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Reduced prevalence of latent TB infection in diabetes patients using metformin and statins

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Keywords

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To the Editors:

Diabetes mellitus increases the risk of TB disease and adverse TB outcomes [1]. Emerging evidence suggests diabetes is also associated with latent TB infection (LTBI), and population-based studies reported the prevalence of LTBI among US adults with diabetes to be more than twice that of adults without diabetes (11.6% vs 4.6%) [2, 3]. Given the rapid increase of global diabetes prevalence in regions with high TB burdens, clinical and public health interventions targeting this co-epidemic would avert substantial morbidity and mortality [4].

Metformin and statins are widely used inexpensive therapies to prevent metabolic and cardiovascular complications among patients with diabetes. Studies in euglycemic mice reported that metformin and statins reduced lung bacillary load in early and late phases of TB infection when administered either alone or in combination with anti-TB drugs [5, 6]. Retrospective data from patients with diabetes and TB from our and other studies provide evidence of metformin efficacy in human TB [5, 7–10]. These studies variously reported that

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CONFLICT OF INTERESTS

A.S. have filed a patent with respect to the use of metformin for controlling Mycobacterial infections (WO2017123161A1). All other authors have no conflict of interests to declare.

use of metformin vs any other diabetic treatment was associated with lower risk of progressing to pulmonary TB disease, lower risk of cavitary TB, lower risk of death during anti-TB therapy, improved sputum conversion rates and lower risk of recurrent TB. Similarly, a population-based cohort study using Taiwanese insurance data reported nearly 50% lower incidence of TB disease in adults using statins compared to matched controls without statin use [11]. Only one small (n=220) study from Singapore examined metformin use in the context of LTBI and did not assess statin use [12].

Whether the relationship between diabetes and LTBI is modified by metformin or statins has not been thoroughly evaluated. If metformin or statin use reduces the risk of LTBI in patients with diabetes, there may be additional rationale for evaluating these therapies as TB prevention tools. This study aimed to determine if the association between diabetes and prevalence of LTBI was different by metformin or statin use.

We conducted a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) 2011–2012, a three-stage probability sample designed to be representative of non-institutionalized US adults [13]. Data collected from NHANES includes an in-person interview, a health examination, and laboratory measurements.

Diabetes and pre-diabetes status were defined by self-report and glycated hemoglobin. Participants who self-reported previous diabetes diagnosis by a healthcare professional were classified as having diabetes regardless of HbA1c. Participants without self-reported history of diabetes were classified by HbA1c as euglycemic (≤5.6%), prediabetes (5.7–6.4%) or diabetes (≥6.5%) following American Diabetes Association guidelines [14]. LTBI prevalence was measured by QuantiFERON-TB Gold In-tube (QFT) according to manufacturer instructions and by 0.1ml purified protein derivative tuberculin skin test (TST) which were read 46–76 hours after placement and indurations ≥10mm were defined as TST positive.

Metformin, statin, and non-metformin diabetes medication use (insulin, sulfonylureas, dipeptidyl peptidase 4 inhibitors) were defined by self-report. During NHANES interviews, all participants were asked to report use of prescription medications during a one-month period prior to the survey date. Those who answered “yes” were asked to present medication containers of all products used. For each medication presented, interviewers entered the product’s complete name into a Computer-Assisted Personal Interviewing system.

We estimated LTBI prevalence (with QFT and TST) stratified by diabetes and pre-diabetes status and by metformin, statin, and non-metformin diabetes drug use. We calculated prevalence differences (PD), odds ratios (OR), and 95% confidence intervals (95%CI) to estimate associations between diabetes and LTBI. We used two-sided Rao-Scott or Wald Chi-square p-values <0.05 to define significance. All analyses accounted for weighted probability designs of NHANES [15]. All data were publically available and de-identified and therefore determined exempt from institutional ethical review board review.

Overall weighted prevalence of LTBI among participants with diabetes was 11.6% (95%CI 7.9–15.3%) by QFT (n=4958) and 7.1% (95%CI 4.8–9.3%) by TST (n=4261), significantly higher than euglycemic participants (4.6% and 4.1%, p-value <0.05) (Table 1). Among

participants with diabetes, 53.8% reported no metformin use, and LTBI prevalence was non-significantly higher in those without metformin use (by QFT [PD, 1.4% 95%CI −3.7–6.4%] and by TST [PD, 2.7%, 95%CI: −0.3–5.7]) compared to those self-reporting any metformin use. Among participants with diabetes, lower prevalence of LTBI was observed among participants with metformin plus two or more other diabetes medications (6.2% by QFT and 1.8% by TST) compared to those not using diabetes medications. After adjusting for age, sex, HbA1c, type of diabetes, income level, and duration of diabetes, the odds of TST positivity among participants with diabetes but without any diabetes medication (aOR 3.9, 95%CI 1.1–13.8) were significantly greater than participants using metformin plus two or more other diabetes medications (data not shown).

