OP0165

JAK3-STAT5 SIGNALING PATHWAY IS INVOLVED IN THE PATHOGENESIS OF GOUTY INFLAMMATION

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Background: Studies have confirmed that JAKs-STATs signaling pathway is involved in the pathogenesis of a variety of autoinflammatory diseases, and has been transformed into the treatment of rheumatic diseases. So far, the research of JAKs-STATs in the mechanism of gout is very limited.
Objectives: To determine whether JAKs-STATs pathway is involved in the pathogenesis of gouty inflammation.
Methods: 1.The transcription and protein phosphorylation levels of 4 JAKs (JAK1, JAK2, JAK3 and Tyk2) and 7 STATs (STAT1, stat2, STAT3, STAT4, STAT5a/5b and STAT6) in PBMCs of 100 gout patients (concluding acute gout (AG) and intermittent gout (IG) patients 50 cases, respectively) and 50 healthy subjects (HC) were measured; 2.To detect the changes of JAK3-STAT5 signal pathway in synovium of rat ankle model of gouty inflammation;3.To explore the changes of JAK3-STAT5 signal pathway in synovium of gouty inflammation model after colchicine treatment.
Results: 1.The phosphorylation levels of JAK3 and STAT5 in PBMCs,the plasma IL-2 level in the AG group were all significantly higher than those in the HC group (P<0.05, respectively; Figure 1G,H), while there were no differences with respect to the other JAKs and STATs molecules between the two groups (P>0.05, respectively); 2.JAK3 and STAT5 phosphorylation levels in synovial tissue of rat ankle, cytokine IL-1β and IL-2 productions in synovial fluid of rat ankle from gout model were all significantly increased (P<0.05, respectively;Figure 1A-F);3.Phosphorylation levels of JAK3 and STAT5,IL-1β and IL-2 levels were significantly reduced after colchicine treatment (P<0.05, respectively;Figure 1A-F)

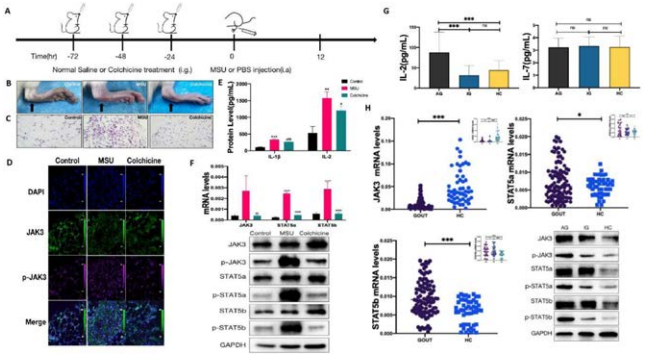

Figure 1. JAK3-STAT5 participates in the pathogenesis of gouty inflammation. In vivo experimental protocol (A-F): A. Male Wistar rats were used. The model Colchicine group was intragastrically administered with 0.104 mg/kg/d colchicine solution, and the Control group was intragastrically administered with the same amount of saline. After 3 days of continuous intragastric administration, the right ankle joint was injected with MSU (8 mg/100μl) or PBS (100 μl) to establish a gout arthritis model(MSU group) or Control group. B. Representative photographs of ankles 12 hr after MSU or PBS injection. C. Representative microscopic photos of ankle tissue sections from Control, MSU and Colchicine groups. D. Representative confocal laser scanning images showed JAK3 protein and its phosphorylated protein staining in ankle tissues in the three groups. Areas staining positive for JAK3 protein are shown in green. Regions staining positive for p-JAK3 protein are shown in red. E. IL-1β and IL-2 production in ankle flushing was detected by ELISA.*P <.05,**P<.01,***P<.001, significantly different from Control group; #P<.05,##P<.01, ###P< .001,significantly different from MSU group. F. At 12 h after MSU injection, JAK3 and STAT5 mRNA, protein in ankle tissues were determined by qRT-PCR and Western blotting, respectively. The panel displays the representative images of JAK3, STAT5, p-JAK3, p-STAT5a and GAPDH protein expression from the three groups.*P <.05,**P<.01,***P<.001, significantly different from Control group; #P<.05,##P<.01, ###P< .001, significantly different from MSU group. G.IL-2 and IL-7 levels in plasma of acute gout(AG), intermittent gout(IG) patients and healthy individuals (HC) were detected using ELISA. *P<.05, **P<.01, ***P < .001. H. JAK3 and STAT5 mRNA, protein levels in PBMCs of AG, IG, and HC groups were measured by qRT-PCR and Western blotting, respectively. *P<.05, **P<.01, ***P < .001.

