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Words of Wisdom

Re: Increased Production and Reduced Urinary Buffering of Acid in Uric Acid Stone Formers is Ameliorated by Pioglitazone

Maalouf NM, Poindexter JR, Adams-Huet B, Moe OW, Sakhaee K

Kidney Int 2019;95:1262–8

Expert's summary:
Maalouf et al administered the PPARγ agonist pioglitazone or placebo daily for 24 wk to 28 adult uric acid stone-formers. Blood and 24-h urine specimens were collected at baseline and at termination of the study. The patients consumed a highly controlled metabolic diet at the time of specimen collections. Insulin resistance, serum uric acid, and serum triglycerides significantly decreased in the pioglitazone cohort but not in the placebo group. Urine pH and ammonium excretion significantly increased in the pioglitazone group but not in the control subjects. Urinary titratable acidity, net acid excretion, and oxalate significantly decreased in the pioglitazone but not in the control group. Body weight did not change in either group over the course of the study. The mean increase in urinary pH in the pioglitazone group was 0.22 units. The authors propose that PPARγ agonists may provide a targeted therapeutic approach for patients with uric acid stones in the future.

Expert's comments:
Uric acid stones comprise approximately 8% of stones sent for analysis [1]. Uric acid stones develop in a low-pH urine environment, where uric acid exists in an undissociated and nonionized form that results in the propagation of urate crystals and stone formation. Uric acid stones are associated with number of medical comorbidities including gout, diabetes, obesity, metabolic syndrome, and bowel disease. This research group has provided great insights into the pathophysiology of uric acid stones and has reported that uric acid stone-formers in addition to low urinary pH have lower ammonium excretion, a blunted ammonium response to an acid load, and higher net acid excretion and titratable acidity [2]. The mechanism underlying higher acid production is unknown [3]. Ammonia is produced in renal proximal tubular cells and normally serves as a buffer for H^+. A lack of available ammonia results in the involvement of other buffers including urate, which fosters the generation of uric acid crystals. The buffering capacity is overcome by the excess acid produced, which lowers urinary pH. This group demonstrated similar metabolic responses in the Zucker rat, a model for metabolic syndrome [4]. They showed that there was diminished expression and activity of Na^+H^+ exchanger 3 (NHE3), which normally drives the transport of H^+ from proximal tubular cells into the lumen of this nephron segment, where it is trapped by ammonia via the formation of ammonium. NHE3 activity is stimulated by insulin. Administration of another PPARγ agonist, rosiglitazone, resulted in higher NHE3 activity, reductions in net acid excretion and titratable acidity, and an increase in urinary ammonium and pH. The responses in this animal model and in patients receiving the drug in this clinical trial are most likely due to reversal of insulin resistance, a known action of PPARγ agonists. This trial was more of a proof-of-concept study as the increase in urine pH was modest and thus the patients would still be required to take alkalizing agents such as potassium citrate, sodium bicarbonate, or sodium citrate to achieve the target urinary pH of 6.5–7.0 for uric acid stone prevention or dissolution [5]. Furthermore, use of pioglitazone, which is associated with bladder cancer risk, would not be embraced by urologists. However, administration of other drugs or measures to reduce insulin resistance in this patient cohort such as weight loss may play a future role in their management.

Conflicts of interest: The author has nothing to disclose.

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Re: Comparison of Population-based Observational Studies with Randomized Trials in Oncology

Soni PD, Hartman HE, Dess RT, et al

J Clin Oncol 2019;37:1209–16

Experts' summary:
In a recent issue of the *Journal of Clinical Oncology*, Soni and colleagues [1] published an interesting analysis comparing the results of population-based observational studies and randomized trials in oncology. The authors identified 350 observational cancer treatment comparisons and matched these to 121 corresponding randomized trials. They found that while 62% of the hazard ratios derived in observational studies fell within the 95% confidence interval of the corresponding randomized trial, there was no significant correlation between the hazard ratio estimates of observational studies and randomized trials.

Experts' comments:
The results of this analysis differ from most previous attempts to examine differences in outcomes between observational studies and randomized trials. Summarizing previous analyses on this methodologic topic, a recent Cochrane review concluded "there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions" [2].

We must therefore ask what differs between this analysis and previous ones. Have more recent observational studies in oncology become less rigorous than observational studies in other fields from decades past? While possible, it seems less likely that this analysis simply demonstrates the well-recognized efficacy-effectiveness gap [3]. Many authors, including the senior author of the paper by Soni et al [4], recognize that there are massive disparities in randomized trials in oncology. This means that patients eligible for the trial significantly differ from the population of patients that they are purported to represent on the basis of age, race, socioeconomic status, and comorbidity. One of the most relevant in oncology trials may be the exclusion of patients with any prior malignancy; according to data from the US National Cancer Institute, approximately one in six patients diagnosed with cancer each year have previously been diagnosed with a different cancer. In the context of non–small-cell lung cancer, Al-Baimani et al [5] demonstrated that 78% of patients treated at their center would be deemed ineligible for a trial. However, 46% of these patients received such systemic therapy. As a result, even when assessing the same question, the population included in observational studies and randomized trials in oncology probably differ. Among 283 randomized trials, the vast majority (83%) had at least one poorly justified exclusion criterion and 37% of all exclusion criteria were poorly justified [6]. These exclusions are even more common in industry-sponsored trials.

Thus, while randomized controlled trials have the greatest internal validity of any study design, their lack of external validity may explain differences between conclusions from observational studies and randomized studies in oncology. To allow for more informative extrapolation of trial results to patients treated in everyday urology and oncology practice, clinical trialists should limit exclusion criteria such that the trial population reflects the general population of patients with the disease.

Conflicts of interest: The authors have nothing to disclose.

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