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Original Research

Use of cystatin C to inform metformin eligibility among adult veterans with diabetes

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ABSTRACT

Aims: Recommendations for metformin use are dependent on eGFR category: eGFR >45 ml/min/1.73 m² – "first-line agent"; eGFR 30–44 – "use with caution"; eGFR<30 – "do not use". Misclassification of metformin eligibility by creatinine-based MDRD GFR estimates (eGFRcr) may contribute to its misuse. We investigated the impact of cystatin c estimates of GFR (eGFRcys) on metformin eligibility.
Methods: In a consecutive cohort of 550 Veterans with diabetes, metformin use and eligibility were assessed by eGFR category, using eGFRcr and eGFRcys. Discrepancy in eligibility was defined as cases where eGFRcr and eGFRcys categories (<30, 30–44, 45–60, and >60 ml/min/1.73 m²) differed with an absolute difference in eGFR of >5 ml/min/1.73 m². We modeled predictors of metformin use and eGFR category discrepancy with multivariable relative risk regression and multinomial logistic regression.
Results: Subjects were 95% male, median age 68, and racially diverse (45% White, 22% Black, 11% Asian, 22% unknown). Metformin use decreased with severity of eGFRcr category, from 63% in eGFRcr >60 to 3% in eGFRcr <30. eGFRcys reclassified 20% of Veterans into different eGFR categories. Factors associated with a more severe eGFRcys category compared to eGFRcr were older age (aOR = 2.21 per decade, 1.44–1.82), higher BMI (aOR = 1.04 per kg/m², 1.01–1.08) and albuminuria >30 mg/g (aOR = 1.81, 1.20–2.73).
Conclusions: Metformin use is low among Veterans with CKD. eGFRcys may serve as a confirmatory estimate of kidney function to allow safe use of metformin among patients with CKD, particularly among older individuals and those with albuminuria.

Introduction

Goals of Healthy People 2020 include developing strategies for safe and effective glycemic control [1]. One key strategy to attain this goal is to promote greater use of metformin. Compared to other oral hypoglycemic agents, metformin is associated with decreased risk of cardiovascular events, slower progression of chronic kidney disease (CKD) and lower death rates [2,3]. Also, metformin does not induce hypoglycemia, a common and potentially very serious adverse side effect of insulin secretagogues, such as sulfonylureas [4].

Because metformin is renally cleared, individuals with severely reduced kidney function who use metformin may be at risk of lactic acidosis [4,5]. Since its introduction to the US market, metformin has thus been labeled with a black box warning contraindicating its use among men with a serum creatinine of ≥1.5 mg/dL and women with a serum creatinine of ≥1.4 mg/dL. As the benefits of metformin have become more widely appreciated, there has been an ongoing debate as to whether these serum creatinine thresholds are too restrictive and whether estimated glomerular filtration rate (eGFR) is a more accurate estimation of kidney function and thus metformin eligibility [6]. The United Kingdom National Institute for Health and Clinical Excellence (NICE) and Kidney Disease Improving Global Outcomes specifically recommend use of metformin for individuals with an estimated glomerular filtration rate (eGFR) of ≥45 ml/min/1.73 m², review and cautious use of lower doses of metformin for individuals with an eGFR of 30–44 ml/min/1.73 m², and not to use metformin for individuals with an eGFR of <30 ml/min/1.73 m² [7,8]. In a 2012 joint position statement, the American Diabetes Association and European Association for the Study of Diabetes concluded that these guidelines appeared very reasonable [9].

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However, metformin is underused among individuals with diabetes and CKD [10]. This is likely multifactorial, including conflicting messages between the FDA and the aforementioned professional societies [10–12]. Clinician concerns about misclassification of kidney function by eGFRcr may also be contributing. The aforementioned recommendations are based upon creatinine estimates of kidney function (eGFRcr), which are influenced by age, gender, ethnicity, and muscle mass. Importantly, these equations do not include muscle mass per se, but use age, gender, and ethnicity to estimate it. Use of creatinine-based estimates of kidney function may thus lead to biases in GFR estimation across and within individuals [13].

Cystatin C estimates of kidney function (eGFRcys) appear to be more accurate than eGFRcr in older, unselected adults, and they have been more strongly associated with health outcomes across numerous research cohorts [14]. eGFRcys is independent of muscle mass [15]. National and international CKD guidelines now recommend the use of cystatin C to confirm eGFR among individuals for whom eGFRcr may be unreliable [16], such as in older, frail adults among whom creatinine generation due to loss of muscle mass may decrease in parallel with GFR decline, effectively masking the actual loss of GFR [17]. This is also of concern for diabetic adults, in whom skeletal muscle mass is also reduced relative to total body mass [18,19].

Our objectives in this study were: 1) to examine independent predictors of metformin use; 2) to compare categorization of kidney function based upon eGFRcys versus MDRD eGFRcr to determine metformin eligibility among adults with diabetes; 3) to identify characteristics associated with different eGFR categories by cystatin C and creatinine.

