The Relationship Between Metformin and Serum Prostate-Specific Antigen Levels

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BACKGROUND. Metformin is the first-line oral antihyperglycemic of choice for individuals with type 2 diabetes. Recent evidence supports a role for metformin in prostate cancer chemoprotection. However, whether metformin indeed influences prostate biology is unknown. We aimed to study the association between metformin and serum prostate-specific antigen (PSA) levels—the primary prostate cancer biomarker.

METHODS. We conducted a cross-sectional study of 326 prostate cancer-free men with type 2 diabetes were recruited between 2004 and 2013 at St. Michael's Hospital. Men were excluded if they had a PSA $\geq$10-ng/ml, or used >2,550-mg/d metformin or supplemental androgens. Multivariate linear regressions quantified the association between metformin dose and log-PSA. Secondary analyses quantified the association between other antihyperglycemics (sulfonylureas, thiazolidinediones) and PSA; sensitivity analyses tested covariate interactions.

RESULTS. Median PSA was 0.9-ng/ml (IQR: 0.5–1.6-ng/ml). Metformin dose associated positively with BMI, HbA1c, diabetes duration, and number of statin, acetylsalicylic acid, diuretic users, and number of antihyperglycemics used, and negatively with LDL-C. In multivariate models, PSA changed by −8% (95%CI: −13 to −2%, $P = 0.011$) per 500-mg/d increase in metformin. Men with diabetes for $\geq$6 years (n = 163) saw a greater difference in PSA per 500-mg/d metformin (−12% [95% CI: −19 to −4%, $P = 0.002$], P-interaction = 0.018). Serum PSA did not relate with sulfonylureas, thiazolidinediones, or total number of antihyperglycemic agents used. Our findings are limited by the cross-sectional design of this study.

Grant sponsor: Canadian Institutes of Health Research; Grant sponsor: Federal Government of Canada; Grant sponsor: Loblaw Brands Ltd; Grant sponsor: Barilla.

Conflicts of Interest/Financial Disclosures: VHJ, CI, NEF, RJH, and DJAJ have no reported conflicts of interest with this work.

Role of the Sponsors: None of the funding organizations or sponsors played any role in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

Aspects of this project were presented at the 79th Scientific Sessions and Annual Meeting of the American Society of Nutrition, in Boston, MA. March 28—April 1, 2015. Abstract available at: The FASEB Journal. 2015: 29(1):Supplement 406.8.

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Received 2 June 2016; Accepted 14 June 2016
DOI 10.1002/pros.23228
Published online 12 July 2016 in Wiley Online Library (wileyonlinelibrary.com).

CONCLUSIONS. Metformin dose-dependently inversely associated with serum PSA, independent of other antihyperglycemic medications. Whether metformin confers a dose-dependent benefit on prostate tumorigenesis and progression warrants investigation. *Prostate 76:1445–1453, 2016.* © 2016 The Authors. *The Prostate* published by Wiley Periodicals, Inc.

KEY WORDS: **metformin; prostate cancer; PSA; antihyperglycemic; cross-sectional; dose-response**

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy among men in the Western world, carrying an estimated lifetime risk of diagnosis of 14–16% [1]; 3–4% of diagnosed men die the disease [2]. There remains a need to identify factors that prevent both prostate cancer development and progression. One solution may include the incorporation of chemoprotective agents, such as 5-α-reductase inhibitors (5-ARIs), which have been reported to reduce both prostate cancer development and progression [3–5]. More recently, the cholesterol-lowering agents, statins, and the anti-inflammatory agents, nonsteroidal anti-inflammatory drugs (NSAIDs), have also shown promise in reducing prostate cancer risk [6,7]. Another emerging agent as a chemopreventative is the oral antihyperglycemic metformin (1,1-dimethylbiguanide hydrochloride) [8]. Metformin's excellent safety profile, affordability and efficacy in glycemic control and mortality not only make it the first-line therapy of choice for diabetics, but also an ideal candidate for cancer chemoprevention.