Any statin use among participants with diabetes was common (46.2%), and the lowest prevalence of LTBI was among those using pravastatin (3.0% by QFT and 2.9% by TST). Among those with diabetes, QFT positivity was significantly higher in participants without any statin use (OR 4.4, 95%CI 1.3–14.9) compared to those with pravastatin use. The association between no statin use and LTBI remained after adjusting for age, sex, income level, metformin use, and Hba1c (aOR 4.8 95%CI 1.4–16.5). The prevalence of TST positivity was also significantly greater among participants without combined metformin-statin use (9.6%) compared to those with combined metformin-statin therapy (4.0%) (p=0.02).

Among adult NHANES participants, the odds of QFT positivity among those with diabetes were significantly greater compared to euglycemic participants in those with (OR 2.6, 95%CI 1.4–5.1) and without statin use (OR 2.9, 95%CI 1.7–4.8). We observed multiplicative interaction between statin use and diabetes with prevalence of TST positivity, which was significantly greater among participants with diabetes and no statin use (9.0%) compared to those with diabetes and any statin use (4.8%) (p=0.03). Interaction with statin use remained significant in multivariable models adjusted for age, sex, BMI, and smoking status (p=0.03); the odds of TST positivity among participants with diabetes was greater in those without statin use (aOR 2.7, 95%CI 1.6–4.8) but not among those with diabetes that used statins (aOR 1.2, 95%CI 0.5–3.0).

Our results enhance recent findings that LTBI is more common among US adults with diabetes.[2] We report that combined metformin and statin use in patients with diabetes was associated with less than half the prevalence of LTBI (TST prevalence 4% among combined statin/metformin use vs. 10% with no statin/metformin use). Whether defined by QFT or TST, the highest prevalence of LTBI among participants with diabetes was observed among those who did not use either metformin or statins and the lowest prevalence was among those who used metformin in combination with two or more other diabetes medications. Among statin use, we report that pravastatin was associated with the lowest prevalence of LTBI by both QFT and TST. Our results also indicate the effect of diabetes on LTBI is different by statin use. Despite limitations of cross-sectional data and the potential for unmeasured confounding, when taken in the context of other studies that reported benefits of metformin and statins with TB disease, our results suggest that patients with diabetes at risk of LTBI may benefit from combination therapy with both metformin and statins. Preventing

LTBI is an essential step in preventing TB disease, and both LTBI and TB disease are complications of diabetes that contribute to substantial morbidity and mortality.

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Table 1:

Diabetes and prevalence of latent tuberculosis by metformin and statin use, NHANES adult participants 2011–2012

