REVIEW

Comparison Between Early-Onset and Common Gout: A Systematic Literature Review

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ABSTRACT

Introduction: Gout is an inflammatory, metabolic disease associated with a high comorbidity burden including cardiovascular disease, hypertension, type 2 diabetes, hyperlipidemia, renal disease, and metabolic syndrome. Approximately 9.2 million Americans have gout, making prognosis and treatment outcome predictors highly important. About 600,000 Americans have early-onset gout (EOG), generally defined as first gout attack at ≤ 40 years of age. However, data on EOG clinical features, comorbidity profile, and treatment response are sparse; this systematic literature review provides insight.

Methods: PubMed and American College of Rheumatology (ACR)/European Alliance of the Associations for Rheumatology (EULAR) abstract archives were searched for early-onset gout, "early onset gout," and ("gout" AND "age of onset"). Duplicate, foreign language, single case report, older (before 2016), and irrelevant/data insufficient publications were excluded. The age of diagnosis categorized patients as having common gout (CG, generally > 40 years) or EOG (generally ≤ 40 years). Applicable publications were extensively reviewed/discussed among authors for inclusion/exclusion consensus.

Results: A total of 283 publications were identified, with 46 (35 articles, 10 abstracts) reviewed and 17 (12 articles, 5 abstracts) ultimately included. Eleven reported clinical characteristics, with 6 EOG-CG retrospective/cross-sectional comparisons. Gout diagnosis preceded cardiometabolic comorbidity and renal comorbidities were less prevalent in EOG than CG patients. EOG patients had more severe disease (more gout flares, polyarticular disease), higher pre-therapy serum urate (SU), and worse oral urate-lowering therapy response. Genetics-focused publications reported higher incidences of dysfunctional urate transporter mutations in EOG patients.

Conclusions: This review suggests that EOG is more recalcitrant to urate-lowering therapy, is associated with urate transporter defects, and carries heavy disease burden. Therefore, early rheumatology referral and urate-lowering in a treat-to-target fashion may benefit EOG patients. Interestingly, EOG patients had fewer cardiometabolic comorbidities at diagnosis than CG patients, presenting a potential "window of opportunity" to attenuate cardiometabolic comorbidity development with SU control. Preventing gout-related suffering

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and health burden is particularly important in these young EOG patients who will live with gout and its sequelae for decades.

PLAIN LANGUAGE SUMMARY

Gout, an inflammatory arthritis caused by high urate levels in the blood (SU), is associated with medical issues, including heart disease, high blood pressure, type 2 diabetes, and kidney disease. Millions of Americans have gout, with some having early-onset gout (EOG), generally the first gout attack at or before 40 years of age. Little information on EOG has been published; this literature review provides insight. More recent articles and major rheumatology meeting presentations (2016 to August 2022) on EOG were reviewed. Publications that were duplicates, not in English, on a single patient, or were not relevant/did contain enough information were excluded. The age at gout diagnosis determined if patients had common gout (CG) or EOG. Of the 283 publications identified, 17 were included in this review. Gout-associated medical issues (heart, metabolic, and kidney-related) were less common in EOG than CG patients and occurred after gout diagnosis in EOG patients. Compared to CG patients, EOG patients more often had severe gout (more gout attacks and affected joints), higher SU, and worse response to oral SU-lowering medications. Genetics-focused publications showed that mutations affecting how urate is removed from the body are more common in EOG patients. Overall, the literature suggests that EOG may be difficult to treat, has a genetic component, and has a heavy disease burden. Therefore, early rheumatology referral and gout management may benefit EOG patients due to a potential "window of opportunity" where proper SU control may prevent gout-related suffering and health burden in young EOG patients who will live with gout and its consequences for decades.

Key Summary Points

Why carry out this study?

About 600,000 Americans have early-onset gout (EOG, generally the first gout attack at ≤ 40 years of age), but data on its clinical features, comorbidity profile, and treatment response are sparse.

