ORIGINAL RESEARCH

Incidence and Predictors of Tuberculosis among Adult Diabetic Patients, Debre Markos Referral Hospital, Northwest Ethiopia, 2018: A Retrospective Cohort Study

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Background: Tuberculosis remains a serious global public health problem. It mainly affects the lungs, and occurs in every part of the world. The link between tuberculosis and diabetes mellitus is essential to inform programs and policies, yet there is a scarcity of information in our study area. Therefore, this study aimed to investigate the incidence and predictors of tuberculosis among diabetic patients at Debre Markos Referral Hospital, northwest Ethiopia.

Methods: This institutionally based retrospective cohort study was undertaken among 433 diabetic patients of Debre Markos Referral Hospital between January 2013 and December 2017. All eligible diabetic patients who met the inclusion criteria were included in the study. Data were entered using EpiData version 3.1 and analyzed using Stata version 14. The survival time of diabetic patients was estimated using Kaplan–Meier survival curves, and survival time among different categorical variables compared using the log-rank test. Both bivariate and multivariate Coxproportional-hazard regression models were fitted to identify independent predictors of tuberculosis among diabetic patients.

Results: Among the cohort of 43326 (6%) developed tuberculosis during follow-up. The overall tuberculosis-incidence rate was 2.4 per 100 with 95% CI. The total time allotted to follow up the study participants was 1,101.5 person-years. Using multivariate Cox regression analysis, history of alcohol consumption (adjusted incidence ratio 4, 95% CI 1.2–13; P=0.02) and history of tuberculosis (12, 95% CI 3–39; P=0.01) significantly increased the risk of tuberculosis, but normal body-mass index and above ($\geq$18.5 kg/m^2) was associated with a rate reduction (0.34, 95% CI 0.14; P=0.80; 0.03) forincidence of tuberculosis.

Conclusion: In this study, we found a high rate of tuberculosis among diabetic patients. Factors significantly linked with increased risk of tuberculosis included history of alcohol consumption, history of tuberculosis, and low body-mass index. Early screening and treatment for tuberculosis is highly recommended at diabetes mellitus follow-up for patients with these risk factors.

Keywords: diabetes mellitus, incidence of tuberculosis, predictors

Background

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, and mainly affects the lungs. TB remains a serious public health challenge throughout the world, most notably in low- and middle-income countries, ranking above HIV/AIDS.[1] Globally, around 10.4 million people fell ill with TB and 1.7 million died from the disease in 2016. The dynamics of transmission vary geographically, with the largest number of new TB cases occurring in Asia and Africa: 45% and 25% respectively.[2,3]

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The association of TB and diabetes mellitus (DM) is a concern for health sectors, as the coexistence of these two highly prevalent diseases has made -existing treatments very complex.[4] The link between TB and DM is considered more prominent in developing countries, where TB is endemic and the burden of DM increasing. Accordingly, it is estimated that about 1.6 million deaths were directly caused by DM —which is 1.69 times more likely to develop into TB than among non-DM individuals — in 2015.[5,6]

Currently, the worldwide prevalence of DM is increasing more quickly than ever (11.7%), which increases TB and makes existing treatments very complex among the coinfected patients.[7] The prevalence of DM and the incidence of TB in Ethiopia have been found to be 6.5% and 164 per 100,000 population, respectively.[1,8] However, evidence suggests that about a third of TB patients initiate care and are referred to health-care facilities with health-extension workers.[9] Even though different interventions have been made by the government, TB incidence in Ethiopia remains high. Therefore, this retrospective cohort study was conducted to identify risk factors of TB among diabetic patients at Debre Markos Referral Hospital, northwest Ethiopia.

Methods
Study Design and Setting
This institutionally based retrospective cohort study was undertaken between January 2013 to December 2017 in the chronic-care follow-up care unit of Debre Markos Referral Hospital. Debre Markos is located 300 km from Addis Ababa, the capital of Ethiopia, and 256 km from Bahir-Dar, the capital of Amhara Regional State. Debre Markos Referral Hospital is the only referral hospital found in East Gojjam Zone, and serves >3.5 million people in its catchment area. Aso, the hospital provides diabetic care services. After submission of the research proposal and getting approval from the Debre Markos university Health Science College ethical review committee (Res/Com/ser/&Post gra/Coor/Off: 781/11/10) the study was conducted.

