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Impact of Metformin Use on the Prognostic Value of Lactate in Sepsis

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Abstract

Objective—To determine if metformin use affects the prevalence and prognostic value of hyperlactatemia to predict mortality in septic adult Emergency Department (ED) patients.

Methods—Single-center retrospective cohort study. ED providers identified study subjects; data was collected from the medical record.

Patients—Adult ED patients with suspected infection and 2 or more Systemic Inflammatory Response Syndrome Criteria. The outcome was 28-day mortality. The primary risk variable was serum lactate (< 2.0; 2.0–3.9; ≥4.0 mmol/L) categorized by metformin use; covariates-

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demographics, Predisposition, Infection, Response, Organ Dysfunction score, and metformin use contraindications.

Setting—Urban teaching hospital; 2/1/2007 to 10/31/2008.

Results—1947 ED patients were enrolled; 192 (10%) were taking metformin; 305 (16%) died within 28-days. Metformin users had higher median lactate levels than non-users [2.2 mmol/L (IQR 1.6–3.2) vs. 1.9 mmol/L (IQR 1.3–2.8)] and a higher, though non-significant, prevalence of hyperlactatemia (lactate ≥ 4.0 mmol/L) (17% vs. 13%) (p=0.17). In multivariate analysis (reference group non-metformin users, lactate < 2.0 mmol/L), hyperlactatemia was associated with an increased adjusted 28-day mortality risk among non-metformin users (OR = 3.18, p < 0.01), but not among metformin users (OR = 0.54, p=0.33). Additionally, non-metformin users had a higher adjusted mortality risk than metformin users (OR = 2.49, p < 0.01). These differences remained significant when only diabetics were analyzed.

Conclusions—In this study of adult ED patients with suspected sepsis, metformin users had slightly higher median lactate levels and prevalence of hyperlactatemia. However, hyperlactatemia did not predict an increased mortality risk in patients taking metformin.

Keywords

Lactate; Metformin; Sepsis; Risk Stratification

Introduction

Each year in the United States, approximately 2.3 million adult patients present to Emergency Departments (ED) for suspected severe sepsis, resulting in more than 200,000 deaths.[1, 2] Accurate risk stratification of this population is essential to optimize treatment and focus limited resources on high-risk patients. Elevated lactate levels are associated with increased mortality risk in severe sepsis and are the most common serologic test used for risk stratification.[3–5] Additionally, hyperlactatemia (lactate ≥ 4.0 mmol/L) is an enrollment criterion for Early Goal Directed Therapy (EGDT), a protocol believed to reduce short-term mortality in sepsis.[6–8] Though potentially beneficial in high-risk patients, EGDT is also resource consumptive, and requires invasive procedures with their associated complications. Hyperlactatemia may be caused by conditions other than sepsis.[9] Even in sepsis, the degree of lactate elevation may be affected by multiple factors, which could impact its prognostic value.[10] Because lactate levels routinely impact vital clinical decisions, it is essential to identify factors such as metformin use that may cause hyperlactatemia independent of sepsis severity.

Metformin is an oral anti-hyperglycemic agent in the biguanide class. Biguanides are known to interfere with mitochondrial metabolism and inhibit hepatic uptake of serum lactate.[11, 12] Unlike other biguanides, metformin use does not appear to increase the prevalence of hyperlactatemia.[13] However, during periods of physiologic stress such as sepsis, metformin use is thought to increase the likelihood of developing hyperlactatemia. Due to this concern, the Food and Drug Administration (FDA) recommends withholding metformin in patients with probable sepsis.[14] Given this knowledge, the prevalence of hyperlactatemia among septic metformin users requires quantification.

Since metformin use could affect lactate levels, it could also interfere with the prognostic value of lactate in sepsis. A metformin user who becomes septic could accumulate lactate as a direct result of sepsis, from the impact diabetes and metformin use has on cellular metabolism, or through a combination of these physiologic mechanisms.[15] Hyperlactatemia in sepsis has consistently been shown to be associated with increased mortality risk,[3–5] but

the association of hyperlactatemia with mortality due to metformin use is less clear.[13] If hyperlactatemia's association with mortality risk in sepsis is affected by metformin use, then risk stratification using lactate in these patients would be less useful. The objective of this study was to determine if metformin use affects the prevalence and prognostic value of hyperlactatemia to predict mortality in adult ED patients with suspected sepsis.