This systematic literature review was performed to examine EOG literature as a whole and provide some insight on these young patients who will live with gout for decades.

What was learned from this study?

A gout diagnosis frequently preceded the onset of cardiometabolic and renal comorbidities in EOG patients and these comorbidities were less prevalent at diagnosis than in their older common gout counterparts.

EOG patients had more severe gout (more gout flares, polyarticular disease), higher pre-therapy serum urate, worse oral urate-lowering therapy response, and higher incidence of urate transporter genetic mutations than common gout patients.

Early rheumatology referral and gout management may benefit EOG patients due to a potential "window of opportunity" where proper SU control may prevent gout-related suffering and health burden in young EOG patients who will live with gout and its consequences for decades.

INTRODUCTION

Gout is the most common inflammatory arthritis in adults, affecting approximately 9.2 million adults in the United States [1] (prevalence of 3.9%) and 41.2 million adults worldwide [2]. The risk of gout increases with age [3], but an estimated 600,000–700,000 patients in the United States develop early-onset gout (EOG), generally thought of as first gout attack before the age of 40 years [1, 4]. Although the 2020 American College of Rheumatology (ACR) gout management guidelines [5] do not specifically make recommendations for managing EOG, both the European Alliance of Associations for Rheumatology (EULAR) [6] and British Society of Rheumatology [7] guidelines recommend rapid initiation of urate lowering therapy (ULT) in patients diagnosed with gout before the age of 40 years.

There is a clear relationship between gout and metabolic syndrome [8, 9], defined by the World Health Organization as the presence of insulin resistance (impaired glucose tolerance, impaired fasting glucose, or type 2 diabetes) with ≥ 2 of the following: obesity, dyslipidemia, hypertension, and microalbuminuria [10]. The prevalences of individual metabolic syndrome components have also been associated with gout and/or hyperuricemia, including hypertension [9, 11–15], insulin resistance/diabetes [15–19], obesity [9, 19, 20], and dyslipidemia [9, 21]. The high prevalence of metabolic syndrome and its components likely contribute to the higher risk of cardiovascular disease [15, 19, 22], events [19, 23–25], and mortality [26–30] in gout patients. Further, chronic inflammation secondary to monosodium urate (MSU) crystal deposition has been shown to increase cardiovascular risk [31–35]. Gout patients also have a higher risk of developing renal insufficiency and end-stage renal disease than their non-gout counterparts [12, 15, 36–40], particularly those with crystalluria [41].

Unfortunately, there is a paucity of data related to the clinical features, comorbidity profile, and treatment response of patients with EOG. Given that EOG patients will live with this progressive, painful, inflammatory arthritis for decades, and the gout-imposed risk of renal [19, 38, 42], cardiovascular [19, 23, 26, 43, 44], and cerebrovascular [19, 25] disease, EOG could have a major and lasting impact on long-term patient health. Further, compared to non-gouty populations, gout patients have decreased quality of life [45, 46], increased disability [2, 47], and higher rates of all-cause death [26, 28]. This systematic literature review was conducted to better understand and characterize patients with EOG.

METHODS

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Literature Review

A systematic search was conducted using PubMed to identify full publications and the ACR and EULAR abstract archives to identify published abstracts that were not yet available in full manuscript form. Articles and abstracts focusing on EOG were identified using the following search terms: early onset gout, "early onset gout", and "(gout AND age of onset)." All literature searches were performed in August 2022.

In an effort to review the most contemporary literature focusing on EOG, only publications from 2016–2022 were included. All publication titles were screened by two authors (AA, LPS) for possible inclusion in this literature review. Items possibly containing data of interest were thoroughly reviewed, and publications meeting any of the following criteria were excluded: not available in English, duplicate publication or data set (e.g., subset of a larger identified data set, meeting abstract of a full publication, literature review), single patient case report, or insufficient/irrelevant data. Publications satisfying inclusion/exclusion criteria were extensively reviewed and discussed by all authors. Unanimous consensus was reached regarding the final included publication list. The PRISMA

flowchart showing literature identification is shown in the Fig. 1.