Epidemiological studies support modest protective effects of metformin on prostate cancer outcomes [9,10]. Studying changes in serum prostate-specific antigen (PSA) values—the most widely employed biomarker in monitoring prostate cancer risk and progression—may provide an important window into the pathobiology of the prostate in response to medications. Indeed improvements in prostate cancer outcomes associated with 5-ARIs, statins, and NSAIDs all correspond with reductions in PSA values [11–13]. However, whether metformin impacts PSA levels or whether metformin dose-dependently influence prostate pathogenesis is unclear [14–16]. Thus to further explore metformin's chemoprotective role while awaiting results from ongoing clinical trials, we investigated the role of different metformin doses on PSA levels in a cross-section of men with type 2 diabetes.

METHODS

Participant Eligibility

Participants were identified from an internal database of individuals who enrolled in five independent randomized nutritional studies for patients with type 2 diabetes between 2004 and 2013 at St. Michael's Hospital (SMH) [17–21]. PSA data were available at trial screening visits. Men were recruited from around the Toronto area using newspaper and transit advertisements. Research Ethics Board approval was obtained at SMH or the University of Toronto and written consent was obtained from all participants.

Only men who reported metformin use or nonuse and dose, and had measured serum total PSA prior to starting an intervention were included. All participants had type 2 diabetes for $\geq$6 months, were on a stable dose of oral antihyperglycemic medications for $\geq$3 months, and free of any significant cardiovascular, renal (serum creatinine $>$150-μmol/L), or liver (serum alanine aminotransferase $>3\times$ upper limit of normal) disease. Men were excluded if they had: a history of prostate cancer (n = 1); a metformin dose $>$2,550-mg/d (maximum recommended dose) (n = 2) [22]; a PSA $\geq$10-ng/ml (n = 4); or a history of 5-ARI or androgen therapy (n = 7). None of the men were receiving insulin therapy, or had a PSA $<$0.1-ng/ml, or a history of prostate surgery.

Exposure Assessment

Serum PSA samples were collected and measured at SMH using the Access Hybertech PSA assay. Biochemical variables were measured following routine hospital laboratory protocol and are described in detail elsewhere [17–21]. Registered dietitians collected medication histories during screening visits. All other demographic and categorical variables were collected through patient interviews prior to receiving an intervention. Serum testosterone was unavailable for analysis.

Primary and Secondary Analyses

The primary analysis continuously modeled metformin dose (at 500-mg/d increments) as an independent variable with PSA as the outcome variable. Two secondary analyses were conducted: (i) the primary analysis was repeated with sulfonylurea and thiazolidinedione dose-equivalents replacing metformin; and (ii) serum PSA was continuously modeled with total number of antihyperglycemic agents used. Sensitivity

analyses explored any modifications to the metformin-PSA relationship.

Statistical Analyses

We took the natural logarithm of PSA to normalize its distribution prior to performing analyses; our results are reported as geometric means of back-transformed log-PSAs. Log-PSA satisfied normality criteria and showed no evidence of heteroscedasticity across metformin doses. Differences in PSA levels between low- (<1,000-mg), intermediate- (1,000 to <2,000-mg), and high- (≥2,000-mg) dose metformin users, and between users versus nonusers of sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 (DPP-4) inhibitors were evaluated as preliminary analyses. Linear regressions assessed the association between log-PSA and metformin dose. The multivariate model was determined a priori to include: age, ethnicity (African, European, Far Eastern, Indian/South Asian, Other), BMI (continuous by category: <25, 25–29.9, 30–34.9, ≥35 in kg/m^2), duration of type 2 diabetes (years), HbA1C (%), and LDL-C, statins (atorvastatin dose-equivalents: nonusers, ≤20, >20 in mg/d), ASA (nonusers, ≤81, >81 in mg/d), and thiazide diuretics (yes/no). Although non-salicylate NSAIDs have been related to PSA levels [11], we did not study them specifically as 98% of our NSAID users used ASA. Secondary analyses linearly regressed dose-equivalents of sulfonylureas (standardized as: nonusers, very low-dose, low-dose, intermediate-dose, high-dose, very high-dose), thiazolidinediones (standardized as: low-dose, intermediate-dose, high-dose), and number of total antihyperglycemics used (1, 2, or ≥3), as additional predictors in the primary multivariate model. DPP-4 inhibitors were excluded from dose-response analyses due to the limited number of users (n = 36). Use of meglitinides (n = 5), α-glucosidase inhibitors (n = 6), and glucagon-like peptide-1 agonists (n = 1) were only considered for the number of total antihyperglycemic used.

