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The Effect of Initiating Pharmacologic Insulin on Serum Uric Acid Levels in Patients with Diabetes: A Matched Cohort Analysis

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Abstract

Objectives—Gout is a common inflammatory arthropathy associated with hyperuricemia. Substantial evidence links hyperuricemia to the metabolic syndrome and diabetes. Rising serum insulin levels correlate with an increase in serum uric acid (UA). The current study evaluated the effect of pharmacologic insulin on serum UA levels in patients with diabetes.

Methods—We conducted a retrospective analysis of previously collected data. The study cohort consisted of patients with both gout and diabetes who had initiated insulin therapy and a matched set of non-insulin users. The change in UA levels was calculated in both groups and compared. Potential confounders were assessed and adjusted for in a matched linear regression model.

Results—23 patients met criteria for insulin initiators and were matched to 23 non-insulin users. In unadjusted analyses, patients started on insulin had a larger increase in UA (mean change 1.25 mg/dl, interquartile range, IQR: −0.7,2.3) in comparison to those not starting insulin (mean change 0.06 mg/dl, IQR: −1.1,0.9). After controlling for baseline UA and time between UA measurements, regression modeling showed that insulin use was significantly associated with an increase in UA ($\beta = 1.25$ mg/dl, p value= 0.02).

Conclusions—Initiation of insulin among patients with diabetes was associated with a statistically significant increase in serum UA levels. This may affect the risk of gout flares and might suggest the potential for prophylactic therapy.

Keywords

gout; diabetes; uric acid; insulin

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INTRODUCTION

Gout is a common inflammatory arthropathy with an increasing prevalence. Gout currently affects some 6.1 million in the U.S and almost all patients have elevated serum uric acid (UA) levels.(1) Hyperuricemia has been implicated in the metabolic syndrome, insulin resistance, hypertension, and congestive heart failure.(1) Several studies have demonstrated an association between increasing UA levels, insulin resistance, and type 2 diabetes.(2–4) In fact, a study focusing on veterans with gout but without diabetes found that 1 in 11 new diagnoses of diabetes were attributable to hyperuricemia.(2) Furthermore, a study following young adults 18–30 years of age for 15 years determined that hyperuricemia was an independent marker for predicting diabetes and pre-diabetes.(3)

The link between hyperuricemia and hyperinsulinemia, a hallmark of type 2 diabetes, is complex; insulin levels correlate inversely with renal UA excretion and in turn UA levels may promote insulin resistance. Several prospective studies in the 1980's suggested that UA levels increased in the pre-diabetic period and then decreased with increasing serum glucose levels and duration of diabetes.(5, 6) Facchini et al were among the first groups to demonstrate that higher levels of insulin resistance resulted in increased serum UA levels attributable to a decrement in renal urate excretion.(7) Investigation on UA and insulin resistance has revealed a bell-shaped curve when UA levels are measured against serum glucose levels.(8) Choi et al demonstrated in a cross-sectional study that UA levels were associated with increasing hemoglobin A1C (HbA1c) levels until a level of 6–6.9%. At higher HbA1c levels, serum UA decreased. A similar relationship was shown in association with fasting glucose levels. The initial increase in UA is posited to be secondary to insulin's inhibition on the renal excretion of UA. Inversely, glucose levels greater than 180mg/dl appears to have a uricosuric effect and are likely responsible for the subsequent decrement in serum UA.(8) Few studies have evaluated exogenous insulin in regards to UA. However, in a euglycemic clamp experiment conducted among healthy individuals, exogenous insulin acutely decreased fractional renal urate excretion presumably due to insulin's effects on renal handling of urate.(9)

We are unaware that the role of exogenous insulin on serum UA levels has been described among patients with diabetes. Understanding the effects of exogenous insulin on UA levels is especially important among patients with diabetes and gout, as insulin initiation could translate into an increase in gout flares. The current study aims to fill this knowledge gap through a longitudinal study of the effect of initiating pharmacologic insulin on serum UA levels in patients with diabetes. We hypothesized that patients with type 2 diabetes started on insulin would have an increase in UA compared to patients with diabetes not started on insulin. The results of such a study could potentially have clinical implications in regards to treatment of gout and hyperuricemia in patients initiating insulin therapy.

METHODS

Source Population and Study Design

We conducted a matched cohort analysis – one group were insulin initiators and the other were not. All subjects had concurrent gout and diabetes.

