1], Arinola OG[1], Rahamon SK[1], Edem VF[1], Ige OM[2]

[1]Les ministères de pathologiechimique, Collège de médecine, Universitéd'Ibadan, Nigeria. [2]Département de médecine, Collège de médecine, Universitéd'Ibadan, Nigeria.

Auteur Correspondant: Dr. KS Akinlade, Unité de recherchemétabolique, Département de pathologiechimique,

University College Hospital/Universitéd'Ibadan, Nigeria. E-mail: ksakinlade@yahoo.co.ukMobile: 08075010718

TITRE COURANT: L'HÉMOGLOBINE GLYQUÉE CHEZ LES PATIENTS ATTEINTS DE TUBERCULOSE MDR INFECTION

ABSTRAIT
Résumé Contexte: Il y a peu d'information sur l'impact possible des medicaments utilisés dans le traitement de la tuberculose multirésistante (TB-MR) sur les niveaux glycémique. Cette étude, par conséquent, évalué les changements dans les niveaux d'hémoglobine glycosylée chez les patients atteints de tuberculose multirésistante.

Matériels et méthodes: Cette etude longitudinale a concerné 21 MDR-TB patients qui ont été suivis pendant 6 mois. L'hémoglobine glyquée (HbA1c) niveau de chaque patient a été determine avant l'entrée en vigueur de la MDR-TB Traitement medicamenteux et à 2, 4 et 6 mois après le traitement dans le cadre d'une étude qui a enquêté sur tous les 2 mois. Les differences dans les moyens ont été évalués à l'aide de la paire de test t de Student et la signification statistique a été fixé à P<0,05.

Résultats: Un patient avait non diagnostiqué le diabète sucré (DS) avec une valeur d'HbA1c de 6,5% et est décédé avant le deuxième mois sample collection; un autre patient est devenu gravement malade; par conséquent, 19 patients ont terminé l'étude. Avant le début de la MDR-TB thérapie, deux patients avaien tpré-diabète avec les valeurs de l'HbA1c de 6,0 % et 5,8 % alors que le taux d'HbA1c des autres patients étaient inférieures à 5,7 %. Il y avai tune reduction significative de la moyenne de l'HbA1c 2 mois après traitement par rapport à la baseline.

Conclusion: Le diabete sucré n'est pas commune chez les Nigérians avec des souches de TB-MR et la TB-MR régime posologique pourrait avoir un effet aigu sur glycémique chez les patients avec MDR change-TB.

Mots-clés: diabète sucré, changement glycémique, de l'hémoglobine glyquée, tuberculose multirésistante therapy.

INTRODUCTION

The increasing incidences of type 2 diabetes mellitus (T2DM) and tuberculosis (TB) worldwide are serious health problems requiring urgent attention. The two disease conditions remain significant causes of morbidity and mortality especially, in the developing countries [1 – 3].

The relationship between DM and TB has been explored by several studies which showed that the risk of TB among diabetics is about 3 times higher than those without diabetes mellitus (DM) (4) even among individuals younger than 40 years of age. Jeon and Murray [4] reported that the diabetes rates among TB patients range from 13% to 50% or even, higher. This is because many TB patients do not know their DM status and therefore, cannot self-report [5]. Also, some TB patients probably died before the manifestation of the classical symptoms of DM, which will warrant DM diagnosis.

The pathophysiology of TB susceptibility in diabetics is not well understood. However, changes in the immune system have been identified to play a prominent role in the pathophysiology [6]. Diabetics have been shown to have impaired innate immune responses to TBwhich worsen the clinical outcomes of TB [3, 7-9]. This is further compounded with the emergence of multidrug resistance tuberculosis (MDRTB).

MDR-TB is a public health problem due to its increasing trend [10, 11]. Its treatment is challenging as it involves combination of a minimum of 5 drugs for at least 20 months [12]. This challenge becomes daunting when MDR-TB coexists withT2DM as it could cause some adverse events such as delayed sputum culture conversion, treatment failure, increased risk of TB recurrence, deaths, and development of secondary drug resistance[5, 13].