Sensitivity analyses compared the metformin-PSA association across subpopulations using interaction variables for: median age (<58 years vs. ≥58 years), median duration of diabetes (<6 years vs. ≥6 years), obesity (BMI <30-kg/m^2 vs. BMI ≥30-kg/m^2), concomitant sulfonylurea, thiazolidinedione, statin, ASA, or thiazide diuretic use (user vs. nonuser), and number of antihyperglycemics used (1 vs. ≥2).

Metformin dose did not show any evidence of multi-collinearity with other predictors in our model. Univariate linear regressions evaluated covariate trends per 500-mg/d metformin. Descriptive data are presented as medians with interquartile ranges (IQR). PSA differences between users versus nonusers, and results for primary and secondary analyses are presented as means and percent estimates with 95% confidence intervals (CIs), respectively. SAS 9.4 software (SAS Institute Inc., Cary, NC) computed all statistical analyses with significance set at two-sided $\alpha < 0.05$. The Tukey–Kramer method adjusted *P*-values for multiple comparisons.

RESULTS

Participant Characteristics

Participant characteristics for the 326 men included in analyses are presented in Table I. Median PSA was 0.9-ng/ml (IQR: 0.5–1.6-ng/ml). The median age was 58 years (IQR: 52–64 years); 85% of men were ≥50 years. Median BMI was 29-kg/m^2 (IQR: 26–33-kg/m^2): 40% and 41% of men were overweight and obese, respectively. Median duration of type 2 diabetes was 6 years (IQR: 3–10 years); 61% of men had diabetes for at least 5 years. Hyperglycemia was sufficiently controlled in most individuals (93% with HbA1c values between 6% and 8%) while dyslipidemia was inadequately controlled among most individuals (57% of individuals with LDL-C >2.0-mmol/L). Most men were of European (56%) or Indian/South Asian (28%) descent. Eighty-nine percent (n = 289) used metformin alone or in combination with other antihyperglycemic medications; 50% used ≥2 oral antihyperglycemics. Forty, 21, and 11% of the cohort used sulfonylureas, thiazolidinediones, and DPP-4 inhibitors, and 70, 54, and 15% of the cohort used statins, ASA, and thiazide diuretics, respectively (Table II). The median dose among users was 1,500-mg/d (IQR: 1,000–2,000-mg/d) for metformin, intermediate-dose (IQR: low-dose to high-dose) for sulfonylureas, intermediate-dose (IQR: intermediate-dose to high-dose) for thiazolidinediones, 20-mg/d (IQR: 10–40-mg/d) for atorvastatin-equivalents, and 81-mg/d (IQR: 81–81 mg/d) for ASA. Men were using a median 1.5 (IQR: 1–2) antihyperglycemic agents, daily.

Metformin dose positively related with BMI, HbA1c, duration of diabetes, and number of statin, ASA, diuretic users, and total number of antihyperglycemic agents; and negatively with LDL-C (*P* for all <0.05).

Metformin Dose and PSA Levels

The relationship between metformin dose and serum PSA is presented in Figure 1. Mean PSA levels were 30% lower (95%CI: 47–13% [$P = 0.012$]) among users compared to nonusers. PSA levels of intermediate- and high-dose metformin users were

