Objectives: This study aimed to evaluate the association of serum vitamin A, vitamin E and folate level with hyperuricemia in the Korean general population.

Methods: The present study included 6023 participants (2722 men and 3301 women) aged ≥ 19 years with available data on serum vitamin A, vitamin E, folate and serum uric acid. General characteristics of participants were compared using the Chi-square test and Student's t test. The association between serum vitamin A, E and folate and serum uric acid levels were evaluated using general linear regression model. Multivariate logistic regression analyses were performed to estimate the effects of these micronutrients on hyperuricemia.

Results: Serum uric acid levels were increased from the lowest quintile of vitamin A levels to the highest quintile after adjustment for covariates ($P_{\text{trend}} < 0.001$ in both sexes). In addition, dose-dependent relationship was observed between vitamin A levels and the risk of hyperuricemia in fully-adjusted analyses ($P_{\text{trend}} < 0.001$ in both sexes). However, neither serum vitamin E nor serum folate was associated with hyperuricemia across analyses models.

Conclusion: This study suggested that vitamin A could be a risk factor of hyperuricemia and further studies are warranted to elucidate underlying mechanism of the observed findings.

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THU0430 RENAL URATE DEPOSITION: SUMMARY OF PUBLISHED EVIDENCE

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Background: Gout is the most common inflammatory arthropathy in U.S. adults. Although the severity of this debilitating disease is often defined by the presence of tophi in the joints, systemic deposition of urate in major organ systems including the renal parenchyma is not as well established. Urate is primarily cleared through the kidneys and patients with gout often have concomitant renal disease along with other comorbidities such as diabetes, coronary artery disease, and hypertension; however, a causal role between these entities has not yet been carefully established. We hypothesize that urate deposits serve as a trigger in the inflammatory nidus to propagate subclinical tissue damage that results in the chronicity of the disease. This could potentially explain its independent role in the development and progression of chronic kidney disease in gout patients.

Objectives: To review the published literature for evidence of urate deposition in the renal parenchyma in patients with gout and summarize the histopathology and imaging findings.

Methods: PubMed (from 1940 to 2020) was used to identify reports of autopsy, pathology and radiology imaging demonstrating urate deposition within the native renal parenchyma in patients with gout. Key words included: gout nephropathy, chronic urate nephropathy, renal tophi, gouty kidney, autopsy findings in gout, and renal imaging in gout. The reference lists from these publications were also used to identify additional articles. Literature referencing urate nephrolithiasis and renal transplants were excluded from the study.

Results: There were 25 articles documenting renal parenchymal urate deposition in gout patients confirmed by autopsy, biopsy and/or radiology imaging in native kidneys. Among the 19 articles examining urate deposition by autopsy and/or biopsy, 100% found urate deposition in the collecting ducts and adjacent medullary interstitium. Based on these findings, the most commonly proposed mechanism for urate deposition is urate crystal precipitation in the collecting ducts with eventual desquamation of the collecting duct walls from inflammation and/or tubular obstruction with subsequent extrusion of crystals into the medullary interstitium. 89% of reports documented inflammatory cells and/or tubulointerstitial fibrosis adjacent to the renal urate deposits. 68% reported cortical thinning or scarring. In addition, 74% of included publications reported renal vascular pathology including arteriosclerosis, glomerulosclerosis and nephrosclerosis. There were 6 imaging articles that all reported abnormal renal ultrasound findings with hyperechogenic renal medullas that were attributed to urate deposition.

Conclusion: There is a growing body of literature documenting urate deposition in the renal parenchyma in gout patients based on autopsy, pathology and imaging findings. Inflammation and fibrosis adjacent to regions of urate deposition and vascular changes were common. Given the strong association of gout with renal disease, there is a critical need to elucidate the mechanism by which urate impairs the renal tissue. Thus dedicated investigation is key to determine the prevalence and clinical significance of urate deposition in the kidneys of gout patients.

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THU0431 PEGLOTICASE RESPONSE RATE IN UNCONTROLLED GOUT PATIENTS CO-TREATED WITH METHOTREXATE: EXPERIENCE IN A COMMUNITY RHEUMATOLOGY PRACTICE

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Background: Pegloticase is an infused biologic approved to treat uncontrolled gout. The drug is highly effective, but patients can develop anti-drug antibodies that interfere with efficacy.¹ Randomized clinical trials have shown that 42% of patients treated with bi-weekly pegloticase had a serum uric acid (sUA) below 6.0mg/dl at 3 and 6 months.² Mild-to-moderate immunomodulation has been shown to lower the prevalence of anti-drug antibody formation in patients with other autoimmune diseases (rheumatoid arthritis, Crohn's disease, juvenile idiopathic arthritis).³ Cases published in the literature suggest that low-to-moderate doses of methotrexate^{4,5} or azathioprine⁶ may also attenuate anti-pegloticase antibody formation in uncontrolled gout patients. Therefore, immunomodulation may allow patients to remain on pegloticase therapy longer and achieve a more complete therapeutic response.