	Diabetes status	QuantiFERON-TB Gold In Tube			Tuberculin Skin Test		
		QFT positive[a] % (95% CI)	Prevalence difference[b] PD% (95% CI)	Odds ratio OR (95% CI)	TST positive[a] % (95% CI)	Prevalence difference[b] PD% (95% CI)	Odds ratio OR (95% CI)
ALL NHANES	Diabetes	11.6 (7.9–15.3)	7.0 (3.1–10.8)[c]	2.7 (1.8–4.1)[d]	7.1 (4.8–9.3)	3.0 (0.6–5.4)[c]	1.8 (1.2–2.8)[d]
	Pre-diabetes	7.0 (5.2–8.7)	2.3 (1.0–3.7)[c]	1.5 (1.2–1.9)[d]	6.5 (2.6–10.4)	2.4 (0.8–5.6)[c]	1.6 (1.0–2.7)
	Euglycemic	4.6 (3.7–5.6)	REF	REF	4.1 (2.6–5.6)	REF	REF
SUBGROUP							
No metformin	Diabetes[e]	12.3 (8.0–16.6)	1.4 (−3.7–6.4)	1.1 (0.7–1.9)	8.4 (5.6–11.2)	2.7 (−0.3–5.7)	1.5 (1.0–2.5)
Any metformin use		10.9 (6.0–15.8)	REF	REF	5.7 (3.1–8.3)	REF	REF
No agent	Diabetes[e]	12.5 (7.5–17.5)	6.3 (−4.4–17.0)	2.2 (0.4–10.5)	10.7 (6.2–15.3)	8.9 (4.4–13.4)[c]	6.5 (2.3–18.1)[d]
Non metformin		11.7 (7.3–16.0)	5.4 (−4.6–15.5)	2.0 (0.4–9.2)	4.7 (1.9–7.6)	2.9 (−0.4–6.2)	2.7 (0.9–8.2)
Metformin only		13.1 (4.8–21.3)	6.8 (−6.0–19.6)	2.3 (0.4–12.3)	8.4 (4.7–12.2)	6.6 (2.5–10.7)[c]	4.9 (1.6–14.9)[d]
Metformin+1[f]		11.4 (4.6–18.2)	5.2 (−4.8–15.2)	1.9 (0.4–9.6)	5.4 (1.3–9.4)	3.6 (−0.5–7.6)	3.1 (1.0–9.3)[d]
Metformin+ ≥2[f]		6.2 (0.0–15.8)	REF	REF	1.8 (0.0–3.8)	REF	REF
No metformin/statin	Diabetes[e]	12.6 (6.4–18.8)	2.1 (−4.4–8.6)	1.2 (0.7–2.3)	9.6 (5.1–14.2)	5.6 (0.4–10.9)[c]	2.6 (1.1–5.9)[d]
Statin		11.8 (7.2–16.4)	1.4 (−6.5–9.2)	1.1 (0.5–2.6)	6.1 (2.5–9.6)	2.1 (−2.9–7.0)	1.6 (0.6–4.4)
Metformin		11.6 (3.8–19.5)	1.2 (−8.3–10.7)	1.1 (0.4–3.0)	8.0 (3.0–13.1)	4.0 (−1.5–9.5)	2.1 (0.8–5.2)
Statin + Metformin		10.4 (4.6–16.3)	REF	REF	4.0 (1.6–6.4)	REF	REF
No statin use	Diabetes[e]	12.1 (6.9–17.3)	9.1 (2.8–15.3)[c]	4.4 (1.3–14.9)[d]	8.9 (4.9–13.0)	6.1 (−0.3–12.4)	3.3 (0.6–18.3)
Simvastatin		12.7 (6.4–19.1)	9.7 (1.3–18.1)[c]	4.7 (1.1–19.7)[d]	4.2 (0.9–7.5)	1.3 (−5.6–8.2)	1.5 (0.2–11.5)
Atorvastatin		12.8 (5.6–20.1)	9.8 (2.1–17.5)[c]	4.7 (1.4–16.0)[d]	4.4 (0.5–8.3)	1.5 (−4.9–8.0)	1.6 (0.2–10.2)
Other statin		9.7 (2.8–16.5)	6.7 (−1.3–14.7)	3.4 (0.8–14.0)	7.9 (3.1–12.8)	5.1 (−2.6–12.8)	2.9 (0.4–19.4)
Pravastatin		3.0 (0.0–6.7)	REF	REF	2.9 (0.0–7.9)	REF	REF

	Diabetes status	QuantiFERON-TB Gold In Tube			Tuberculin Skin Test		
		QFT positive[a] % (95% CI)	Prevalence difference[b] PD% (95% CI)	Odds ratio OR (95% CI)	TST positive[a] % (95% CI)	Prevalence difference[b] PD% (95% CI)	Odds ratio OR (95% CI)
Any statin use[g]	Diabetes	11.0 (7.3–14.8)	6.5 (2.0–11.1)[c]	2.6 (1.4–5.1)[d]	4.8 (3.1–6.5)	1.2 (−2.3–4.7)	1.3 (0.5–3.4)
	Pre-diabetes	5.4 (2.3–8.5)	0.9 (−1.5–3.3)	1.2 (0.8–2.0)	5.0 (0.0–10.1)	1.3 (−4.0–6.7)	1.4 (0.4–4.7)
	Euglycemic	4.5 (2.4–6.6)	REF	REF	3.7 (0.8–6.5)	REF	REF
No statin use	Diabetes	12.2 (6.8–17.6)	7.6 (2.2–13.0)[c]	2.9 (1.7–4.8)[d]	9.0 (4.8–13.3)	4.9 (0.8–9.0)[c]	2.3 (1.3–3.9)[d]
	Pre-diabetes	7.5 (5.5–9.5)	2.8 (0.9–4.8)[c]	1.7 (1.2–2.2)[d]	7.1 (2.6–11.5)	2.9 (−0.9–6.7)	1.7 (1.0–3.0)[d]
	Euglycemic	4.7 (3.7–5.6)	REF	REF	4.2 (2.8–5.6)	REF	REF

abbreviations: QFT: QuantiFERON-TB Gold In Tube test; CI: confidence interval; PD: prevalence difference; OR: odds ratio; TST: tuberculin skin test

a. Among NHANES 2011–2012 adult participants, N=4958 had valid diabetes and QFT results; TST positive defined by induration ≥ 10 mm, N=4261 had valid diabetes and TST results

b. Taylor series variance estimation for 95% CI of prevalence difference

c. Rao-Scott Chi-square p-value <0.05

d. Wald Chi-square p-value <0.05

e. Among participants with diabetes and with QFT results (N=791) or TST results (N=685) available

f. Metformin in combination with any 1 or 2 other diabetes medications

g. Wald Chi-square test for interaction p-value < 0.03 between diabetes status and statin use with LTBI measured by TST