Methods

Study Design

We performed a single-center retrospective cohort study of adult patients hospitalized from a single, urban ED for suspected sepsis. Findings from a portion of this cohort have been reported previously.[16] The Institutional Review Board of XXXXX Hospital approved the study with a waiver of informed consent.

Study Setting and Population

A protocol was in place during the study to routinely test a serum lactate level, and other markers of organ dysfunction, on adult patients having laboratory studies in the ED for a suspected infection, as recommended by consensus guidelines.[17] All patients with lactate testing during the study were evaluated for inclusion. Patients were enrolled in the study if they were adults (21 years of age or older), had a serum lactate level tested in the ED, had a provider suspected infection as reported in the Electronic Medical Record (EMR), and two or more Systemic Inflammatory Response Syndrome (SIRS) Criteria (using initial ED vital signs and laboratory studies). The SIRS criteria include: body temperature < 96.8°F or > 100.4°F; heart rate > 90 beats per minute; respiratory rate > 20 breaths per minute; and a white blood cell count less than 4,000 cells/mm^3 or greater than 12,000 cells/mm^3, or greater than 10% immature neutrophils (band forms).

The study was entirely performed at XXXXX Hospital, a 450-bed urban teaching hospital with an annual ED census of 95,000 patients. For patients with repeat ED visits during the study period, only the initial visit was used. Patients were enrolled from 2/1/2007 to 10/31/2008.

Study Protocol

All data was collected from the EMR. Trained research associates abstracted the medical records of all patients with lactate levels tested in the ED during the study period. Published recommendations for quality chart-abstraction were followed.[18] Specifically, data abstractors were trained in advance, used standardized data abstraction sheets, were routinely audited, and were blinded to the study hypothesis. Ten percent of subjects had all variables collected by a second blinded abstractor to confirm reliability of the results (kappa 0.80 or greater for all variables).

Serum lactate (mmol/L) levels were measured using a serum-based immunoassay (Unicel Synchron, Beckman Coulter Inc., Brea, CA). Arterial or venous lactate testing was allowed to improve protocol compliance, similar to other ED lactate screening studies.[3–5] Previous studies have demonstrated that venous lactate levels correlate with arterial lactate levels, as well as with short-term mortality risk, in adult ED patients with suspected sepsis.[3, 19] Only initial serum lactate levels, tested prior to hospital admission, were used. Determination of whether patients were taking metformin on ED arrival was made by review of patient reported medication use for the initial ED visit. Patients reporting use of any medication containing metformin were considered metformin users for study purposes. The primary outcome was 28-day mortality. For patients who were discharged alive prior to 28-days from the initial ED encounter, the Social Security Death Index (SSDI) was queried (more

than one year following the initial ED evaluation) to confirm whether the patient survived to 28 days.[20]

Data Analysis

Summary and descriptive statistics were generated for the study cohort. The prevalence of hyperlactatemia among metformin and non-metformin users was investigated using χ^2. To quantify associations between metformin use, lactate levels and mortality, a logistic regression model was developed, with the outcome of 28-day mortality. The primary measure of interest was a metformin/lactate level interaction variable that represented the six possible combinations of three serum lactate categories (<2.0; 2.0–3.9; ≥4.0 mmol/L), categorized by metformin use. The lactate cutoffs correspond to levels previously reported to be associated with different mortality risks in septic adult patients.[3, 21] For study purposes, only a lactate level ≥ 4.0 mmol/L was considered to be hyperlactatemia as it represents a cutoff associated with significant mortality risk that is commonly used to determine need for aggressive interventions.[17]

Patient demographics were evaluated for possible inclusion in the model. Additionally, to adjust for illness severity, the Predisposition, Infection, Response, Organ Dysfunction (PIRO) score was included.[22] This scoring system was chosen as it has been internally and externally validated in similar populations of adult ED patients with suspected sepsis and includes variables that could be abstracted from the EMR.[22] The PIRO score was developed for the outcome of mortality in sepsis from a logistic regression model using adjusted odds ratios of categorized serum lactate levels as well as 16 other clinical variables routinely available for septic ED patients. For this analysis, adjusted odds ratios of categorized lactate levels for mortality were determined, adjusted by the 16 other PIRO clinical variables. This analysis allowed for the determination of lactate's association with mortality risk, as modified by other available markers of illness severity.