Data Analysis

Available data were collated using an Excel spreadsheet for qualitative and quantitative analysis. Studies of similar type (e.g., claims-based, medical record data) were separately examined to avoid potential confounding of results. Patient demographics, comorbidity burden, and gout characteristics were examined and compared between EOG and CG populations. Because this systematic literature review was exploratory in nature and meant to be hypothesis generating, statistical analyses were not performed. Continuous parameters are presented as means and categorical data are presented as n (%). In some publications, continuous data were presented as median (Q1, Q3). In these cases, the mean was estimated as (median + Q1 + Q3)/3, as has been shown to be appropriate for systematic literature reviews and meta-analyses [48].
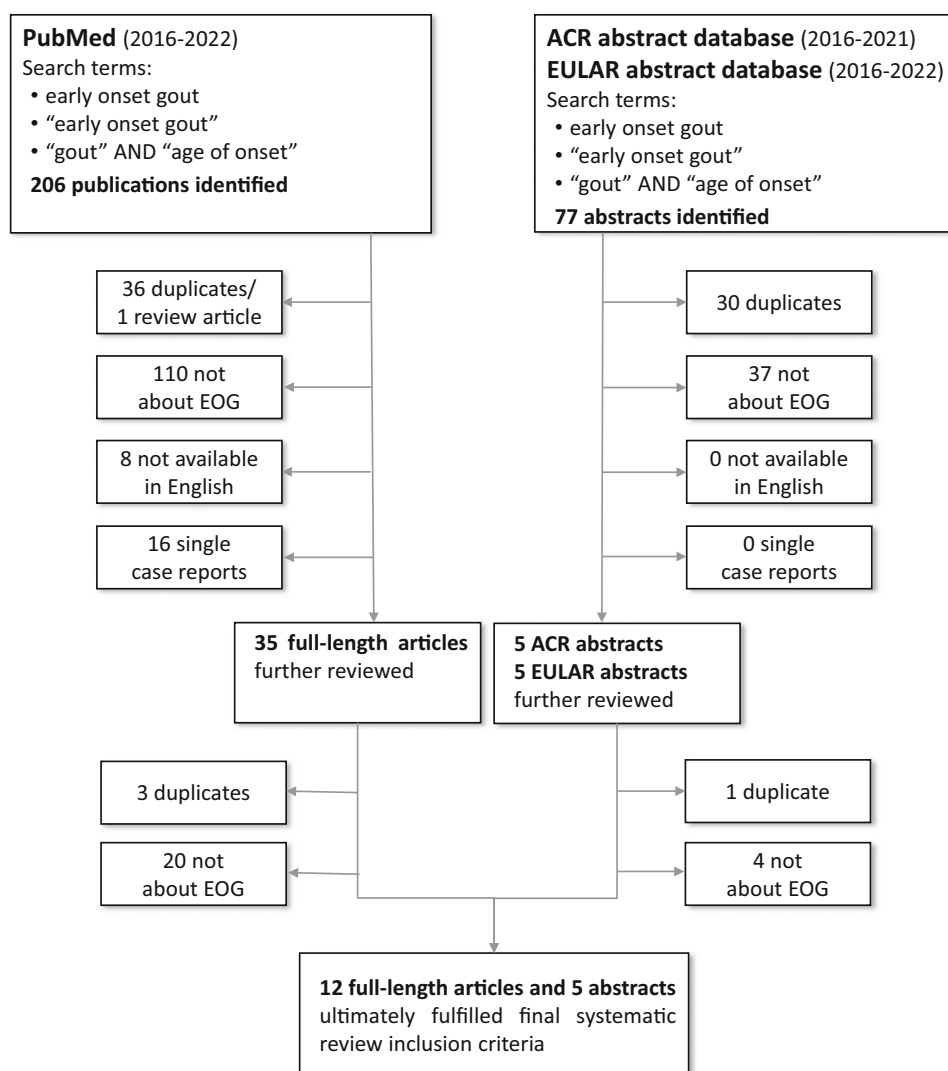
Fig. 1 Flowchart of early-onset gout literature identification and inclusion/exclusion. *EOG* early-onset gout, *ACR* American College of Rheumatology, *EULAR* European Alliance of Associations for Rheumatology