Population
The study population for this study were all adult (≥18 years old) diabetic patients registered with Debre Markos Referral Hospital for chronic follow-up care from January 1, 2013 to December 30, 2017.

Inclusion and Exclusion Criteria
All diabetic patients who fulfilled the inclusion criteria of being registered adult diabetic patients from January 1, 2013 to December 30, 2017 in the chronic-care follow-up clinic of Debre Markos Referral Hospital were included in the study. However, we excluded diabetic patients with gestational DM, incomplete data or unavailable medical records, had been transferred in and who had had TB at the time of DM diagnosis.

Data-Collection Procedures
A 5-year institution-based retrospective follow-up study was conducted using chart review at Debre Markos Referral Hospital chronic-care follow up clinic on adult diabetic patients who had been registered from January 1, 2013 to December 30, 2017. All eligible patients were included in the study (census method) after ethical clearance had been obtained from the Institutional Review Committee of the College of Health Sciences, Debre Markos University (Res/Com/ser/&Post gra/Coor/Off: 781/11/10), and verbal informed consent was obtained from the patients. Medical record number of patients were obtained from electronic database and health management information–system registry books that had been used for the routine care of DM from January 1, 2013 to December 30, 2017. Then, by using the record numbers of the patients, their medical records were identified and their status assessed for the development of TB starting from diabetic follow-up initiation (first follow-up visit) to the end of the study using validated data-collection checklists.

Variables
The dependent variable for this study was incidence of TB among diabetic patients. Independent variables were socio-demographic factors (age, sex, and residence), personal behaviors (smoking, alcohol use, and both smoking and alcohol use), and clinical characteristics (type of DM, BMI, duration of DM, glycemic control, anti-DM medications, history of TB treatment, close contact with TB patients, and history of renal failure).

Data Analysis
Data collection–checklist tools adapted from a previous study in Ethiopia were used for data collection.[10] We used EpiData Version 3.1 for data entry and Stata version 14 for data analysis. The necessary assumption of the Cox proportional-hazard regression model was checked using the Schönfeld residual

test and log–log plots. Diabetic cohort characteristics of continuous data were described in terms of central tendency (mean or median), dispersion (SD or IQR) and frequency distribution for categorical data. Finally, outcomes of diabetic patients were dichotomized into censored or event categories. Kaplan–Meier survival curves were used to estimate survival time, and log-rank tests to compare survival curves. Bivariate Cox proportional-hazard regression was fitted for each explanatory variable, and those with $P \leq 0.25$ in bivariate analysis were fitted to the multivariate Cox proportional-hazard regression model. HRs with 95% CIs and P-values were used to measure the strength of association and identify statistically significant predictors. In multivariat analyses, variables with $P < 0.05$ were considered significant predictors of TB.

Results
Sociodemographic Characteristics of Study Participants
In this retrospective cohort study, 433 diabetic patients at Debre Markos Referral Hospital from January 1, 2013 to December 30, 2017 were included. Figure 1. Nearly half 187 43.2%) the patients were aged <18 years. The median age of patients was 39 (18–79 years). In addition, about 241 (55.7%) participants were male and 270 (62.5%) rural residents.

Clinical and Behavioral Characteristics of Patients
This study revealed that about 33 (7.6%) patients were positive for HIV and 34 (7.9%) had a history of renal failure. The duration of DM in all patients varied from date of initiation to 5 years of follow-up. A toal of 53 (12.2%) participants had a family history of DM, and 224 (51.7%) had type 1 DM. About 197 (45.5%) patients were on oral hypoglycemic agents, and 362 (83.6%) were normal and overweight. About eight (1.9%) were smokers, 16 (3.7%) had a history of alcohol consumption, and only five (1.2%) had a history of both alcohol consumption and smoking (Table 1).