Additionally, the FDA has defined relative contraindications to metformin use based on the increased likelihood of lactic acidosis from certain conditions (liver and renal dysfunction, serum acidosis and hypoxia).[14] However, published reports have demonstrated that physicians frequently prescribe metformin in spite of these contraindications[23] with no apparent impact on the incidence of lactic acidosis or patient outcomes.[24, 25] Such patients were therefore included in the study, but potential confounding caused by these contraindications was adjusted for by inclusion in the logistic regression model. A medical history of diabetes mellitus was expected to exhibit significant collinearity with metformin use, which raises the possibility that any observed impact of metformin use in the model could actually be due to the associated medical history of diabetes. To account for this concern, the model was repeated only for the sub-group of patients with a known history of diabetes mellitus.

We quantified the effects of covariates on mortality rates by including them individually in separate logistic regression models that already included the metformin/lactate level interaction variable. Covariates significant at the $p = 0.05$ level were simultaneously included in a multivariate logistic regression model, and those remaining significant at the $p = 0.05$ level were retained in the final model. The final model was confirmed using stepwise Aikaike Information Criterion methods, which compares the fit of different regression models.[26]

Metformin use has not previously been shown to effect mortality in sepsis, but metformin has antioxidant and vasoactive properties that could be protective in sepsis.[27–29] This study was not designed to identify a protective effect of metformin use in sepsis. However, to distinguish any association of metformin use with mortality from metformin's impact on

lactate's prognostic utility, contrasts of the final model were performed. Contrasts allowed for comparisons of the different metformin/lactate groups to each other, in addition to reference group comparisons. In this way, the relative impact of metformin use on mortality risk for the entire cohort, and among different lactate stratum, could be analyzed. Calculations were performed in SAS v9.2 (Cary, NC) and R (http://www.r-project.org/).

Results

Lactate levels were tested on 2650 adult patients in the ED during the study period. Of these patients, 1947 (73%) had two or more SIRS criteria and an ED provider suspected infection. These patients made up the study population. Baseline characteristics are reported in table 1. Seventeen hundred fifty-five subjects were not taking metformin, while 192 (10%) subjects were taking metformin. Subjects taking metformin had a higher median lactate level than non-metformin users [2.2 mmol/L (IQR 1.6–3.2) vs. 1.9 mmol/L (IQR 1.3–2.8)]. Additionally, the prevalence of hyperlactatemia was higher among metformin users than non-users, though this finding did not achieve statistical significance (17% vs. 13%, $p = 0.17$). Twenty-eight day all cause mortality for the cohort was 16% (95% Confidence Interval 14.0 to 17.3%) (table 1).

Among all subjects, elevated lactate levels were associated with higher 28-day mortality (table 1). Additionally, metformin users had a significantly lower unadjusted 28-day mortality risk than non-metformin users (8% vs. 17%; $p < 0.01$). Multivariate regression models showed that compared to the reference group of non-metformin users with lactate levels < 2.0 mmol/L, non-metformin users with lactate levels ≥ 4.0 mmol/L had a higher adjusted mortality risk (OR = 3.18, $p < 0.01$). There was no significant difference in mortality risk between the reference group and any of the metformin users, regardless of categorized lactate levels (table 2a). The modified PIRO score, patient age, and creatinine level > 1.4 mg/dL were also found to be significant predictors of mortality and were included in the model. Gender, serum bilirubin, race, diabetes mellitus, anion gap, and percent oxygen saturation were not significant predictors of mortality at the $p = 0.05$ level. Results of the multivariate analysis were similar when restricted to only diabetics in the study population (table 2b).