Table 1 Characteristics of patients with early-onset gout and common gout at diagnosis/first gout flare

	Study type	Early onset gout			Common gout		
		N (patients)	Mean age (years)	Male (%)	N (patients)	Mean age (years)	Male (%)
Perng et al. 2021 [64]	Claims-based	–	–	–	–	–	–
Amatucci et al. 2022 [63]	Claims-based	68,709	33.2	71.6	933,375	66.3	61.9
Zhang et al. 2016 [65]	Pro survey/MR	449	29.5	98.7	329	50.4	97.3
Li et al. 2017 [55]*	Pro survey/MR	99	24.2	99.0	402	51.7	87.3
Li et al. 2022 [56]	Pro survey/MR	387	28.8	100	233	51.8	86.9
Li et al. 2018 [61]*	Retro MR review	69	23.5	98.6	111	51.4	90.1
Li et al. 2019 [57]	Retro MR review	227	31.6	97.8	100	61.0	71.0
Pascart et al. 2019 [59]	Retro MR review	120	32.8	96.7	865	57.2	86.6
Herrou et al. 2019 [62]*	Retro MR review	39	24.8	97.4	174	55.4	83.3
Suh et al. 2021 [60]	Retro MR review	38	29.1†	–	45	50.3†	–
Gao et al. 202 [58]*	Retro MR review	1700	25.3	98.6	7277	47.8	94.3
Pro/retro MR average		–	**27.7**	**98.5**	–	**53.0**	**90.0**
Pro/retro MR weighted average		–	**27.0**	**98.7**	–	**49.3**	**93.1**

Early-onset gout defined as first gout flare/diagnosis before 40 years of age (*indicates defined as < 30 years of age by study). Weighted averaging based on the number of patients in a study. †only included male patients, mean obtained from median (Q1, Q3) [48]

Pro prospective, *MR* medical record, *Retro* retrospective

RESULTS

Literature Search

The literature search identified a total of 283 references (Fig. 1). After removing 66 duplicate publications, 1 review article, 16 single patient case reports, eight publications not available in English, and 147 categorized as inapplicable/lacking sufficient information, a total of 35 articles and ten abstracts were extensively reviewed for eligibility and discussed by the authors. Ultimately, 12 full-length publications and five abstracts were included in the final systematic review. Unanimous consensus among the authors to include all articles was reached. Of the 17 included publications, six focused on the genetic component of EOG [49–54], ten focused on the clinical aspects of EOG [55–64], and one had aspects of both [65]. Of the clinically focused publications, six were retrospective, cross-sectional comparisons between EOG and CG cohorts [57–62], three were prospective comparisons between EOG

Table 2 Average comorbidity prevalence in studies with medical record data

	Early onset gout				Common gout			
	All studies	China	US	France	All studies	China	US	France
Hypertension (%)	37.6	30.2	41.0	54.4	64.7	53.7	90.0	77.9
Obesity (%)	45.7	34.7	64.8	81.7	35.5	22.2	55.0	82.7
BMI, kg/m^2, mean	28.0	26.6	34.0	29.2	28.2	25.5	44.1	28.6
Diabetes (unspecified) (%)	9.4	7.6	12.3	11.7	23.6	19.5	44.0	15.5
Type 2 diabetes (%)	20.0	5.2	–	34.8	28.0	13.7	–	42.9
Hyperlipidemia/dyslipidemia (%)	47.5	52.8	46.8	34.6	58.3	56.4	90.0	47.1
Coronary artery disease (%)	1.2	0.8	1.4	1.7	13.2	7.1	35.0	11.3
CKD (eGFR < 60 ml/min/1.73 m^2) (%)	9.7	6.6	–	15.8	25.5	22.8	–	30.9
eGFR, ml/min/1.73 m^2, mean	93.4	93.7	–	91.7	74.2	76.3	–	63.4