Subjects, materials and methods

Study design and study participants

This was a cross-sectional study using data from a cohort of adult Veterans with diabetes who were receiving primary care at the San Francisco Veterans Administration Medical Center (SFVAMC). Veterans were eligible for this study if they were included in the local Medical Practice Performance Measures Dashboard, a local diabetes registry designed to improve the quality of diabetes care delivered to adult Veterans, and if they received their medications from the SFVAMC pharmacy. The first 550 patients who met these criteria were included in this study. The study protocol was approved by the Committee of Human Research at the SFVAMC and University of California, San Francisco.

Data collection

Participant demographic information (age, gender, race/ethnicity), body-mass index (BMI), co-morbid conditions from the problem list (hypertension, cardiovascular disease, congestive heart failure), diabetes medication use (metformin, sulfonylurea, insulin, thiazolidinedione), and laboratory data (glycosylated hemoglobin, urinary albumin-to-creatinine ratio, serum creatinine, MDRD eGFRcr) were ascertained by chart review between November 2013 and March 2014. Only data updated in the prior three months were abstracted. Serum creatinine and MDRD eGFR measures were obtained for clinical purposes and were available to clinicians. CKD-EPI eGFRcr and cystatin C were obtained only for research purposes and were not available to clinicians. The creatinine assay was IDMS standardized. Cystatin C measures were performed on a Beckman Synchron DX600 analyzer with reagents produced by Gentian (Norway) and distributed by Beckman. Intra-assay coefficients of variation for cystatin C, estimating within-run precision, ranged from 0.80 to 1.71% with mean serum concentrations between 0.96 and 2.95 mg/L. Inter-assay coefficients of variation for cystatin C, estimating day-to-day precision, ranged from 2.76 to 3.37% with mean serum concentrations between 1.01 and 3.93 mg/L.

Definitions

Metformin eligibility by clinical eGFR category was defined using the most recent recommendations [6,9]: first line agent if eGFR >60 ml/min1/.73 m^2; first line agent if eGFR 45–60 ml/min/1.73 m^2; use with caution if eGFR 30–44 ml/min/1.73 m^2; do not use if eGFR <30 ml/min/1.73 m^2. Discrepancy between eGFRcys and MDRD eGFRcr was defined as cases where clinical eGFR categories differed by GFR estimate and the eGFR values were at least 5 ml/min/1.73 m^2 apart.

Covariates

Candidate covariates included demographic characteristics (age, gender, race/ethnicity), co-morbid conditions (hypertension, hyperlipidemia, cardiovascular disease, congestive heart failure), BMI, treatment of diabetes using glycosylated hemoglobin and urine albumin-to-creatinine ratio (ACR). We examined the relationship of continuous parameters including age, BMI, glycosylated hemoglobin and ACR using smoothing splines to determine whether associations with outcomes were linear [20]. In the final models, we dichotomized glycosylated hemoglobin (≥7%, ≥5.30 mmol/mol) and ACR (>30 mg/g). Multiple imputation with the Markov chain Monte Carlo method was used to impute missing covariates, with 10 imputations to yield ~95% relative efficiency [21].

Statistical methods

Participant characteristics and diabetic medication use were compared by eGFR category using the Kruskal–Wallis test for continuous parameters and χ^2 tests for categorical parameters. Multivariable relative risk regression with a robust variance estimator and a Poisson working model was used to identify predictors of metformin use [22]. We used stepwise backward selection with a significance level of $\alpha = 0.05$ to remove candidate covariates that were not associated with the outcome. In addition to the candidate covariates listed above, either eGFRcr or serum creatinine was included in the models for metformin use. Reclassification of metformin eligibility by eGFR estimating equation was also performed across the clinical eGFR categories. We calculated the number-needed-to-screen (NNS) by cystatin C to identify a patient with an eGFR of <30 ml/min/1.73 m^2, as this person would not be eligible for metformin. Multinomial logistic regression was used to identify factors associated with bidirectional discrepancy between eGFRcys and eGFRcr categories using agreement between methods ("same category") as the reference group. Sensitivity analyses were performed using eGFRcr defined by CKD-EPIcr [23] to broaden generalizability of study results to institutions that use CKD-EPIcr estimates of GFR for clinical purposes. All analyses were conducted using the SAS system, version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of the study population

Overall, the 550 cohort subjects were 95% male, of diverse racial/ethnic backgrounds (45% White, 22% Black, 11% Asian, 22% unknown), and had a median age of 68 years. The median MDRD eGFRcr, CKD-EPI eGFRcr and eGFRcys were 73 ml/min/1.73 m^2, 69 ml/min/1.73 m^2, and 59 ml/min/1.73 m^2, respectively. Characteristics included in our analysis are summarized in Table 1, stratified by