Patients were selected from a linked dataset of information from an electronic medical record (EMR) and Medicare claims data from the Centers for Medicare & Medicaid Services (CMS). This linked data set includes male and female patients receiving care at Brigham and Women's Hospital who are Medicare beneficiaries and had a diagnosis of gout and hyperuricemia as noted in the EMR. From this cohort, we selected patients who had a diagnosis of diabetes (defined as HbA1c > 6.5%, ICD-9-CM code 250.x or use of diabetic medications) in the EMR or claims data to form the potentially eligible subject pool for the current study. Medicare Part D (medication) claims for the potentially eligible subjects were screened for insulin initiation. The final study cohort consisted of a subset of the above patients who had clear evidence in the EMR of insulin initiation. The date of insulin therapy initiation was confirmed through chart review using the EMR. All subjects had serum UA levels measured via enzymatic colorimetric testing (Roche, Indianapolis IN) at two time points, one prior to and one after insulin initiation.

The matched cohort of patients who did not start insulin was selected from the potentially eligible cohort of patients, all with a diagnosis of gout and diabetes. Lack of insulin use was confirmed through a review of the EMR. These patients were matched 1:1 to subjects in the insulin treatment cohort. Matching was based on gender and age at the first UA measurement (+/- 5 years). Due to concern of differing lengths of time separating UA measurements, patients were also matched according to the duration between UA measurements (+/- 180 days).

Patients who started or titrated allopurinol during the timeframe between UA measurements were excluded from analysis in both the insulin and non-insulin cohort. Patients on a stable dose of allopurinol during the study duration were permitted.

The date of the first UA measurement was the start of follow-up (index date) for both the insulin and non-insulin cohort. Follow up continued until the second UA measurement

This study was approved by the Partners Healthcare Human Subject Committee.

Covariates

Variables potentially related to UA levels were assessed from a review of the EMR. Subject demographics (age, gender) were assessed at the index date. We assessed the use of medications known to have a potential effect on UA levels, including allopurinol, hydrochlorothiazide, losartan, tacrolimus or cyclosporine; the use of these medications were assessed from the index date until the end of follow-up. The uric acid lowering medications febuxostat and pegloticase were not included in this study as they were given US Federal Drug Administration approval in 2009 and 2010 respectively. The majority of our data was collected prior to these dates; additionally, neither of these medications was noted during chart review. The use of oral hypoglycemic medications including metformin, glyburide, glipizide, and rosiglitazone was assessed at the index date. Information for other potential confounders, such as HbA1c (%), serum creatinine (mg/dl), and body mass index (BMI, kg/m²), were assessed from the EMR, using the value closest to the first measured UA. A subsequent HbA1c measurement, if available, was recorded at follow up closest to the time

of the second UA measurement. The length of time measured in days separating the two UA measurements was also considered a covariate.

Outcome

The primary outcome was the change UA level (mg/dl) for the insulin versus the matched non-insulin cohort. For the insulin cohort the first UA considered was the measurement closest to and preceding the date of insulin initiation, and the second UA measurement considered was the first UA level obtained at least 3 months after insulin initiation. For the non-insulin cohort, the first and second UA measurements were based on the length of time separating the UA measurements in the respective matched insulin user. The maximum time separating the two UA measurements was 8.3 years with a mean of 2.9 years separating UA measurements in insulin users and 2.8 years separating measurements in non-insulin users.

Statistical Analyses

Characteristics of the two cohorts were compared using means and percentages. T-test was used to compare the insulin and non-insulin group for continuous variables while a fisher exact analysis was used to binary variables. The difference between the changes in UA levels was calculated and graphically displayed. The mean (interquartile range, IQR) for the two cohorts' change in UA was compared. A p-value of < 0.05 was considered significant. Because of differences in the two cohorts, we examined the adjusted difference in UA changes using a matched linear regression model. The primary analysis considered all covariates for inclusion in the adjusted models. Only those with p-values < 0.05 were considered for the fully adjusted model. Sensitivity analyses forced in medications (allopurinol, hydrochlorothiazide, losartan, tacrolimus or cyclosporine). To examine the influence of extreme values, we excluded the subject with the largest change in uric acid in both cohorts and re-ran the primary model.

All analyses were conducted using SAS version 9.3 (Cary NC).

RESULTS

Twenty-three patients with gout and diabetes met criteria as insulin initiators, and a matched cohort of 23 non-insulin users was chosen based on the selection criteria. As shown in Table 1, HbA1c at the index date, BMI, and use of oral hypoglycemics were statistically significantly higher in the insulin users. Initial UA level, HbA1c at follow up, creatinine, length of time between UA measurements and medications usage, aside from oral hypoglycemics, did not significantly differ between the two cohorts.