Mean data represents average across applicable studies with data

BMI body mass index, *CKD* chronic kidney disease (eGFR < 60 ml/min/1.73 m^2), *eGFR* estimated glomerular filtration rate, *US* United States

and CG patients [55, 56, 65], and two were claims-based analyses comparing EOG and CG populations [63, 64].

Clinical Characteristics of Early-Onset Gout and Common Gout Patients

Eleven publications made comparisons between patients with EOG and patients with CG, with patients deriving from France, China, Korea, Taiwan, and the United States. Six studies were retrospective in nature and examined existing data sets, three studies were prospective in nature and had accompanying dietary investigations, and two studies were insurance claims-based analyses. EOG was defined as gout diagnosis/first acute gout flare before the age of 40 years in seven studies and before the age of 30 years in four studies. Of the nine studies with medical record data, gout was defined using ACR/EULAR criteria in five [57, 58, 60, 61, 65].

Patient Characteristics

Mean patient age at first gout flare/gout diagnosis ranged from 23.5–32.8 years in EOG patients and 47.8–61.0 years in CG patients (Table 1). The proportion of male patients was high in both EOG (96.7–100%) and CG

(71.0–97.3%) cohorts, but was consistently higher in EOG patients. However, a similar proportion of male patients was noted in one Chinese population (EOG: 98.7 vs. CG: 97.3%; Table 1) [65].

Comorbidity burden was consistently lower in patients with EOG than in those with CG. In studies with medical record data, hypertension, diabetes, hyperlipidemia/dyslipidemia, coronary artery disease, and chronic kidney disease (CKD) were all less prevalent in patients with EOG (Table 2). Of note, CKD prevalence was markedly lower in EOG patients across all studies, as reflected in available eGFR data. Average mean eGFR across studies was 93.4 ml/min/1.73 m^2 in EOG cohorts and 74.2 ml/min/1.73 m^2 in CG cohorts. The identified claims-based analysis that examined cardiometabolic and renal comorbidities showed lower cardiorenal comorbidity prevalence in EOG than CG patients in the United States, with lower rates of hypertension (34 vs. 77%), cardiovascular disease (% not provided), type 2 diabetes (13 vs. 39%), and CKD (5 vs. 20%) at the time of first gout diagnosis code [63]. Similar trends were observed here in studies with medical record data in US, Chinese, and French populations. Amatucci et al. [63] also showed that, in

Table 3 Gout characteristics in patients with early-onset gout and common gout

	Early onset gout				Common gout			
	All studies	Asia*	US	France	All studies	Asia*	US	France
Gout duration, years, mean	6.9	5.2	–	11.9	6.5	4.9	–	11.2
Tophi present (%)	29.9	20.8	65.0	39.5	30.5	23.8	75.0	28.4
Serum urate								
At baseline, mg/dl, mean	9.2	9.5	8.7	8.6	8.4	8.3	8.4	8.7
> 8 mg/dl (%)	–	–	78.5	–	–	–	73.5	–
> 10 mg/dl (%)	–	50.0	–	–	–	29.5	–	–
< 6 mg/dl with ULT	39.1	–	35.4	41.0[†]	50.3	–	53.3	48.9[†]
Number of joints involved, mean	–	5.6	–	–	–	4.9	–	–
Acute gout flares								
Flares in prior year, mean	6.0	7.7	–	3.4	5.4	7.4	–	2.5
> 2 flares/year (%)	–	–	92.4%	96.7%	–	–	53.8%	92.7%
Polyarticular gout attack (%)	–	–	–	49.6%	–	–	–	34.8%