TABLE I. Clinical and Demographic Characteristics of Included Participants

Metformin Dose (mg)	0–499	500–999	1,000–1,499	1,500–1,999	2,000–2,499	≥2,500	*P*-Trend	Overall
Participants (No. [%])	37 (11%)	25 (8%)	97 (30%)	38 (12%)	113 (35%)	16 (5%)	–	326 (100%)
Age (years)	62 (58–71)	57 (49–60)	58 (51–64)	60 (53–62)	58 (53–64)	60 (56–65)	0.100	58 (52–64)
BMI (kg/m^2)	26.9 (24.4–31.6)	27.8 (25.6–30.3)	28.3 (25.7–33.4)	27.8 (25.7–33.4)	30.3 (27.2–33.9)	30.3 (28.8–32.6)	0.001	28.8 (25.7–33.1)
HbA1c (%)	6.90 (6.60–7.60)	6.90 (6.60–7.30)	7.10 (6.70–7.50)	7.05 (6.70–7.60)	7.10 (6.80–7.60)	7.50 (7.05–7.85)	0.011	7.10 (6.70–7.60)
Duration of T2DM (years)	7 (5.0–10.0)	3.0 (2.0–6.0)	4.5 (2.0–8.0)	5.0 (2.0–10.0)	7.0 (4.0–14.0)	9.0 (5.0–11.5)	0.015	6.0 (3.0–10.0)
LDL-C (mmol/L)	2.66 (1.99–3.12)	2.28 (1.93–2.55)	2.35 (1.57–2.92)	2.15 (1.61–2.60)	2.01 (1.41–2.42)	2.20 (1.59–2.92)	<0.001	2.14 (1.58–2.76)
Ethnicity (No. [%])								
African	0 (0%)	1 (4%)	6 (6%)	0 (0%)	3 (3%)	1 (6%)	0.644	11 (3%)
European	24 (65%)	12 (48%)	47 (48%)	17 (45%)	72 (64%)	10 (63%)		182 (56%)
Far Eastern	1 (3%)	2 (8%)	10 (10%)	4 (11%)	4 (4%)	1 (6%)		22 (7%)
Indian/South Asian	11 (29%)	9 (36%)	30 (31%)	14 (37%)	22 (19%)	4 (25%)		90 (28%)
Other	1 (3%)	1 (4%)	4 (4%)	3 (8%)	12 (11%)	0 (0%)		21 (6%)
Antihyperglycemics (No. [%])								
Metformin	1 (3%)	25 (100%)	97 (100%)	38 (100%)	113 (100%)	16 (100%)	–	290 (89%)
Sulfonylureas	28 (76%)	3 (12%)	20 (21%)	14 (37%)	56 (50%)	8 (50%)	0.596	129 (40%)
Thiazolidinediones	10 (27%)	3 (12%)	16 (16%)	4 (11%)	27 (24%)	8 (50%)	0.167	68 (21%)
No. antihyperglycemics (No.)	1 (1–1)	1 (1–1)	1 (1–2)	2 (1–2)	2 (1–2)	2 (1.5–3)	<0.001	1.5 (1–2)
Other medications (No. [%])								
Statins	21 (57%)	16 (64%)	66 (68%)	28 (74%)	84 (74%)	12 (75%)	0.031	227 (70%)
ASA	16 (43%)	9 (36%)	53 (55%)	18 (47%)	68 (60%)	11 (69%)	0.014	175 (54%)
Thiazide diuretics	1 (3%)	5 (20%)	13 (13%)	8 (21%)	19 (17%)	4 (22%)	0.049	50 (15%)

TABLE II. Medication Use Among Included Participants

Medication	Users (No. [%])
Metformin	
<1,000 mg	26 (9)
1,000–1,999 mg	135 (47)
≥2,000 mg	129 (44)
Sulfonylureas	
Nonuser	197 (60)
Low dose	43 (13)
High dose	57 (17)
Thiazolidinediones	
Nonuser	258 (79)
Low dose	38 (12)
High dose	30 (9)
DPP-4-inhibitors	
No	290 (89)
Yes	36 (11)
Statins	
Nonusers	99 (30)
5–20 mg	126 (39)
≥20 mg	101 (31)
ASA	
Nonusers	151 (46)
≤81 mg	146 (45)
>81 mg	29 (9)
Thiazide diuretics	
No	276 (85)
Yes	50 (15)

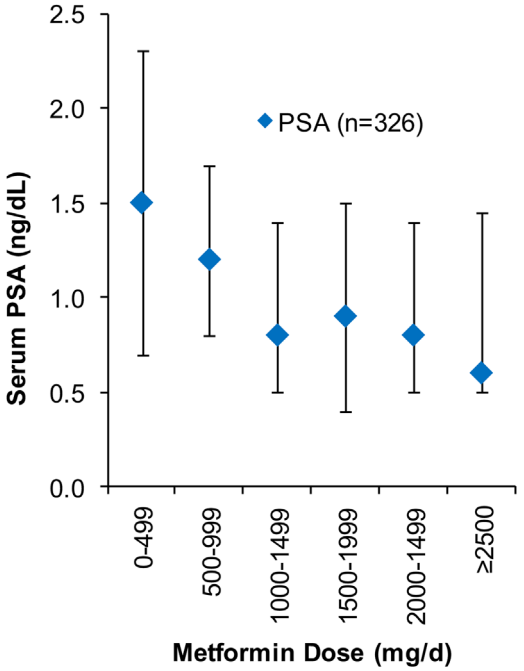

Fig. 1. Distribution of PSA across metformin dose categories. The diamond represents median PSA at each dose threshold. The vertical bars represent interquartile ranges.