Objectives: To examine pegloticase treatment response in patients co-treated with methotrexate.

Methods: This retrospective chart review included patients from a single community rheumatology practice who began pegloticase (8mg every 2 weeks) therapy between January 2017 and September 2019 and were co-treated with methotrexate. Unless contraindicated, methotrexate co-treatment with pegloticase is now standard in this practice and all patients undergo close monitoring of laboratory parameters including serum uric acid level (sUA), blood counts, and liver function tests (LFTs). To maximize the number of cases, patients administered methotrexate in any form were included. Collected data included demographic information, laboratory values, methotrexate treatment parameters (timing with respect to pegloticase therapy, dose, route), pegloticase response parameters (number of infusions, duration of therapy), and adverse events. Main outcome measures included the number of pegloticase infusions administered (responder defined as ≥ 12 infusions administered) and therapy duration.

Results: Ten patients (9 male) were included. All patients had visible tophi and average patient age was 52.3 ± 13.5 years. Nine patients began subcutaneous methotrexate (25mg weekly) an average of 19.9 ± 7.0 days (range: 14 to 35 days) before the first pegloticase infusion. The remaining patient began oral methotrexate (12.5mg weekly) 14 days after the first pegloticase infusion. Eight of 10 patients (80%) were considered responders, receiving an average of 15.5 ± 3.8 pegloticase infusions (range: 12-21 infusions) over 31.8 ± 9.5 weeks (range: 22.1 to 48.3 weeks). In these 8 responders, mean sUA was 0.2 ± 0.0 mg/dL immediately prior to the last pegloticase infusion. All 10 patients had an initial, rapid decrease in sUA, but two patients discontinued treatment before infusion 12. One patient had increased sUA with a mild infusion reaction, and one patient was lost to follow-up after infusion 5. No new safety concerns emerged. A gout flare occurred in 1 patient and was treated with prednisone. LFT and blood cell parameters were stable over the study period, except in two patients. One had a mild, transient LFT elevation that resolved without treatment, one had an LFT elevation and pancytopenia that improved with methotrexate discontinuation and transfusion, respectively. This patient remained on pegloticase and continued as a responder.

Conclusion: This case series suggests that methotrexate, when used as a co-therapy with pegloticase, allows more patients to complete therapy and to achieve the full therapeutic response. No new safety concerns emerged.

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THU0433 TREATMENT WITH PEGLOTICASE IMPROVES HEPATIC FIBROSIS ESTIMATED BY FIBROSIS-4 INDEX IN SUBJECTS WITH CHRONIC REFRACTORY GOUT

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Background: Hyperuricemia is associated with non-alcoholic fatty liver disease (NAFLD)^{1,2}, but the relationship to fibrosis remains uncertain³. Moreover, it is not known whether lowering serum urate will affect the course of NAFLD. The availability of data from two randomized trials of pegloticase, a pegylated recombinant mammalian uricase, that profoundly decreases serum urate afforded the opportunity to test the hypothesis that lowering urate might improve NAFLD.

Objectives: To determine whether treatment of chronic refractory gout patients with pegloticase was associated with improvement in NAFLD determined by Fibrosis 4 index (Fib4).

Methods: Databases from patients with chronic refractory gout who participated in two randomized 6 month clinical trials (RCTs) of pegloticase were analyzed⁴. Sub-sets who had persistent urate lowering to levels <1 mg/dL in response to biweekly pegloticase (Responders, n=36) were compared to those who received placebo (n=43). Since liver biopsy information was not available on these subjects, we relied on Fib4, a validated non-invasive estimate of liver fibrosis in a variety of liver diseases^{5,6} calculated from measurements of AST, ALT, platelet count and age (Age x AST/platelets x ALT). A Fib4 value of 1.3 is an indication that further evaluation of liver disease is warranted.