The unweighted mean of all studies with available data is provided. *includes studies from China and Korea. [†]The single French study noted higher febuxostat dose needed in EOG patients to achieve target SU [62]

both EOG and CG patients, comorbidity prevalence at first gout diagnosis code was higher and comorbidity prevalence following gout diagnosis grew faster than in the general US population of similar age. Similar observations were made in a Chinese EOG cohort included in the current analysis for hypertension (EOG: 59.9% vs. Chinese population of similar age: 20.0%), diabetes (6.7 vs. 3.2%), and metabolic syndrome (31.7 vs. 6.1%) [65]. In contrast, obesity rates were higher in patients with EOG than in patients with CG, except in France where the rate was consistent between groups [59]. Mean body mass index was similar between EOG and CG populations, with the exception of the US, where BMI was higher in patients with CG.

The remaining claims-based study examined new-onset glaucoma risk in Taiwanese patients with and without gout. Gout patients who were 20–39 years of age had the highest risk of developing glaucoma among gout patients and compared to their non-gout counterparts [64].

Gout Characteristics

In eight of nine studies (88.9%) with medical record data, authors reported more severe disease in EOG patients than in CG patients [55, 57–62, 65]. This conclusion was based on SU at diagnosis, gout duration, and the proportion of patients with acute gout flare, polyarticular disease, tophi, and target SU with oral ULT therapy (Table 3). In EOG and CG patients, gout duration (EOG: 6.9 vs. CG: 6.5 years) and proportion of patients with tophi (29.9 vs. 30.5%) were similar. However, SU at baseline/diagnosis was higher in EOG patients in eight of nine studies (88.9%) and fewer patients achieved target SU with ULT (39.1 vs. 50.3%). One French study also noted that a significantly higher febuxostat dose was required in patients with EOG to achieve target SU (dosing information not provided) [62]. Further, rates of ULT use were higher in EOG than CG patients in the US study (87.0 vs. 67.9%) [57] and similar between EOG and CG patients in one French study (68.9 vs. 67.9%) [59]. In that same French

cohort, ULT duration was also longer in EOG patients (11.3 vs. 6.6 years) [59].

Four of six studies (67%) with gout flare details indicated signs of more severe articular disease in patients with EOG. This included increased gout flare frequency, a higher proportion with ≥ 2 flares/year, and/or a higher proportion with polyarticular flares (one US, two French, one Chinese cohorts; Table 3) [57, 59, 62, 65]. In a Chinese cohort, patients with EOG also had a higher number of involved joints than their CG counterparts (5.2 vs. 3.8) [55]. Both studies that were not indicative of more severe articular disease reported on Chinese populations [55, 56]. Ankle/mid-foot involvement was noted in 63 vs. 48% of EOG vs. CG patients in a Chinese cohort [65], gout involvement outside of the 1st MTP joint was noted in 54 vs. 41% of EOG vs. CG patients in a French cohort [59], and first gout flare was noted in the foot/ankle (excluding the 1st MTP joint) in 31.5 vs. 20.0% of EOG vs. CG patients in the US cohort [57].

Genetics of Early-Onset Gout

Our systematic literature review identified six full-length publications and one abstract with novel and relevant information related to EOG genetics. Patient and/or gout characteristics were briefly described in the presence of urate-transporter (ABCG2) [49–53], solute carrier (SLC) [53, 54], or aldehyde dehydrogenase (ALDH) [53] mutations. Though these mutations are rare in the general population, nearly one-third of a small EOG cohort (7 of 26 patients [27%]) had a "probably pathogenic" ABCG2, SLC, or ALDH mutation [53]. Further, some identified clinical studies showed that EOG populations consistently had a family history of gout more often than CG populations (United States: 20.3 vs. 11.0% [N = 227, 100] [57]; France: 38.1 vs. 16.7% [N = 120, 865] [59], 60.6 vs. 24.6% [N = 39, 174] [62]; China: 37.0 vs. 32.6% [N = 387, 233] [56], 25.9 vs. 18.1% [N = 1700, 7277] [58], 42.0 vs. 30.6% [N = 69, 111] [61]).