Contrasts were performed to determine the effect of metformin use on mortality risk. Among all study subjects, after adjustment for lactate level, modified PIRO score, age and serum creatinine level, individuals not taking metformin were 2.5 times more likely to die within 28 days when compared to individuals taking metformin (OR = 2.49, 95%CI 1.38 – 4.73, $p < 0.01$). These results were similar when the analysis was restricted only to diabetic patients in the study cohort (OR 2.62, 95%CI 1.32 – 5.17, $p < 0.01$). Among patients with low to moderate lactate elevation (<4.0 mmol/L) there was no difference in adjusted mortality risk when stratified by metformin use. In contrast, patients with lactate levels ≥4.0 mmol/L not taking metformin had more than a 5 times greater adjusted mortality risk than metformin users (OR 5.95, 95%CI 1.68 – 21.10, p=0.01). This finding was similar when only diabetics were included in the analysis (OR 6.16, 95%CI 1.52 – 25.02, p=0.01).

Discussion

In this study of adult ED patients with suspected sepsis, metformin use was associated with slightly higher median lactate levels and prevalence of hyperlactatemia, though this difference was not statistically significant. As demonstrated in previous studies,[3, 4] 28-day mortality risk was higher in this cohort with increasing categorized lactate levels. However, among metformin users, we did not observe the same association between elevated lactate

levels and increased mortality. Indeed, we found no association whatsoever between hyperlactatemia and mortality in patients taking metformin in the study population.

The lack of association between hyperlactatemia and mortality risk for metformin users could be due to several factors. Metformin users could have been less ill at study entry than non-users, but in this study metformin users had similar illness severity to non-metformin users. Additionally, when adjusted for illness severity, hyperlactatemia was still not associated with mortality risk among metformin users.

Metformin use could lead to lactate accumulation by a mechanism distinct from that of sepsis. This accumulated lactate could affect the prevalence of hyperlactatemia among metformin users, resulting in a different association of lactate with mortality risk in these patients. Metformin users had a slightly higher prevalence of hyperlactatemia in this study but hyperlactatemia had a much lower associated mortality risk in these patients. Additionally, contrasts demonstrated that the impact of metformin use on mortality was most pronounced at high lactate levels, implying that lactate accumulation may have partially occurred by a different mechanism in these patients. Causality cannot be determined from this study design, but further investigation of this finding is warranted.

Alternatively, metformin use could be protective in the setting of sepsis, which could impact the association of lactate with mortality risk in these patients. In this study, non-metformin users had higher 28-day mortality risk than metformin users, even when adjusted for lactate levels and other important covariates. This study was not designed to identify a protective effect of metformin use in sepsis, but metformin does have potentially beneficial physiologic effects in sepsis, including vasoactive and anti-inflammatory properties.[27, 28, 30] Additionally, metformin has been found to inhibit expression of lipopolysaccharide induced nitric oxide synthase in an experimental model, which could decrease systemic vasodilatation in sepsis.[29] These physiologic characteristics of metformin use could have a protective effect in septic patients, but further study is needed to determine this association.

Previous research has demonstrated that diabetics may have equivalent or better outcomes from critical illness than non-diabetics, even when adjusted for illness severity.[31, 32] Diabetics could also have a different prevalence and prognostic value of lactate levels in sepsis. As expected, metformin use was strongly associated with a history of diabetes in this study. To account for the possibility that the observed impact metformin use had on lactate levels and mortality could actually have been related to an associated medical history of diabetes, the analysis was repeated among only diabetics. Results of this analysis were similar to that of the overall study population. This finding demonstrates that the apparent effect of metformin use on the prognostic value of hyperlactatemia in sepsis is more likely associated with metformin use than with a history of diabetes mellitus.

This study had multiple limitations. First, providers in the ED prospectively identified patients, but all data was collected from the EMR. The risk of misclassification bias was mitigated by following previously published guidelines for medical record abstraction[18] and by restricting the analysis to objective clinical findings (demographics, comorbidities, laboratory results, vital signs). Metformin use was also collected from the EMR, and that information could have been reported in error. However, during the study period, a protocol was in place whereby the ED triage nurse recorded the patient's current medication use, and the treating ED provider confirmed the list, decreasing the likelihood of misclassification error.