Although screening for diabetes mellitus is recommended as at the time of diagnosing TB [14], the use of simple methods such as estimating fasting or random plasma glucose levels as well as oral glucose tolerance test (OGTT) administration have been reported to be problematic and do not correlate perfectly. This has been attributed to the possible interference of TB infection with glycaemic control [5, 15]. This made the estimation of glycatedhaemoglobin (HbA1c) a very useful tool in the determination of glycaemic control in TB patients. HbA1c reflects average blood glucose level over the previous eight to 12 weeks [16] but approximately, 50% of the HbA1c is determined by the blood glucose levels in the preceding 4 weeks.

Due to sole focus on curing MDR-TB, the possible impact of drugs used in the treatment of MDR-TB on glycaemic changes is not usually given appropriate attention. Ethionamide and pyrazinamide have been reported to be rare cause of hypoglycaemia [17, 18].In diabetics, ethionamide tends to make insulin regimen more difficult, and can result in hypoglycemia and poor glucose regulation [19].Therefore, it is important to understand the interplay between MDR-TB treatment course and glycaemic changes with a view to helping clinicians make informed decision in the management of MDR-TB patients with diabetes mellitus. Thus, this serves as the basis for this study.

MATERIALS AND METHODS

Subjects

This longitudinal study involved a batch of 21 MDR-TB patients at the MDR-TB Referral Centre, University College Hospital (UCH), Ibadan, Nigeria.Usually, the UCH MDR-TB Referral Centre enrolls 2 batches of MDR-TB patients per year. Each batch usually consists of a maximum of 25 patients which are treated over a course of 6 to 8 months. After each batch is discharged, the center is fumigated and kept closed for a month before another batch is admitted. The patients in this study were part of a study which investigated them every 2 months.

Ethical consideration

The study participants were recruited after obtaining an approval from the University of Ibadan/University College Hospital Joint Ethics

Review Committee. Also, informed consent was obtained from each participant before enrolment.

Data collection
A short-structured questionnaire was used to obtain information on demographic characteristics, social and medical history. Height (m), body weight (kg) and body mass index (kg/m^2) were taken using standard methods.

Sample collection and laboratory analysis
About 2 ml of venous blood was collected from each participant into lithium heparin containing sample bottles. Thereafter, glycatedhaemoglobin (HbA1c) level of each sample was determined using an automated boronate affinity assay (Clover A1c® Self, Infopia Co., Ltd, Korea).

Statistical analysis
Differences in means were assessed using the paired and unpairedStudent's t-test. Results are presented as mean ± standard deviation or frequency (percentage). *P*-values less than 0.05 were considered as statistically significant.

RESULTS
A total number of 21 MDR-TB patients formed a batch that was admitted into the Referral Centre and they were all enrolled into this study. However, a patient died before the second month sample collection while another was critically ill, therefore, 19 patients completed the study. The patient that died had undiagnosed DM with an HbA1c value of 6.5%.In addition, the patient had HIV infection. The other patient that was critically ill had an HbA1c value of 4.9%.

As shown in Table 1, 18 patients were underweight while just only one had normal weight (19.27 kg/m^2). Also, only one patient has a family history of diabetes.

Comparing the MDR-TB patients without HIV with MDR-TB patients with HIV before the commencement of MDR-TB therapy, the mean body weight, BMI and HbA1c level between the two groups were not significantly different (Table 2).

Before the commencement of MDR-TB therapy, two patients had pre-diabetes with HbA1c values of 6.0% and 5.8% while the HbA1c values of the remaining patients were less than 5.7%.One of the patients with pre-diabetes had irregular pattern of changes over the course of treatment (6.0%, 4.8%, 5.3% and 6.1% at baseline, 2, 4 and 6 months post-therapy respectively). However, the other patient with pre-diabetes had progressive decline in HbA1c level over the course of treatment (5.8%, 4.9%, 4.6% and 4.5% at baseline, 2, 4 and 6 months post-therapy respectively).