Results: At baseline, the mean Fib4 values were 1.40 ± 0.86 in pegloticase responders and 1.04 ± 0.53 in subjects receiving placebo. As shown in figure 1, subjects receiving placebo exhibited a change of 0.26 ± 0.41 in the Fib4 score over the six months of the RCTs compared with 0.13 ± 0.62 in the pegloticase responders (p=0.048; by linear regression). When only the subjects with a Fib4 value > 1.3 were considered, a significant difference in the change in the Fib4 values over the 6 months of the trial between pegloticase responders and those receiving placebo was also observed (-0.15 ± 0.67 vs 0.37 ± 0.42 , p=0.004, by linear regression). The correlations between serum urate area under the curve (AUC) over the 6 months of the trial and the change in Fib4 value was $r_s = 0.33$, p=0.0004 (Spearman rank-order correlation coefficient). Finally, multiple linear regression analysis indicated serum urate AUC (as a surrogate measure for group) is the main contributor to the change in Fib4 (p=0.018 by linear regression).

Figure 1. Impact of Pegloticase Therapy on NAFLD Estimated by Fibrosis-4 Index

Conclusion: The data are consistent with the conclusion that persistent lowering of serum urate had a significant impact on Fib4 levels, implying a possible effect on the course of NAFLD. The results support a more complete analysis involving biopsy examination of the impact of urate on liver inflammation and fibrosis.

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THU0434 LEFLUNOMIDE CO-THERAPY WITH PEGLOTICASE IN UNCONTROLLED GOUT

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Background: Pegloticase is a PEGylated biologic for uncontrolled gout that has well-established efficacy. However, anti-drug antibody (ADA) development causes many patients to discontinue treatment before receiving the full therapeutic course.¹ ADAs bind to the pegloticase molecule, leading to reduced therapeutic efficacy and discontinuation of therapy.² Emerging data indicates that co-treatment with pegloticase and immunomodulating agents may prevent ADA development, allowing more patients to receive a full course of treatment. Prior case reports describe the results of pegloticase treatment with methotrexate, azathioprine or cyclosporine³⁻⁶; however, the literature does not contain information on the use of leflunomide with pegloticase.

Objectives: To evaluate overall pegloticase responder rate in uncontrolled gout patients co-treated with leflunomide.

Methods: This retrospective study was conducted in a rheumatology practice where an immunomodulatory agent is typically used in conjunction with pegloticase. Patients co-treated with oral leflunomide (20 mg/day) and pegloticase (8 mg/infusion) were included. Extracted data included demographics, gout characteristics, pegloticase therapy parameters (serum uric acid [sUA], number of infusions), leflunomide therapy parameters (timing with respect to the first pegloticase infusion, dose, route), adverse events (e.g., gout flare, infusion reactions), and safety information (clinical laboratory parameters). Prior to each infusion all patients were administered a standard prophylaxis regimen of fexofenadine the night before and day of infusion, solumedrol day of infusion. The primary outcome was the proportion of pegloticase responders, defined as those receiving ≥ 12 infusions.

Results: At data collection, 10 patients (5 male, 72.7 ± 12.5 years old, baseline sUA = 6.59 ± 3.15 mg/dL) had been co-treated with pegloticase and leflunomide. 4 patients (40%) received ≥ 12 infusions of pegloticase; 2 patients began treatment but were lost to follow-up, though neither of these patients experienced a rise in sUA during therapy. Of the 6 patients described, 4 met the primary outcome for a responder and 2 were lost to follow-up, resulting in 4/6 or 66% response rate. The 4 remaining patients had not reached their 12th infusion at time of data cutoff and were ongoing with a mean of 8.0 ± 1.6 infusions (range: 6-10 infusions). No new safety concerns emerged. One patient had 3 gout flares during treatment and 1 patient required emergency care because of loss of consciousness and wooziness prior to pegloticase infusion due to pre-medication with solumedrol. No clinically meaningful laboratory value changes occurred, with the exception of a mild and transient ALT rise in 1 patient.

Conclusion: Preliminary evidence suggests that low-to-moderate immunomodulation can minimize or prevent ADA formation against pegloticase and increase the number of patients fully benefitting from pegloticase. No prior studies have examined the effect of leflunomide on pegloticase responder rates. The current study indicates that oral leflunomide may be a viable immunomodulator for patients with uncontrolled gout undergoing pegloticase therapy.

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THU0435 CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) CRYSTALS BUT NOT BASIC CALCIUM PHOSPHATE (BCP) CRYSTALS INDUCE SYNDECAN-4 EXPRESSION IN CARTILAGE

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