Additionally, hyperlactatemia is an enrollment criterion for EGDT. Performance of EGDT was recommended during the study period for patients with persistent hypotension (systolic blood pressure < 90 mmHg or lactate ≥4.0 mmol/L), but compliance with the protocol was

limited. A quality assurance review of EGDT protocol compliance during a portion of the study period found that less than 20% of EGDT candidates had the 6-hour therapeutic bundle completed as recommended. Enrollment in this clinical intervention was not measured for the entire cohort, but the relatively large size of the study, and low protocol compliance, makes it less likely that EGDT use would be significantly imbalanced between groups.

A further limitation is that patients were not followed prospectively after discharge from the hospital. Use of the SSDI to determine survival outcomes of discharged patients has previously been validated,[20] but it is possible that some patients discharged prior to 28-days from the initial ED encounter may have died and were not entered into the SSDI. Finally, the study was entirely performed at one hospital. The external validity of these results is unknown and further study, in other settings, may be warranted.

We found that ED patients hospitalized for suspected sepsis that were on metformin had a slightly higher prevalence of hyperlactatemia than non-metformin users. Additionally, in this cohort, categorized serum lactate levels did not demonstrate useful prognostic utility in adult ED patients with suspected sepsis who were actively taking metformin. Alternative prognostic markers for mortality risk should be considered in these patients.

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Table 1

Patient demographics and clinical characteristics for all subjects stratified by metformin use and 28-day mortality.

Variable	All Subjects	Non Metformin Users	Metformin Users	Survivors	Non-Survivors
n (%)	1947	1755 (90%)	192 (10%)	1642 (84%)	305 (16%)
Age (years)	72 ± 17.4	72 ± 17.7	71 ± 13.7	70 ± 17.6	81 ±12.5
Gender (Male) (%)	938 (48%)	846 (48%)	92 (48%)	801 (49%)	137 (45%)
Race					
White	928 (48%)	851 (48%)	77 (40%)	755 (46%)	173 (57%)
Asian	384 (20%)	342 (19%)	42 (22%)	323 (20%)	61 (20%)
Black	230 (12%)	199 (11%)	31 (16%)	202 (12%)	28 (9%)
Hispanic	242 (12%)	217 (12%)	25 (13%)	224 (14%)	18 (6%)
Other	161 (8%)	144 (8%)	17 (9%)	136 (8%)	25 (8%)
Not reported	2 (0.1%)	2 (0.1%)	0 (0%)	2 (0.1%)	0 (0%)
Vital Signs					
Temperature (F°)[a]	100.3 ± 2.3	100.3 ± 2.3	100.6 ± 2.1	101 ± 2.2	99 ± 2.5
Heart Rate (beats/min)[a]	105 ± 21.5	105 ± 21.5	105 ± 21.0	105 ± 20.9	104 ± 24.3
Respiratory Rate (breaths/min)[a]	22 ± 5.2	22 ± 5.2	22 ± 5.2	21 ± 4.9	23 ± 6.1
Systolic Blood Pressure (mm Hg)[a]	126 ± 31.1	125 ± 30.9	133 ± 31.8	128 ± 30.4	112 ± 31.0
Oxygen Saturation (%)[a]					
Median (IQR)	97 (95–99)	97 (95–99)	96 (94–98)	97 (95–99)	97 (93–100)
Comorbidities					
Diabetes Mellitus	535 (27%)	343 (20%)	192 (100%)	456 (28%)	79 (26%)
Chronic Pulmonary Disease	479 (25%)	432 (25%)	47 (24%)	382 (23%)	97 (32%)
Chronic Renal Insufficiency	316 (16%)	297 (17%)	19 (10%)	237 (14%)	79 (26%)
Congestive Heart Failure	425 (22%)	392 (22%)	33 (17%)	320 (19%)	105 (34%)
Sepsis Categories					
Suspected Sepsis	387 (20%)	350 (20%)	37 (19%)	367 (22%)	20 (7%)
Severe Sepsis[b]	1334 (69%)	1,196 (68%)	138 (72%)	1125 (69%)	209 (69%)
Septic Shock[c]	226 (12%)	209 (12%)	17 (9%)	150 (9%)	76 (25%)