TABLE 1: GENERAL CHARACTERISTICS OF THE STUDY PARTICIPANTS

	(n = 19)
Age (years)	**33.42 ± 8.54**
Height (m)	**1.65 ± 0.08**
Body weight (kg)	**44.40 ± 8.18**
BMI (kg/m^2)	**16.13 ± 2.35**
BMI category	
Underweight	**18 (94.74%)**
Normal weight	**1 (5.26%)**
Gender	
Male	**13 (68.42%)**
Female	**6 (31.58%)**
Smoking	
Yes	**3 (15.79%)**
No	**16 (84.21%)**
Alcohol consumption	
Yes	**4 (21.05%)**
No	**15 (78.95%)**
HIV status	
Positive	**5 (26.32%)**
Negative	**14 (73.68%)**
Diabetes mellitus history	
Yes	**1 (5.26%)**
No	**18 (94.74%)**

Values are in mean ± standard deviation or frequency (percentage), BMI=body mass index, HIV=human immunodeficiency virus

There was a significant reduction in the mean HbA1c level at 2 months posttherapy compared with the baseline. H3owever, the HbA1c levels increased slightly after the 2ndmonth of therapy but no significant change was observed in the HbA1c levels at 4 and 6 months of MDR-TB therapy compared with baseline (Table 3).

TABLE 2: GLYACTEDHAEMOGLOBIN LEVELS AND BODY MASS INDEX IN MDR-TB PATIENTS WITHOUT HIV AND MDR-TB PATIENTS WITH HIV BEFORE COMMENCEMENT OF MDR-TB THERAPY

	MDR-TB-HIV (n = 14)	MDR-TB+HIV (n = 5)	*P*-values
Age (years)	**32.14 ± 9.11**	**37.00 ± 6.08**	**0.288**
Height (m)	**1.64 ± 0.08**	**1.68 ± 0.07**	**0.342**
Body weight (kg)	**43.99 ± 9.03**	**45.56 ± 5.83**	**0.723**
BMI (kg/m²)	**16.16 ± 2.68**	**16.03 ± 1.20**	**0.916**
HbA1c (%)	**4.96 ± 0.56**	**4.94 ± 0.55**	**0.954**

TABLE 3: GLYCATEDHAEMOGLOBIN LEVELS AT COMMENCEMENT OF MDR-TB THERAPY, 2, 4 AND 6 MONTHS POST THERAPY IN ADULTS WITH MULTIDRUG RESISTANT TUBERCULOSIS

	HbA1c values	HbA1c values	*P*-values
Baseline vs 2 months	**4.95 ± 0.55**	**4.70 ± 0.43**	**0.037***
Baseline vs 4 months	**4.95 ± 0.55**	**4.83 ± 0.50**	**0.298**
Baseline vs 6 months	**4.95 ± 0.55**	**4.81 ± 0.55**	**0.256**
2 months vs 4 months	**4.70 ± 0.43**	**4.83 ± 0.50**	**0.149**
2 months vs 6 months	**4.70 ± 0.43**	**4.81 ± 0.55**	**0.430**
4 months vs 6 months	**4.83 ± 0.50**	**4.81 ± 0.55**	**0.789**

DISCUSSION

The interaction between tuberculosis and diabetes mellitus is well established. However, routine screening for diabetes is not routinely carried out on TB patients as many clinicians are not aware of this important link [20 – 22]. Also, there is the dearth of information on possible impact of drugs used in the treatment of MDR-TB on glycaemic homeostasis.

Reports have shown that the prevalence of DM among TB patients appears to be high[23, 24].In this study, majority of the patients had normal HbA1c level while only one patient had pre-diabetes. This observation probably indicates that DM might not be too common among Nigerians with MDR-TB. It is also possible that most TB patients die before DM diagnosis.