Incidence of Tuberculosis among Diabetic Patients
Patients were followed for a total of 1,101.5 person years (PYs). The mean, median, and range of follow-up were 2.5, 2, and 4.8 years with (IQR 3), respectively. During follow-up, 26 (6%) patients were new TB cases (events). The overall incidence-rate ratio of TB was found to be 2.4 per 100 PYs with 95% confidence. Among the 26 individuals reporting TB, 15 (57.7%) were male and 20 (76.9%) had pulmonary TB. Of these 20 (76.9%) with pulmonary TB, only four (20%) had a history of TB. Moreover, a relatively higher proportion of TB patients 14 (53.6%) were aged 18–35 years. In addition, incidence
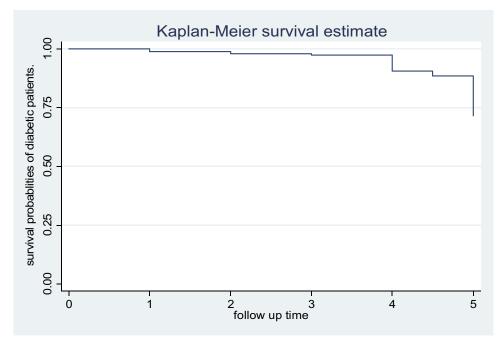

Figure 1 Kaplan–Meier curve of tuberculosis survival for diabetic patients at Debre Markos Referral Hospital from January 01, 2013 to December 30, 2017

Table 1 Baseline Sociodemographic, Clinical, and Behavioral Characteristics of People Living with Diabetes at Debre Markos Referral Hospital from January 1, 2013 to December 30, 2017

	Characteristics	n	Percentage	PYs	TB	TBID
Sex						
	Male	241	55.7	55.7	15	0.27
	Female	192	44.3	44.3	11	0.25
Age, years						
	18–35	187	43.2	489.9	14	0.03
	36–50	157	36.3	385.2	9	0.02
	>50	89	20.6	226.4	3	0.02
	Median	39.9				
Place of residence						
	Urban	163	37.6	441.3	10	0.02
	Rural	270	62.4	660.2	16	0.02
BMI (kg/m^2)	<18.5	71	16.4	212.5	13	0.06
	≥18.5	362	83.6	889	13	0.01
HIV serostatus						
	Positive	33	7.6	79.4	3	0.04
	Negative	400	92.4	1,022.1	23	0.02
Type of DM						
	Type I	224	51.7	593.1	19	0.03
	Type II	209	48.3	508.4	7	0.01
Blood-glucose level (mg/dL)						
	≤70	14	3.2	47	1	0.02
	70–130	165	38.1	417.3	8	0.02
	≥130	254	58.7	637.2	17	0.03
History of TB						
	Yes	9	2.1	23.5	5	0.21
	No	424	97.9	1,078	21	0.02
History of close contact						
	Yes	5	1.1	10	3	0.3
	No	428	98.8	1,091.5	2	0.15
Duration of TB since DM diagnosis						
	≤1year	12	46.2	27	12	0.44
	1–3 year	14	53.9	63.5	14	0.22
DM medications had been/being used						
	OHA	197	45.5	492.3	6	0.01
	Insulin	226	52.2	580	18	0.03
	Both OHA and insulin	10	2.3	29.2	2	0.07
History of smoking						
	Yes	8	1.9	22	1	0.05
	No	425	98.2	1,079.5	25	0.02
History of alcohol						
	Yes	16	3.7	47	5	0.11
	No	417	96.3	1,054.5	21	0.02
History of both smoking and alcohol						
	Yes	5	1.2	10	0	0
	No	428	98.9	1,091.5	26	0.02

Abbreviations: BMI, body-mass index; DM, diabetic mellitus; TB, tuberculosis; TBID, tuberculosis incidence density.

was higher among rural residents (16, 61.5%) and those that had 1–3 years' (14, (53.8%) follow-up. More than half 19 (73.1%) TB + DM patients had type 1 DM.

Tuberculosis-Incidence Density

In this study, 433 participants were followed for different periods over 5 years, producing 1,101.5 PYs of observation. The mean, median, and range of follow-up time were 2.5, 2, and 4.8 years (IQR=3), respectively. Within follow-up, 26 patients were found to have post-DM TB (new cases), with an overall TB incidence density of 2.4 per 100 PYs with 95% confidence (Table 2, Figures 2–4).