Patients started on insulin had a greater increase in UA with an increase in mean UA levels from 6.41mg/dl to 7.66mg/dl (mean change 1.25 mg/dl, interquartile range, IQR: $-0.7, 2.3$) in comparison to those not starting insulin, mean increase from 6.17mg/dl to 6.23mg/dl (mean change 0.06 mg/dl, IQR: $-1.1, 0.9$ p = 0.06 comparing the two groups). Figure 1 plots the change in UA for each subject, illustrating an upward trend in UA levels for the cohort initiating insulin when compared to the non-insulin group.

We considered the covariates listed in Table 1 as potential confounders. Regression model A in Table 2 takes into account insulin use and the baseline serum UA level. We found that insulin use was associated with significant increase in the change in UA (1.29mg/dl, p value= 0.029). As baseline HbA1c and BMI differed between the insulin and non-insulin initiators, these were considered for the adjusted regression model, as was length of time separating UA measurements and creatinine. Only length of time separating UA measurements had a p-value < 0.05 and was advanced to the final adjusted model. The final linear regression (model E in Table 2) includes insulin use, baseline serum UA, and length of time separating UA measurements. The adjusted analysis continues to show a statistically significant increase in the UA levels among insulin initiators (1.25mg/dl, p value= 0.02). In sensitivity analyses that excluded the extreme values, the estimated difference in uric acid was reduced to 0.87 (p value= 0.09).

DISCUSSION

As noted above previous cross sectional and prospective studies have demonstrated increased UA levels in patients in a state of insulin resistance or pre-diabetes.(5–8) The study by Choi et al found two interesting relationships, one being the bell-shaped curve of UA when plotted against HbA1c and glucose. The second relationship was a linear increase in UA levels with increasing insulin and c-peptide levels. This suggests a complex and intricate balance of insulin, glucose and UA. Patients in a hyperinsulinemic state have increasing UA levels until they accrue high enough serum glucose levels to tip the balance in favor of UA excretion.(8) Furthermore, these findings imply that insulin has a direct effect on UA handling, separate from that of glucose. The unique consequences of hyperinsulinemia and hyperglycemia on UA levels is thought to stem from differing effects on renal UA excretion.(8) Our study sought to expand on this second observation by using a longitudinal cohort to evaluate the effects of exogenous insulin on UA levels. In our study, the subset of insulin starters did experience a significant increase in UA compared to those patients that did not start insulin; this finding remained after statistical adjustment. Our analysis suggests that pharmacologic insulin administration was associated with a 1.25mg/dl increase in UA levels.

From a mechanistic standpoint insulin has been shown to have an inverse relation with renal urate excretion (9, 10). The effect of insulin on renal excretion of UA is likely due to increased urate reabsorption via the urate-anion exchanger urate transporter-1 (URAT 1) or through the sodium-dependent anion co-transporter in the proximal tubule.(11) Thus, insulin resistance and the associated high plasma insulin levels beget hyperuricemia. Conversely, elevated UA levels may contribute to insulin resistance through a reduction in nitric oxide (NO). Insulin requires NO for glucose uptake, and UA has been shown to decrease NO bioavailability and thus potentially plays a role in insulin resistance.(12) There is clear interplay between insulin and UA levels; however, it remains debated as to whether elevations in UA precede or functions as a marker of insulin resistance. The current study, showing that UA levels increase with the initiation of insulin, when taken in concert with prior data, suggests that insulin likely contributes to elevations in UA. The mechanism for these findings may be secondary to the direct effect of exogenous insulin on uric acid

handling on the renal proximal tubule, or due to subsequent decrement in serum glucose levels and resultant decrease in uric acid excretion, or a combination of both.

This study demonstrated increases in UA levels with insulin initiation, raising the question of whether the noted UA elevation is clinically relevant. Evidence again from Choi showed that a daily serving of beer increased UA levels by 0.4mg/dl, which correlated with a second study finding that daily beer was associated with a 50% increased risk of incident gout.(13) Though an extrapolation, if an increase in UA levels of 0.4mg/dl conferred a 50% increase of gout, this suggests that an increase in UA levels of 1.25mg/dl may confer an increase in gout risk.

Limitations of the current study include its relatively small sample size and retrospective design. Due to the small number of patients identified that matched our criteria, we were concerned for over-fitting our model. We attempted parsimonious use of covariates. Yet, models D and E in the regression analysis include greater than 3 covariates and may be over-fit; we caution against over-interpretation of these models. It is important to note that the β -coefficient remains relatively constant even after adding covariates. Thus, the effect of insulin on UA levels did not significantly change with the addition of covariates. Due to limitations in the electronic record and lack of recorded BMI at each visit, we were unable to assess this covariate over time.