Good clinical outcomes have been achieved during a six-month course of tuberculosis treatment using the right combination of drugs to which the infecting *M. tuberculosis* complex bacilli are susceptible [25]. Based on this, we only monitored the glycaemic changes in the patients in the first 6 months of the MDR-TB treatment. Our observed significant reduction in HbA1c level at 2 months post therapy compared with baseline could indicate that MDR-TB drug regimen may have an acute effect on glycaemic homeostasis. Tabarsi *et al.* [13] reported that there were changes in HbA1c during the first three-months of anti-TB treatment. Also, Tag El Din *et al*. [26] reported that most of the side effects of MDR-TB drugs usually appear within the first 3 months.In addition, our observation could be due to the glucose lowering effects of some of the MDR-TB drug regimen [27]. Holden and Hiltz [17] reported that ethionamide could be a rare cause of hyperglycaemia. Also, Pestana [18] reported that pyrazinamide may cause hypoglycemia. Although HbA1cis not a good measure of hypoglycaemia, Lipska *et al.* [28]reported that severe hypoglycemia was common among patients with type 2 diabetes across all levels of glycemic control and that the risk tended to be higher in patients with either near-normal glycaemia or very poor glycemic control.

Although the aim of this study was not to assess BMI, the observed low BMI in MDR-TB patients before commencement of therapy further supports the widely reported malnutrition in TB patients. Tang *et al*. [29] showed that low BMI is an independent risk factor for poor outcome in patients with MDR-TB.

Therefore, improvement on nutritional status of MDR-TB patients may facilitate favourable treatment outcome.

Inability to determine fasting plasma glucose (as fasting samples could not be ensured in the patients), glycated albumin or fructosamine are some of the limitations in this study.

It could be concluded from this study that diabetes mellitus is not common among Nigerians with MDR-TB and that MDR-TB drug regimen might have an acute, but not a prolonged, effect on glycaemic changes in MDR-TB patients. Therefore, there is need for tight glycaemic monitoring in MDR-TB patients with diabetes mellitus at the early months of commencement of MDR-TB treatment with a view to achieving optimal glycaemic control.

Acknowledgement The authors would like to appreciate the cooperation of the entire Nursing staff of the MDR-TB Referral Centre, University College Hospital, Ibadan.

Conflict of interest

The authors have no competing interest to declare.

REFERENCES

1. Danaei, G., Finucane, M. M., Lu, Y., Singh, G. M., Cowan, M. J., Paciorek, C. J.*et al*. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants.Lancet 2011; 378(9785):31-40.
2. World Health Organization. Global tuberculosis control: WHO Report 2013. Available: http://apps.who.int/iris/bitstream/10665/91355/1/9789241564656_eng.pdf.Accessed on 11th January, 2016.
3. Olayinka, A. O., Anthonia, O., Yetunde, K. Prevalence of diabetes mellitus in persons with tuberculosis in a tertiary health centre in Lagos, Nigeria. Indian J EndocrMetab 2013;17:486-489.
4. Jeon, C. Y., Murray, M. B.Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies.PLoS Med 2008; 5(7):e152.
5. Fisher-Hoch, S. P. Worldwide increase in diabetes: implications for tuberculosis control. Research and Reports in Tropical Medicine 2014; Volume 2014:35—44
6. Gomez, D. I., Twahirwa, M., Schlesinger, L. S., Restrepo, B. I. Reduced Mycobacterium tuberculosis association with monocytes from diabetes patients that have poor glucose control. Tuberculosis 2013; 93 (2):192–197.
7. Jiménez-Corona, M. E., Cruz-Hervert, L. P., García-García, L., Ferreyra-Reyes, L., Delgado-Sánchez, G., Bobadilla-Del-Valle, M. *et al*.Association of diabetes and tuberculosis: impact on treatment and post-treatmentoutcomes.Thorax 2013;68(3):214-220.
8. Restrepo, B. I., Schlesinger, L. S. Host-pathogen interactions in tuberculosis patients with type 2 diabetes mellitus. Tuberculosis 2013; 93:S10–S14.
9. Delgado-Sánchez, G., García-García, L., Castellanos-Joya, M., Cruz-Hervert, P., Ferreyra-Reyes, L., Ferreira-Guerrero, E. *et al*.Association of PulmonaryTuberculosis and Diabetes in Mexico: Analysis of the NationalTuberculosisRegistry2000-2012. PLoS One 2015;10(6):e0129312.
10. Sharma, S. K., Mohan, A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest 2006;130(1):261-272.
11. World Health Organization. Multidrug-resistant tuberculosis (MDR-TB) 2012 update. Available: http://www.who.int/tb/publications/MDRFactSheet2012.pdfaccessed on 11th January, 2016
12. Caminero, J. A., Sotgiu, G., Zumla, A., Migliori, G. B. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis 2010;10(9):621-629.
13. Tabarsi, P., Baghaei, P., Marjani, M., Vollmer, W. M., Masjedi, M. R., Harries, A. D. Changes in glycosylatedhaemoglobin and treatmentoutcomes in patients with tuberculosis in Iran: a cohortstudy. J Diabetes MetabDisord 2014; 13(1):123.
14. World Health Organization; Stop-TB Partnership. New Laboratory Diagnostic Tools for Tuberculosis Control. Geneva: World Health Organization; 2008. Available: http://www.who.int/tdr/publications/dis-ease/tuberculosis/en/ accessed on: 11th January, 2016.
15. American Diabetes Association. Standards of medical care in diabetes – 2010. Diabetes Care 2010;33(Suppl 1):S11–S61.