Predictors of Time to TB Occurrence among Diabetic Patients

On bivariate Cox regression analysis, significant predictors ($P \leq 0.25$) of TB included HIV serostatus, history of renal failure, family history of DM, blood-glucose level, BMI, type of DM, diabetic medication, history of TB and history of alcohol consumption. To determine independent predictors of TB, a multivariate Cox proportional adjusted hazard model was fitted after the proportional hazard assumption had been checked with a global test (0.94), log-rank test for significantly associated variables on multivariate analysis (BMI 0.02, history of TB 0.001, history of alcohol consumption 0.001), and by graphic assessment. Finally, only history of alcohol consumption, history of TB, and BMI remained significant predictors of TB ($P<0.05$). Accordingly, those with DM who had a history of alcohol consumption had four times the risk of developing TBcompared to those who had no history of alcohol consumption (incidencerate ratio (4, 95% CI 1.2, 13); P=0.02)) and patients who had a history of TB had 12 times the risk of developing TB compared to those who had no history of TB (incidence-rate ratio 12, 95% CI 3,39; P=0.01). Conversely, patients who were normal and overweight (BMI ≥ 18.5 kg/m^2) were less likely to develop TB (incidence-rate ratio 0.34. 95% CI 0.14–0.80; P=0.03) than their underweight (<18.5 kg/m^2) counterparts.

Discussion

Despite numerous interventions to prevent TB, it remains a serious global public health concern, especially in low- and middle-income countries. Therefore, we conducted this retrospective cohort study to determine the incidence of TB among diabetic patients at Debre Markos Referral Hospital, Ethiopia. The overall incidence rate of TB at Debre Markos Referral Hospital was found to be 2.4 per 100 PYs with 95% confidencew among diabetic patients. Our figure is higher than results of a number of studies conducted in Texas (0.31 per 100PYs), China (0.30 per 100PYs, 0.22 per 100PYs), and Tanzania (1.7 per 100 PYs).[11–13] These variations among studies could be explained in part by differences in sample size, study settings, follow-up periods, and sociodemographic characteristics of study participants. In addition, the distinction might be the use of sophisticated screening and diagnostic techniques for early testing and detection prior to disease progression in developed countries like the US and China. This is supported by other studies showing that sophisticated screening and diagnostic techniques for early testing and detection reduced the incidence of TB disease.[7,14]

Though the findings of this study are consistent with a study conducted in India (2.2 per 100 PYs),[15] they are inconsistent with one in north India (0.655 per 100 PYs).[16] This might be due to differences in population and study layout (a prospective study was conducted on patients with type 2 DM) in north India, which had relatively decent insulin secretion and glycemic control that prevented the development of complications and coinfections compared to type 1 DM. Conversely, our finding is much lower than the TB incidence reported in Australia (5.8 per 100 PYs) and Ethiopia (Black Lion [3.8 per 100PYs][17] and Dessie [6.2 per 100PYs] referral hospitals[18]). In the same way, these variations among studies could be explained in part by differences in sample size, study settings, follow-up periods, and sociodemographic characteristics of study participants. In this study, nearly half (48%) the respondents had type 2 DM, which is more common in advanced ages with minimal complications, including TB, because of relatively decent insulin secretion for glycemic control.[11] In addition, most respondents in this study were rural residents, and so socioeconomic and demographic factors, such as problems in getting to the health-care organization, may have played a part.

In this cohort study, a history of alcohol consumption was significantly associated with TB. Accordingly, patients with a history of alcohol consumption were four times as likely to develop TB than patients with no history of TB(incidence-rate ratio 4, 95% CI 1.2–13; P=0.02). This is consistent with studies in Texas,[19] Australia,[20] India,[21] and Ethiopia.[22] However, this study contradicts findings reported from US,[23] UK [24] and China.[25] Variations among studies could be attributable to differences in sample size,

Table 2 Tuberculosis Incidence Density Rate Stratified by Sociodemographic, Clinical, and Behavioral Characteristics of Diabetic Patients at Debre Markos Referral Hospital from January 1, 2013 to December 30, 2017