Conclusion: IL-2-JAK3-STAT5 signaling pathway is involved in the regulation of gouty inflammation. Colchicine could treat gouty inflammation through inhibiting IL-2-JAK3-STAT5 pathway; JAK3 is expected to be a therapeutic target for acute gouty inflammation.
Disclosure of Interests: None declared
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OP0166

CHRONIC KIDNEY DISEASE AND AMPLIFICATION OF SERUM URATE IMPACT ON GOUT RISK: POPULATION-BASED STUDY OF > 450,000 UK BIOBANK PARTICIPANTS

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Background: Serum urate (SU) is a necessary causal factor for development of gout, while chronic kidney disease (CKD) is associated with increased inflammatory biomarkers, cytokines, and reduced AMPK activity levels. Furthermore, CKD has been found to be associated with an increased risk of incident gout, even beyond (i.e., independent of) SU levels. As such, the impact of SU may be enhanced by presence of CKD, but this hypothesis has not been evaluated.
Objectives: To prospectively examine whether CKD modifies the relation between SU levels and risk of incident gout.
Methods: We conducted a prospective cohort analysis of UK Biobank participants with urate and creatinine levels available from baseline blood samples (2006-2010), and no prior diagnosis of gout or urate lowering therapy use. CKD Stage ≥ 3 status (eGFR <60 mL/min) was determined from latest CKD-Epi equations (*NEJM* 2021; *JASN* 2021).[1,2] Incident cases of gout were ascertained from linked hospitalisation, primary care, and death records. Participants were

Table 1. Cumulative incidence and hazard ratio (HR) of incident gout according to baseline serum urate levels and CKD status

CKD Stage ≥ 3								**Hyperuricemia (Dichotomous)**	
Serum urate, mg/dL	**<5**	**5.0 to < 6.0**	**6.0 to < 7.0**	**7.0 to < 8.0**	**8.0 to < 9.0**	**9.0 to < 10.0**	**≥10**	**<7.0**	**≥7.0**
N cases	6	15	28	95	150	104	87	49	436
10-Year Cumulative Incidence	0.6%	1.1%	1.7%	7.6%	19.1%	28.0%	42.0%	1.2%	16.6%
Incidence Rate Ratio	1.0 (Ref)	1.7	2.7	12.3	33.8	56.1	107.7	1.0 (Ref)	15.2
No CKD									
Serum urate, mg/dL	**<5**	**5.0 to < 6.0**	**6.0 to < 7.0**	**7.0 to < 8.0**	**8.0 to < 9.0**	**9.0 to < 10.0**	**≥10**	**<7.0**	**≥7.0**
N cases	393	446	1056	1769	1251	363	84	1,895	3,467
10-Year Cumulative Incidence,	0.2%	0.4%	1.4%	6.0%	15.6%	23.5%	27.5%	0.5%	8.8%
Incidence Rate Ratio	1.0 (Ref)	2.1	8.0	34.6	96.9	155.9	198.8	1.0 (Ref)	20.2
Joint Effect of Serum Urate and CKD									
Serum urate, mg/dL	**<5**	**5.0 to < 6.0**	**6.0 to < 7.0**	**7.0 to < 8.0**	**8.0 to < 9.0**	**9.0 to < 10.0**	**≥10**	**<7.0**	**≥7.0**
Age-, Sex-, and Race- Adjusted HR									
No CKD	1.0 (Ref)	1.9	7.0	29.8	83.0	133.3	170.3	1.0 (Ref)	15.7
CKD	3.2	5.1	7.8	34.1	93.3	155.9	302.3	2.5	30.5
Fully adjusted HR*									
No CKD	1.0 (Ref)	1.8	6.4	25.8	69.4	108.7	132.9	1.0 (Ref)	12.5
CKD	3.1	4.7	6.8	28.9	75.2	121.1	241.8	2.3	22.4