32% (95%CI: 51–13% [adjusted-$P = 0.044$]) and 37% (95%CI: 50–14% [adjusted-$P = 0.018$]) lower, respectively, compared to the low-dose group. PSA levels were not different between intermediate- and high-dose users. Metformin dose was inversely related with PSA in univariate analyses ($P = 0.005$). In multivariate analyses, we identified a −7.6% (95% CI: −13.1 to −1.8% [$P = 0.011$]) relative difference in PSA for every 500-mg/d increase in metformin dose up to a maximum dose of 2,550-mg/d (Fig. 2). Accordingly, individuals using ≥2,500-mg/d of metformin had a 33% lower PSA level relative to men taking <500-mg/d.

A sensitivity analysis using a mixed model, treating individuals as blocks for multiple PSA measures (30 men had three PSA measures, 126 had two, and 170 had one) did not modify our results ($P = 0.020$).

Other Oral Antihyperglycemics and PSA

Mean PSA was similar between users and nonusers of sulfonylureas (difference: −1.3% [95%CI: −17.2 to 17.7%, $P = 0.886$]), thiazolidinediones (difference: 6.7% [95%CI: −13.1 to 31.1%, $P = 0.553$]), and DPP-4

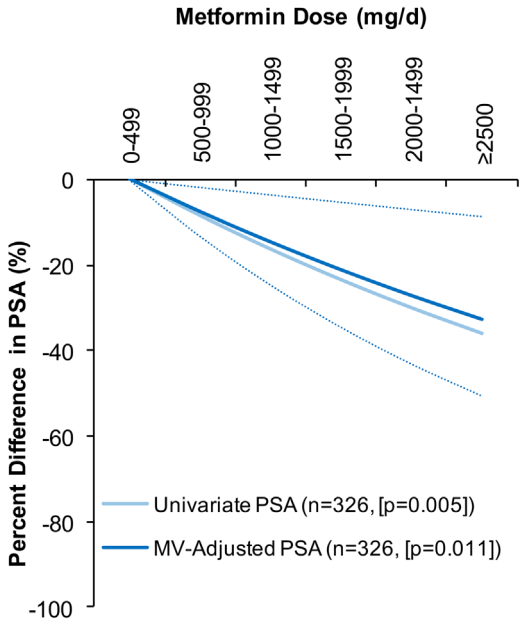

Fig. 2. Regression-predicted percent difference in serum PSA levels across continuously modeled metformin doses, compared to men using <500-mg/d metformin. The light solid line presents the univariate relationship in all men (n = 326). The dark solid link presents the multivariate-adjusted relationship in all men with the dotted line representing the corresponding 95%CIs (n = 326). The multivariate-adjusted model adjusted for age, ethnicity, BMI, duration of diabetes, serum LDL-C, glycated hemoglobin, NSAIDs, statins, and thiazide diuretics.

inhibitors (difference: −3.3% [95%CI: −26.2 to 26.7%, $P = 0.805$]). PSA was not associated with sulfonylurea dose-equivalents (PSA difference per 1-unit increase: 1.1% [95%CI: −4.7 to 7.2%, $P = 0.727$]) or thiazolidinediones dose-equivalents (PSA difference per 1-unit increase: 3.7% [95%CI: −6.4 to 14.9, $P = 0.483$]) in multivariate analyses. Mean PSA did not differ between men using 1 versus ≥2 antihyperglycemic medications (difference: −5.7% [95%CI: −25.5 to 19.4%, $P = 0.831$]). Serum PSA did not change with increasing number of antihyperglycemic agents used: −3.9% (95%CI: −20.5 to 16.2%, $P = 0.682$). Including sulfonylurea and thiazolidinedione dose-equivalents, and number of total antihyperglycemics as covariates did not affect the metformin-PSA association.