ABCG2 Mutations

Zaidi et al. [49] examined three previously reported study populations, including those of the Genetics of Gout in Aotearoa study [66] (Aotearoa cohort; Eastern Polynesian, Western Polynesian, and New Zealand European ancestral origin subgroups), the Eurogout consortium [67] (Eurogout cohort, established by the European Crystal Network), and lesinurad clinical trials [68–71] (Ardea cohort). The ten loci most strongly associated with serum urate, as identified by Yang et al. [72], were examined in all cohorts. For their age at diagnosis groupings, the youngest tertile was diagnosed with gout at < 35 years of age and the oldest tertile was diagnosed with gout at > 50 years of age. The ABCG2 rs2231142 mutation was strongly associated with the development of gout before 35 years of age. Further, across all examined populations, patients with the ABGC2 mutation were more likely to be diagnosed with gout before 40 years of age (OR [95% CI]): 1.60 [1.41, 1.83]). The association remained significant in the Eastern Polynesian and New Zealand European ancestral origin subgroups. Regarding the remaining nine SNPs, though not statistically significant, the data suggest that several other mutations carry a higher adjusted OR for the development of gout before 35 years of age.

Zhang et al. [65] specifically examined ABCG2 protein function in a Chinese gout population, estimated using SNP sequencing of the two most common polymorphisms (rs2231142, rs72552713) and an established ABCG2 function prediction model [73]. A high prevalence of ABCG2 protein dysfunction was found in both EOG (79.5%, N = 449) and CG (86.4%, N = 329) patients, with a younger mean age of gout onset in those with the lowest ABCG2 function (full function: 37.1 years, three-quarters function: 36.7 years, one-half function: 38.0 years, one-quarter function: 30.4 years). Further, pediatric gout has been reported in patients with a strong family history of EOG that was linked to ABCG2 mutations [50, 51]. Together, these genetic findings strongly link pathogenic ABCG2 mutations and the development of EOG.

SLC and ALDH Mutations

Huang et al. [54] identified a two-generation pedigree with familial EOG. A father and son were affected by EOG, with both having a rare missense SLC16A9 mutation that was deemed to be "possibly pathogenic." Protein function was not examined, but findings from older studies have shown an association between SLC16A9 mutations and serum urate levels [74, 75]. A mutation in SLC22A11 has also been reported in a patient with EOG [53]. Though different loci than the genetic anomalies described above, most SLC22A12 mutations have been shown to increase susceptibility to hyperuricemia [76].

One published case of an ALDH16A1 mutation in a patient with EOG was identified in the examined time period [53]. Though the ALDH16A1 protein is thought to be inactive, its proper interaction with hypoxanthine–guanine phosphoribosyltransferase (HPRT1), a key enzyme involved in the purine salvage pathway may be needed for optimal HPRT1 function [77]. Of note, although most genetic mutations result in impaired urate excretion, patients with an ALDH16A1 mutation likely have impaired purine salvage, which results in urate overproduction [78].

DISCUSSION

This systematic literature review identified seven publications that explored the genetics of uncontrolled gout and 11 publications that compared the clinical characteristics of EOG and CG populations. Distinct and consistent differences were identified with respect to genetic predisposition to gout, gout severity, and overall patient health at gout diagnosis.