	Frequency	PYs	TB	TB IDR	Crude HR (95% CI)	Adjusted HR (95% CI)	*P*-value
Sex							
Male	241	55.7	15	0.27	1.8 (1.2–3.2)		
Female	192	44.3	11	0.25	1.0		
Age, years							
18–35	187	489.9	14	0.03			
36–50	157	385.2	9	0.02			
>50	89	226.4	3	0.02			
Place of residence							
Urban	163	441.3	10	0.02	1		
Rural	270	660.2	16	0.02	0.72 (0.04–11)		
Clinical characteristics **HIV serostatus**							
Positive	33	79.4	3	0.04	1		
Negative	400	1022.1	23	0.02	0.52 (0.15–1.7)		0.32
History of renal failure							
Yes	34	78.1	2	0.002	1		0.99
No	399	1023	24	0.02	1.1 (0.24–4.3)		
Family history of DM							
Yes	53	89.4	4	0.003	1		
No	380	1,011.7	22	0.02	1.1 (0.35–3)		0.96
Type of DM							
Type I	224	593.1	19	0.03	1	1	
Type II	209	508.4	7	0.01	0.4 (0.2–1)	1.6 (0.29–8.4)	0.24
BMI (kg/m^2)							
<18.5	71	212.5	13	0.06	1	1	
≥18.5	362	889	13	0.01	0.2 (0.1–0.6)	0.34 (0.14–0.8)	0.03
Blood-glucose level (g/dL)							
<70	14	47	1	0.02	1		
70–130	165	417.3	8	0.02	1.1 (0.12–8.1)		0.99
≥130	254	637.2	17	0.03	1		
History of TB							
Yes	9	23.5	5	0.21	24 (6.6–52)	12 (3–39)	0.01
No	424	1,078	21	0.02	1	1	
History of close contact with TB							
Yes	5	10	3	0.3			
No	428	1,091.5	2	0.15			
Duration of TB since DM diagnosis							
≤1year	12	27	12	0.44	1		
1–3 years	14	63.5	14	0.22	0.4 (0.2–1.1)		
DM medications							
OHGAs	197	492.3	6	0.01	1		
Insulin	226	580	18	0.03	2.7 (1.1–6)	2.8 (0.46–16)	0.26

(*Continued*)

Table 2 (Continued).

	Frequency	PYs	TB	TB IDR	Crude HR (95% CI)	Adjusted HR (95% CI)	P-value
OHA + insulin	10	29.2	2	0.07	8 (0.8–54)	6 (0.8–46)	0.08
BMI (kg/m^2)							
<18.5	71	212.5	13	0.06	I	I	
≥18.5	362	889	13	0.01	0.2 (0.13–0.6)	0.34 (0.1–0.8)	0.03
Behavioral characteristics							
History of smoking							
Yes	8	22	I	0.05	I		
No	425	1,079.5	25	0.02	0.6 (0.1–4.3)		
History of alcohol							
Yes	16	47	5	0.11	8.5 (1.4–11)	4 (1.2–13)	0.02
No	417	1,054.5	21	0.02	I	I	
History of smoking and alcohol							
Yes	5	10	0	0			
No	428	1,091.5	26	0.02			

Abbreviations: BMI, body-mass index; DM, diabetic mellitus; TB, tuberculosis; OHGAs, oral hypoglycemic agents.

study settings, follow-up periods, and sociodemographic characteristics of study participants.

Furthermore, one of the most significant predictors of TB among diabetic patients was a history of TB. Accordingly, patients with a history of TB were 12 times as likely to develop TB than their counter parts (incidence-rate ratio 12, (95% CI 3–39); P=0.01), which is consistent with a study conducted in Australia[20] and studies in Ethiopia.[17,18,22] In addition, our study demonstrated that patients with BMI ≥18.5 kg/m^2 were at higher risk of TB than their counterparts (BMI <18.5 kg/m^2, incidence-rate ratio 0.34, 95% CI 0.14–0.80; P=0.03), which aligns with previous studies conducted in southeastern Amhara,[26] Ethiopia (systematic review),[22] Egypt,[27] the US,[23,28] and China (adjusted HR 0.89, 95% CI 0.76–1.03).[25]
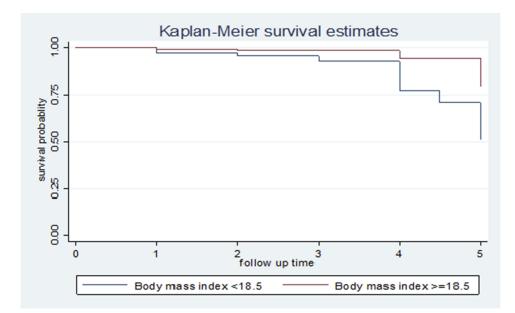