Interactions With Metformin and PSA

The metformin-PSA association tended to be stronger in men who were older (≥58 years: −10% [95%CI: −18 to −1%], $P = 0.028$), not obese (−9% [95%CI: −16 to −1%], $P = 0.025$), had diabetes for ≥6 years (−12% [95%CI: −19 to −4%], $P = 0.002$), and among statins nonusers (−9% [95%CI: −17 to −1%], $P = 0.041$), thiazolidinedione users (−18% [95%CI: −27 to −9%], $P = 0.001$), and users of ≥2 antihyperglycemics (−12% [95%CI: −20 to −4%], $P = 0.007$) (Fig. 3). This interaction was only significant for duration of diabetes (P-interaction = 0.018).

DISCUSSION

Metformin is the oral antihyperglycemic of choice for people with type 2 diabetes. A growing body of evidence supports a chemoprotective role for metformin in prostate cancer, although whether metformin impacts the intraprostatic environment remains unclear. Our study identified a significant non-linear inverse relationship between metformin dose and serum PSA in prostate cancer-free men with type 2 diabetes, independent of both other antihyperglycemics and number of total antihyperglycemics used.

Findings in the Context of the Literature

To the best of our knowledge, this is the first study to assess the relationship between metformin dose and serum PSA levels. In vitro experiments report reductions in PSA gene expression and dose-dependent reductions in cancer cell viability with metformin treatment [23–26]. Two observational studies in European populations identified 11–15% lower PSA levels in metformin users compared to nonusers [14,15]. The implications of these results are complicated, however, as the studies did not adjust for prostate cancer status, or diabetes status and severity—both known modifiers of metformin dose, PSA levels and prostate cancer risk [27,28]. In a "window of opportunity" neoadjuvant trial, Joshua et al. found a 10% non-significant PSA reduction in 22 men with stage T2a-T3b disease when treated with 2,000-mg/d of metformin for a median 41 days ($P = 0.08$) [29]. Likewise, Rothermundt et al. treated 44 men with metastatic chemotherapy-naïve castration-resistant disease with 2,000-mg/d of metformin for a median 85 days and found a prolongation of PSA doubling time in 23 patients, and >50% PSA reductions in two patients [16]. The difference in PSA we observed between nonusers and high-dose users (≥2,000-mg/d) was substantially greater than the trial findings, potentially suggesting a diminished efficacy for metformin to lower PSA in men with more advanced cancer. Nevertheless, the available evidence is consistent with the current findings suggesting a lower PSA among metformin users.

The metformin-PSA association was stronger among men with diabetes for ≥6 year, compared to <6 years. The implications of this interaction are unclear as some studies show a lower PSA among men with greater diabetes durations [28], while others do not [27]. The existence of a temporal link between metformin use and PSA cannot be ruled out.

Potential Mechanisms

Metformin has been shown to decrease PSA gene expression both through androgen receptor down-regulation and androgen-receptor independent mechanisms [23,25,26]. Furthermore, metformin may indirectly lower PSA through its anti-inflammatory [30] and hypolipidemic [31] capacity, as reductions in both cholesterol and systemic inflammation have independently been associated with lower PSA levels [11,13]. Lastly, since increasing doses of metformin correlated with markers of worsening diabetes, a worsening diabetes status may be responsible for lowering PSA [27,32]. However, the lack of a PSA association across increasing doses of either sulfonylureas or thiazolidinediones, or increasing number of antihyperglycemic agents used, lends support toward a link independent of other antihyperglycemics, or diabetes severity.

Implications for Practice and Research

While awaiting definitive answers regarding the causal relationship between metformin and PSA and prostate cancer, we take our observations of a metformin-PSA dose-response as objective evidence of metformin at least influencing prostate biology. As