Variable	All Subjects	Non Metformin Users	Metformin Users	Survivors	Non-Survivors
Laboratory Data					
White Blood Cell Count (10^3/mm^3)	13 ± 8.0	14 ± 8.3	13 ± 8.0	13 ± 7.1	16 ± 11.6
Immature Neutrophils (10^3/mm^3)					
Median (IQR)	1 (0–13)	1 (0–13)	1 (0–14)	1 (0–13)	2 (0–17)
Platelets (10^3/mm^3)	258 ± 129	258 ± 129	262 ± 120	255 ± 123	277 ± 152
Glucose (mg/dL)	158 ± 105	153 ± 102	210 ± 117	158 ± 107	159 ± 89
Creatinine (mg/dL)	1.6 ± 1.4	1.6 ± 1.5	1.3 ± 0.7	1.5 ± 1.4	1.9 ± 1.5
Bilirubin, total (mg/dL)	1.2 ± 0.9	1.2 ± 0.9	1.1 ± 0.5	1.1 ± 0.8	1.4 ± 1.4
Anion gap (mEq/L)	10.3 ± 3.8	10.2 ± 4.0	10.5 ± 3.3	10.0 ± 3.5	11.5 ± 4.8
Lactate (mmol/L)					
Median (IQR)	1.9 (1.3–2.9)	1.9 (1.3–2.8)	2.2 (1.6–3.2)	1.8 (1.2–2.7)	2.5 (1.7–4.5)
Categorical Lactate					
0 –1.9 mmol/L	994 (51%)	919 (52%)	75 (39%)	891 (54%)	103 (34%)
2.0 – 3.9 mmol/L	691 (35%)	606 (35%)	85 (44%)	578 (35%)	113 (37%)
≥ 4.0 mmol/L	262 (13%)	230 (13%)	32 (17%)	173 (11%)	89 (29%)
PIRO Score	11 ± 5.0	11 ± 5.0	11 ± 4.7	10 ± 4.8	14 ± 4.8
Metformin Use	192 (10%)	--	--	177 (11%)	15 (5%)
28-Day Mortality	305 (16%)	290 (17%)	15 (8%)	--	--

[a] Triage or first ED vital sign recorded.

[b] Defined as sepsis with objective evidence of organ dysfunction.[22]

[c] Defined as persistent hypotension (systolic blood pressure < 90 mmHg) following an isotonic fluid bolus.

Continuous, parametric values presented as mean ± SD, continuous non-parametric data presented as median (interquartile range), categorical data presented as frequency (percentage) among groups.

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Table 2

Multiple logistic regression demonstrating adjusted odds ratio for 28-day inpatient mortality categorized by metformin use and categorized lactate.[a]

a) Model for all patients in the study cohort (n=1947)

Parameter	Lactate Stratum	n	Odds Ratio	95% C.I.	*p*
Non Metformin Users	<2.0 mmol/L	919		Reference[b]	
	2.0 – 3.9 mmol/L	606	1.27	0.92 – 1.78	0.15
	≥ 4.0 mmol/L	230	3.18	2.12 – 4.66	<0.01
Metformin Users	< 2.0 mmol/L	75	0.59	0.21 – 1.70	0.32
	2.0 – 3.9 mmol/L	85	0.77	0.34 – 1.78	0.54
	≥ 4.0 mmol/L	32	0.54	0.15 – 1.83	0.33

b) Model including only diabetics within the study cohort (n=535)

Parameter	Lactate Stratum	n	Odds Ratio	95% C.I.	*p*
Non Metformin Users	<2.0 mmol/L	168		Reference[b]	
	2.0 – 3.9 mmol/L	127	1.41	(0.72,2.78)	0.32
	≥ 4.0 mmol/L	48	3.68	(1.62,8.38)	<0.01
Metformin Users	< 2.0 mmol/L	75	0.60	(0.19,1.88)	0.38
	2.0 – 3.9 mmol/L	85	0.81	(0.32,2.07)	0.66
	≥ 4.0 mmol/L	32	0.60	(0.16,2.25)	0.45

[a]The model was adjusted for patient age (OR = 1.04 for every year older than 21, $p < 0.01$), modified PIRO score (OR = 1.11 for each point increase in scoring system, $p < 0.01$), and serum creatinine > 1.4 mg/dL (OR = 1.77, $p = 0.01$);

[b]Reference group: 21 year old subject with a lactate < 2.0 mmol/L not taking metformin.