16. Nathan, D. M., Turgeon, H., Regan, S. Relationship between glycatedhaemoglobin levels and mean glucose levels over time. Diabetologia 2007; 50:2239-2244.
17. Holden, H. M., Hiltz, J. E. The tuberculous diabetic. Can Med Asso J 1962; 87:797.
18. Pestana,E. A.TuberculoseemGruposEpidemiológicosParticulares. En: Pina J., editors. A TuberculosenaViragem do Milénio. Lisboa: Lidel; 2000. 501-12.
19. The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis, 2nd Edition. Partners In Health. Boston, USA. USAID TB CARE II;Management of adverse drug effects; Endocrine: Dysglycemia and hyperglycemia. 2013. Available: https://drtbnetwork.org/924-endocrine-dysglycemia-and-hyperglycemia; accessed on 7thJanuary, 2016.
20. Dooley, K. E., Chaisson, R. E. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis2009;9(12):737-746.
21. Koh, G. C. K. W., Wiersinga, W. J. Tuberculosis and Diabetes Mellitus: Convergence of Two Epidemics: F1000 Ranking: "Changes Clinical Behavior". Faculty of 1000. Available: http://www.medscape.com/viewarticle/714503. Accessed on 3rd December, 2015.
22. Syed Sulaiman, S. A., Mohd Zain, F. A., Abdul Majid, S., Munyin, N., MohdTajuddin, N. S., Khairuddin, Z., Ban Hing, L. Tuberculosis among diabetic patient. WebmedCentral Infectious Diseases 2011;2(12):WMC002696
23. Jeon, C. Y., Murray, M. B. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 2008;5(7):e152
24. Balakrishnan, S., Vijayan, S., Nair, S., Subramoniapillai, J., Mrithyunjayan, S., Wilson, N. *et al.* High diabetes prevalence among tuberculosis cases in Kerala, India.PLoS One 2012;7(10):e46502.
25. Gelband, H. Regimens of less than six months for treating tuberculosis.Cochrane Database Syst Rev 2000;(2):CD001362.
26. Tag El Din, M. A.,El Maraghy, A. A., Abdel Hay, A. R. Adverse reactions among patients being treated for multi-drug resistant tuberculosis at Abbassia Chest Hospital. Egyptian Journal of Chest Diseases and Tuberculosis 2015;64(4): 939–952.
27. Guptan, A., Shah, A. Tuberculosis and diabetes: an appraisal. Ind J Tub 2000; 47(3): 1-8.
28. Lipska, K. J., Warton, E. M., Huang, E. S., Moffet, H. H., Inzucchi, S. E., Krumholz, H. M. *et al.*HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study.Diabetes Care2013;36(11):3535-3542.
29. Tang, S., Tan, S., Yao, L., Li, F., Li, L., Guo, X.*et.al.*Risk factors for poor treatment outcomes in patients with MDR-TB and XDR-TB in China: retrospective multi-center investigation.PLoS One 2013;8(12):e82943.