Figure 2 Kaplan–Meier survival curves comparing tuberculosis-free survival probability of diabetic patients based onr body-mass index.
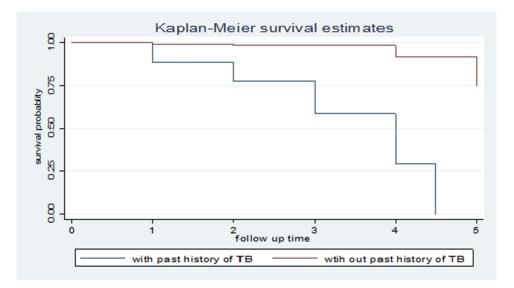
Figure 3 Kaplan–Meier survival curves comparing tuberculosis-free survival probability of diabetic patients based on their history of tuberculosis.
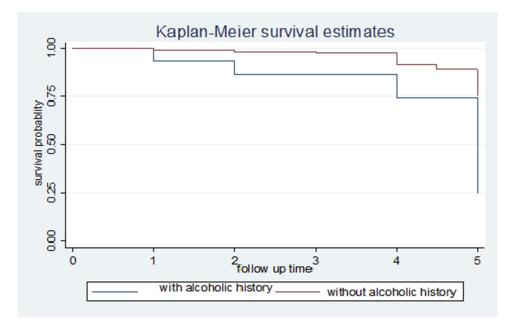

Figure 4 Kaplan–Meier survival curves comparing tuberculosis-free survival probability of diabetic patients based on their history of alcohol consumption.

Conversely, this study's findings contradict those of the study conducted in Ethiopia at Black Lion hospital.[10] This could be due to difference in socio-demographic characteristics as more than half the respondents in this study were rural residents and underweight. It is known that most commonly, underweight patients are considered immunocompromised to withstand TB infection. In addition, most respondents in this study were rural residents, so suchproblems as getting to the health -care organization, may have played a part.

Limitations

The main strength of this study is it was conducted using retrospective cohort design. Therefore, we were able to include a range of sociodemographic, clinical, and behavioral factors, which were very important in determining seroconversion. Despite these strengths, this study has a number of limitations. Firstly, it was conducted at a hospital; therefore, diabetic patients at home could have been missed. Moreover secondary data were used, and consequently some important variables, such as a history of cancer, chemotherapy, adherence status, glycated

hemoglobin, and organ transplantation, might have been missed. Furthermore, the impact of provider training, supplies, equipment, and setup were notexplored.

Conclusion

In this 5-year diabetic cohort, the overall incidence of TB was high. Pulmonary TB accounted for the highest proportion. History of alcohol consumption and history of TB were found to be independent predictors of TB, but being normal and overweight (BMI ≥18.5 kg/m^2) was found to be an independent positive factor associated with decreased risk of TB occurrence. Special attention should be given patients who have a history of alcohol consumption, history of TB, and low BMI to reduce the risk of TB incidence by improving modifiable risk factors. All diabetic patients should be screened for TB in clinical practice to prevent the occurrence of TB as early as possible. Furthermore, a prospective cohort study should be conducted to clarify relationships between predictors and TB incidence among diabetic patients.

Abbreviations

BMI, body-mass index; DM, diabetes mellitus.

Data-Sharing Statement

The data set will not be shared, in order to protect participants' identities, but is available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical clearance was obtained from the Institutional Review Committee of the College of Health Sciences, Debre Markos University (Res/Com/ser/&Post gra/Coor/Off: 781/11/10). Oral permission was obtained from hospital administrations. Each diabetic patient received an explanation about the purpose of study, and verbal informed consent was obtained from each participant prior to proceeding. The ethical committee formally waived the need for formal written consent, since the study was done through interviewing and reviewing medical records of the couples. Therefore, the committee declared that this study was less invasive inasmuch as confidentiality was maintained. To ensure confidentiality, all collected data were coded and locked in a separate room prior to the data-entry process. Participant names were not included in the data-collection format, and data were not disclosed to any person other than the principal investigators.

Author Contributions

All authors contributed to data analysis, drafting, or revising the article, gave final approval of the revision to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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