EOG patients had more severe and harder to treat disease than their CG counterparts, as noted by increased flare rates, polyarticular involvement, and/or hyperuricemia that was more recalcitrant to oral ULT. These findings were consistent across Chinese, French, Korean, and US populations and are supported by genetic studies, which suggest that renal urate transporter anomalies play a role in EOG development, particularly ABCG2 mutations

that affect transporter function and subsequent urate excretion. Given that patients with EOG had overall higher SU and were less likely to achieve target SU levels during ULT use, genetic mutations associated with gout may make this population with genetically driven gout less responsive to xanthine oxidase inhibitors, which slow the production of urate but do not increase urate excretion. In fact, the presence of an ABCG2 loss-of-function polymorphism has been shown to predict poor SU-lowering response to allopurinol [79, 80], perhaps because, in addition to urate transport, allopurinol transport into the cell is also affected by such mutations [80].

EOG patients may provide important clues on the systemic extra-articular impacts of gout. Included publications consistently showed lower cardiometabolic and renal comorbidity in patients with EOG compared to those with CG; most notably, hypertension, diabetes, coronary artery disease, and CKD. It is known that initiating oral ULT that complies with ACR treatment guidelines leads to improvement in arterial endothelial function and lowers levels of systemic inflammation that are elevated in gout patients, even during intercritical periods [81]. Further, a recent study suggests that, in patients who initiated intense ULT with pegloticase, gout flare led to a prolonged elevation in the neutrophil-to-lymphocyte ratio [82], a biomarker for systemic inflammation. Given that these comorbidities have an inflammatory component to their etiologies, that gout flares put patients at risk for subsequent cardiovascular events [83], and that urate deposition volume is positively associated with cardiovascular risk and overall mortality [35], systemic inflammation in gout patients is of great interest and further study is underway.

Obesity rates were higher in EOG patients than in CG patients in all US and Chinese populations examined. This finding is consistent with other studies showing that obesity is an independent risk factor for developing gout [84–86] and is associated with a younger age of gout onset [86]. Both French populations examined, had similar BMI/obesity prevalence in EOG and CG patients [53, 59]. This discrepancy between the French and other populations

may be related to the low obesity rate in France near the time of data collection (approximately 15% in 2017 [87]).

Our study had several limitations. First, the relevant number of publications that satisfied inclusion criteria was small. Second, our results may have been influenced by biases inherent to systematic literature reviews including publication and selection biases. Third, the definition of EOG was not consistent across all studies potentially leading to some overlap between groups and a potentially non-homogeneous population across studies. This lack of a uniform definition for EOG emphasizes the need for formalizing EOG as a distinct subset of the gout population. Fourth, patient medication compliance is a known challenge in managing gout, particularly in younger patients (< 45 years) [88]. However, the influence of compliance on our findings cannot be commented on because, of the 3 studies that did not exclude patients with prior ULT use [58, 59, 62], compliance information was not provided. Lastly, causality of gout for the comorbidities reported on cannot be determined from this analysis. Our findings are hypothesis generating but larger longitudinal studies with consistent EOG definition are needed to better examine patient characteristics and understand the relationship between gout and its associated comorbidities.

CONCLUSIONS

In conclusion, the literature suggests that patients with EOG present with more severe disease and are more recalcitrant to oral ULTs than patients with CG, with underlying genetic defects in urate transporters playing a large role in gout development. Therefore, those with EOG may benefit from earlier and more aggressive ULT therapy to adequately achieve their target SU. Because a large proportion of EOG patients do have a genetic predisposition to hyperuricemia, this finding is of particular importance in the young EOG population. First, patients with EOG must live with the condition for decades, making them particularly susceptible to the pain and disability associated with gout. Second, at gout diagnosis, the EOG

population had a much lower cardiovascular, renal, and metabolic comorbidity burden than seen in the CG population. Therefore, referral to a rheumatologist early in the disease course may be warranted for SU management. Though more rigorous study is needed, the temporal separation between gout diagnosis and cardiometabolic comorbidity development suggests there may be a window of opportunity when early SU control in EOG patients may attenuate gout progression and subsequent comorbidity development.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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