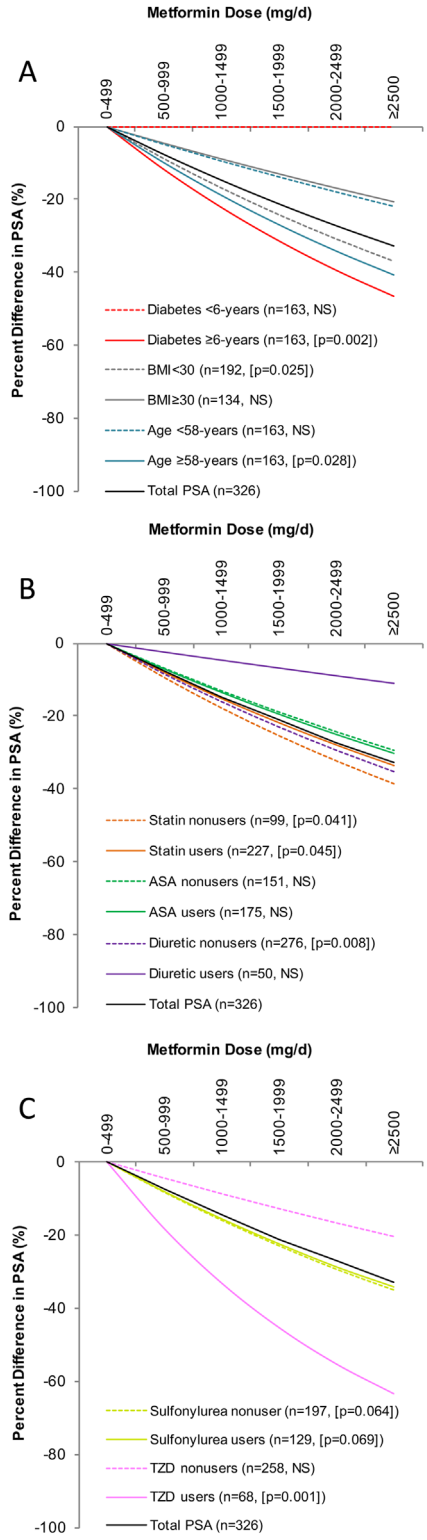

Fig. 3. Regressionpredicted percent differences in serum PSA levels across metformin doses within covariate subpopulations. Each line represents the multivariate-adjusted relationship at each of the following subpopulations: median diabetes duration, median age, obesity (**A**); statin, ASA, and diuretic use status (**B**); and sulfonylurea and thiazolidinedione (TZD) use status (**C**).

similar pathways are proposed for both metformin's PSA lowering and putative antitumor effects, it is possible that the lower PSA we observed may indicate metformin-mediated changes to the intraprostatic micro environment, and consequently, reductions in the risk of developing prostate cancer or progression of undiagnosed indolent prostate cancer.

Several implications arise if these results are confirmed in larger cohorts. Most importantly, metformin's dose-dependent relationship with PSA raises the key question of whether a corresponding relationship exists for prostate cancer outcomes. Indeed one study of patients with diabetes identified a significant 42% reduction in the risk of mortality from all cancers for every 1,000-mg/d increase in metformin dose compared to nonusers [33]. Likewise, Margel et al., found a 24% reduction in the risk of prostate cancer-specific mortality for every 6-months of cumulative metformin exposure after diagnosis [10]. If a metformin dose-response is confirmed for prostate cancer outcomes, classifying all doses as users—as the current epidemiological literature has done—may underestimate the true chemoprotective potential of metformin.

Lastly, some factors may modify PSA levels without corresponding changes in cancer risk [34], thus how metformin influences PSA-screening warrants investigation. On one hand, a raised PSA among high-dose metformin users may more accurately predict the presence of prostate cancer than a raised PSA among low-dose users or nonusers, improving the PSA test's positive predictive value. On the other hand, low PSA levels among high-dose users may lead clinicians to falsely perceive these men as low risk for prostate cancer and thus less likely to require biopsies, potentially leading to delayed diagnoses. Our results advocate for metformin dose-adjusted interpretations of PSA levels, particularly at the screening stage.

Limitations

This study has several limitations. First, the cross-sectional nature of this research prevents causal inferences or temporal assessments, limiting the direct clinical relevance of these findings. Second, we only included prostate cancer-free men with diabetes and only 3% of the population was of African descent, limiting our external validity beyond this demographic. Lastly, we were unable to study the metformin dose-response at different PSA thresholds (i.e., <2.0 vs. ≥ 2.0-ng/ml, etc.), as the metformin dose range was insufficient and significantly differed between PSA subgroups.

CONCLUSIONS

This cross-sectional analysis identified a significant inverse non-linear association between metformin dose and serum PSA levels in 326 prostate-cancer free men with type 2 diabetes. The association appears independent of other metabolic or clinical modifiers of serum PSA, and was not confounded by nor replicated with other antihyperglycemic agents. These results, and the impact of metformin dose on prostate cancer development and progression need to be confirmed in larger cohorts.

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