*Adjusted for age, sex, race, body mass index, hypertension, diuretic use, smoking, and consumption of alcohol, coffee, meat, fish, poultry, and milk.

followed from baseline up to 10 years or until gout diagnosis, death, or end of study period (Dec 31/19).
We calculated 10-year cumulative incidence of gout according to baseline SU category and CKD status and evaluated their individual and joint impact on gout risk using multivariable Cox proportional hazards models.
We further assessed for additive and multiplicative interactions[3] between levels of SU and inverted eGFR, on a standardized continuous scale per SD.
Results: We included 458,244 individuals (45% male, mean age 56.5 years), of whom 6,559 had CKD at baseline, and documented 5,847 cases of incident gout over 4,442,866 person-years.
10-year cumulative incidence of gout ranged from 0.2% (baseline SU < 5 mg/dL) to 33% (baseline SU ≥ 10 mg/dL), and in each category incidence was higher for those with CKD than without (Table 1; Figure 1**-left**), Multivariable hazard ratio (HR) for the joint effect of CKD and highest SU level (≥ 10 mg/dL), compared to non-CKD and lowest SU (<5mg/dL), was 242 (95% CI: 189 to 309) (Figure 1**-right**).
There was a significant additive interaction between continuous SU and eGFR (relative excess risk due to interaction=0.16 [0.09 to 0.24], p < 0.001), with HRs of 3.7 (3.6 to 3.8) per SD increase of SU, 1.2 (1.2 to 1.3) per SD increase of inverted eGFR, and 4.1 (3.9 to 4.2) for their joint effect. Their multiplicative interaction was also significant (p < 0.001).
Conclusion: These large prospective cohort data suggest CKD presence enhances the effect of elevated SU levels on risk of incident gout. They support roles of CKD-associated factors beyond SU in developing gout, such as reduced AMPK activity levels and altered inflammatory factors in CKD, which warrant further investigation.
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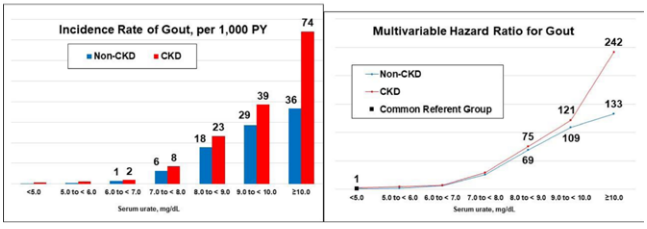
[3] *ARD* (2021) PMID 34857519

Figure: 10-year incidence rate (left) and multivariable hazard ratio (right) for incident gout, according to serum urate level and CKD status.



Disclosure of Interests: Natalie McCormick: None declared, Leo Lu: None declared, Chio Yokose: None declared, Amit Joshi: None declared, Yuqing Zhang: None declared, Hyon Choi Consultant of: Ironwood, Selecta, Horizon, Takeda, Kowa, and Vaxart., Grant/research support from: Ironwood and Horizon
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OP0167 ULTRASONOGRAPHY IN THE PREDICTION OF GOUT FLARES: A 12-MONTH PROSPECTIVE OBSERVATIONAL STUDY

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Background: Gout flares are a distinctive feature of gout. Although imaging techniques, such as ultrasonography (US), can visualise monosodium urate (MSU) crystals and synovial inflammation and estimate their burden, the role of imaging in predicting gout flares has not been fully investigated.
Objectives: To evaluate whether US findings indicative of MSU deposits and subclinical inflammation predict gout flares over 12 months.
Methods: Participants with gout on urate-lowering therapy (ULT) for at least the preceding six months were enrolled consecutively in this 12-month prospective, observational, single-centre study.
A nested case-control analysis was performed. Cases were participants with at least one gout flare in the follow-up period while controls did not self-report any gout flares. Clinical assessment was scheduled at 6-month intervals. In addition, at baseline, each patient underwent an US examination using a standardised scanning protocol including the following sites: knees, ankles, 1st metatarsophalangeal joints, elbows, wrists and 2nd metacarpophalangeal joints. The US findings indicating MSU deposits [i.e., aggregates, double contour (DC) sign and tophi] and inflammation [i.e., Power Doppler (PD) signal] were identified according to the 2015 Outcome Measure in Rheumatology definitions (Figure 1).