We matched on age, gender and length of time separating UA measurements, but there still may be residual confounding. There were variations in the length of time separating UA measurements, however the cohorts were matched based on length of time separating UA measurements with a statistically insignificant difference found between the two groups. Additionally, time was considered a covariate and included in regression analysis allowing us to determine the independent effect of insulin on UA levels. We looked at the implication of several medications that are known to influence UA levels, however, other medications may also affect UA. The addition of various medications in secondary analyses only increased the effect estimates. However, due to the small sample sizes of medication users, the p-values were not all statistically significant. A strength of this study is the longitudinal design with data collected as part of routine care without surveillance bias. Patients came from a variety of clinical practices overseen by physicians at Brigham and Women's Hospital, however, as the facility is a tertiary center patients may not be representative of the general population.

In conclusion, this study supports prior evidence that increasing serum insulin levels correlate with an increase in UA levels. Given our findings, it would be useful to follow-up with a study to determine the risk of incident gout and gout flares in patients recently started on insulin. The relatively modest UA increases we observed may have clinically significant effects on gout flares. It also raises the question about whether certain at risk patients should be prophylactically treated for hyperuricemia prior to initiating insulin.

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Figure 1.

Change in uric acid (UA) levels for individual patients over study period. Patients started on insulin had a greater increase in UA (mean change 1.25 mg/dl, interquartile range, IQR: -0.7,2.3) in comparison to those not starting insulin (mean change 0.06 mg/dl, IQR: -1.1,0.9, 1.1; p value= 0.06). UA1= first uric acid measurement. UA2= second uric acid measurement. **A**, Change in UA in each of the 23 non-insulin initiators. **B**, Change in UA in each of the 23 insulin initiators.

Table 1

Characteristics of insulin and non-insulin users

	Insulin (n=23)	Non-Insulin (n=23)	P value ^a
Characteristics	<i>Mean (IQR) or n (%)</i>		
Age, years	57 (47, 64)	57 (50, 64)	0.88
Female	12 (52.2)	12 (52.2)	0.99
Interval between UA measurement, days	1059 (208, 1771)	1017 (177, 1764)	0.89
HbA1c, % at index date	8.9 (7.5, 10.9)	6.0 (5.4, 6.5)	<0.0001
HbA1c, % at follow up date	7.2 (5.7, 7.9)	6.2 (5.8, 6.4)	0.3
Creatinine, mg/dl	1.2 (1, 1.4)	1.1 (0.9, 1.1)	0.3
BMI, kg/m ²	38.1 (32.8, 39.1)	30.3 (28.9, 33.6)	0.0006
Serum UA, mg/dl	6.4 (4.6, 8.2)	6.2 (4.8, 7.8)	0.72
Use of relevant medications			
Allopurinol	2 (8.7)	3 (13)	0.99
Hydrochlorothiazide	10 (43.5)	4 (17.4)	0.11
Losartan	1 (4.4)	0 (0)	0.99
Tacrolimus	0 (0)	1 (4.4)	0.99
Cyclosporine	1 (4.4)	2 (8.7)	0.99
Oral Hypoglycemics	19 (82.3)	2 (8.7)	<0.0001

IQR= interquartile range (25%, 75%); UA=uric acid; BMI= body mass index

^aP value: t-test for continuous variables and fisher exact test for binary variables

Table 2

Regression analysis of covariate effects on change in uric acid in insulin initiators

Model	β	95% CI	P value
A Crude Model: Insulin + UA1	1.29	0.15, 2.44	0.03
B Model A + age + Length of time between UA1 & UA2	1.25	0.16, 2.34	0.03
C Model B + HbA1c	1.47	-0.06, 3.00	0.06
D Model C + Creatinine + BMI	1.33	-0.28, 2.94	0.1
E Insulin+UA1+Length of time between UA1 & UA2	1.25	0.18, 2.33	0.02
Medication Use			
F Model D + Allopurinol	1.36	-0.12, 2.84	0.07
G Model D + Hydrochlorothiazide	1.41	-0.17, 2.99	0.08
H Model D + Losartan	1.45	-0.07, 2.96	0.06
I Model D + Tacrolimus	1.48	-0.04, 3.00	0.06
J Model D + Cyclosporine	1.61	0.03, 3.20	0.05

β = beta co-efficient, covariate effect on change in uric acid; 95% CI=95% confidence interval; HbA1c= Hemoglobin A1C; BMI= body mass index; UA1=first uric acid measurement; UA2= second uric acid measurement.