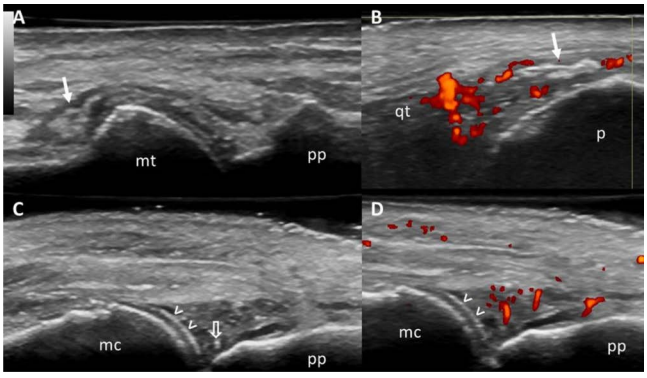

Figure 1.

Summated scores were calculated for each US finding.
During follow-up visits, patients were asked to report any gout flares using an internationally-validated definition [1].
Multivariate logistic regression analysis was used to measure the association between baseline US findings and the occurrence of gout flares over 12 months. US scores were tested separately, including the following covariates: age, gender, disease duration, presence of subcutaneous tophi, current serum urate>360 µmol/l, increasing dose of ULT during the study period and ongoing flare prophylaxis. In addition, multivariate zero-inflated Poisson regression analysis was used to investigate the association between US findings and the number of flares over 12 months.
Results: Eighty-one gout participants were enrolled, and 71 completed the study. Thirty (42.3%) of 71 participants experienced at least one flare over 12 months, with a median of 2.0 flares. There was no difference among baseline clinical and laboratory characteristics of patients with and without flares except for the presence of subcutaneous tophi (23.3% vs 4.9%; p=0.02) and higher current SU levels (360.8 vs 301.4 µmol/l mol/L, p=0.01).
Participants with flares had a greater baseline US burden of MSU deposits (2.0±1.8 vs 0.5±0.9, p=0.01 for DC sign; 2.1±2.3 vs 0.8±1.0, p=0.01 for tophi; 2.6±2.0 vs 1.6±1.6, p=0.03 for aggregates) and of subclinical inflammation (3.73±3.53 vs 0.82±1.44, p<0.01).
The baseline extent of MSU deposits and subclinical inflammation estimated by US was significantly associated with gout flares over 12 months in multivariate logistic regression analyses. DC sign score (aOR: 2.20, 95%CI: 1.22-4.34; p=0.01), tophi score (aOR: 2.16, 95%CI: 1.12-4.18; p=0.02) and PD score (aOR: 1.63, 95%CI: 1.12-2.40; p=0.01) predicted gout flares, whereas aggregates score (aOR: 1.40, 95%CI: 0.94-2.10; p=0.10) did not reach the statistical significance. Similar results were obtained in multivariate Poisson regression models (aIRR for DC score: 1.39, 95%CI: 1.18-1.64, p<0.01, aIRR for tophi score: 1.30, 95%CI: 1.17-1.45, p<0.01, aIRR for PD score: 1.29, 95%CI: 1.19-1.40, p<0.01, aIRR for aggregates score: 1.13, 95%CI: 1.00-1.29, p=0.05).
Conclusion: Baseline US findings indicating MSU deposits and subclinical inflammation are independent predictors of gout flares over 12 months.
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OP0168 DEVELOPMENT OF AN ULTRASOUND SCORING SYSTEM FOR CPPD EXTENT: RESULTS FROM A DELPHI PROCESS AND WEB-RELIABILITY EXERCISE BY THE OMERACT US WORKING GROUP

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