Review

One year in review 2018: gout

L. Punzi[1], A. Scanu[2], P. Spinella[3], P. Galozzi[2], F. Oliviero[2]

[1]Centre for Gout and Metabolic Bone and Joint Diseases, Rheumatology, SS Giovanni and Paolo, Venice, Italy
[2]Rheumatology Unit, and [3]Clinical Nutrition Unit, Department of Medicine - DIMED, University of Padova, Italy.

Leonardo Punzi, MD, PhD
Anna Scanu, PhD
Paolo Spinella, MD
Paola Galozzi, PhD
Francesca Oliviero, PhD

Please address correspondence to: Prof. Leonardo Punzi, Centre for Gout and Metabolic Bone and Joint Diseases, Padiglione Mendicanti I piano, Ospedale Civile SS. Giovanni e Paolo, Castello 6777, 30122 Venezia, Italy
E-mail: punzileonardo@gmail.com

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ABSTRACT

Gout is the most common form of inflammatory arthropathy, and is associated with excruciating pain, major impairment of quality of life, and increased risk of comorbidities and mortality.

Although gout has somehow been neglected by researchers and clinicians in the past, in more recent times there has been a renewed interest in this disease, which has led to major improvements in its management.

This article reviews the new clinical and experimental evidence about gout that emerged in 2017 and in the first half of 2018.

Introduction

Gout is the most common form of inflammatory arthropathy, with an estimated prevalence of up to 4% in Western countries (1). This condition is caused by hyperuricaemia, which leads to crystallisation, aggregation and deposition, of monosodium urate (MSU) crystals that accumulate in joints and soft tissues over time (2, 3). These crystals induce an acute inflammatory reaction characterised by a massive leucocyte recruitment and the local release of cytokines, chemokines, reactive oxygen species and proteolytic enzymes (3).

Once established, gout is associated with excruciating pain, joint swelling and redness, as well as with several comorbidities related, in particular, to kidney and cardiovascular conditions, which lead to an increased risk of mortality in these patients, especially in those with tophi (1, 4, 5).

Although gout has somehow been neglected by researchers and clinicians in the past (6, 7), in more recent times there has been a renewed interest in this disease, which has led to major improvements in its management. Indeed, the number of publications on gout has almost doubled from 2009 to the end of 2017 (Fig. 1).

In line with the editorial policy of this journal to publish yearly updates on the most relevant topics of rheumatology, we will provide here an overview of the recent literature on novel treatments in gout (8-22). This article reviews the new clinical and experimental evidence about gout that emerged in 2017 and in the first half of 2018. Relevant papers published from January 2017 were identified by a PubMed search, last update at the beginning of July 2018; papers were then selected for inclusion according to the authors' judgement.

Genetics

A combination of inherited genetic variants and environmental exposure is known to influence serum urate levels and the risk of developing gout.

GWAS

Over the past decade, several genome-wide association studies (GWAS) have systematically assessed the genome for urate-associated loci (23). These loci are dominated by proteins involved in urate transportation (*i.e.* SLC family genes) or they are associated with metabolic pathways (*i.e.* glucokinase regulatory gene and members of aldehyde dehydrogenase gene family and apolipoproteins gene family). Nakayama *et al.* (24) performed a follow-up GWAS of gout and subtypes in 1,396 cases, replicating loci not reaching genome-wide significance in the original 2015 Japanese GWAS (25). At a genome-wide level, novel associations with gout at the urate transporter genes (*SLC22A12, SLC17A1*) and *HIST1H2BF–HIST1H4E* gene were reported. Two more loci (*NIPAL1* and *FAM35A*) were associated with renal underexcretion gout subtype.

Another GWAS in 1,888 male Chinese gout patients reported four novel loci (*PKC-ε, MARCKS, Pitx2* and *MSX2*) strongly associated with tophi occurrence (26).

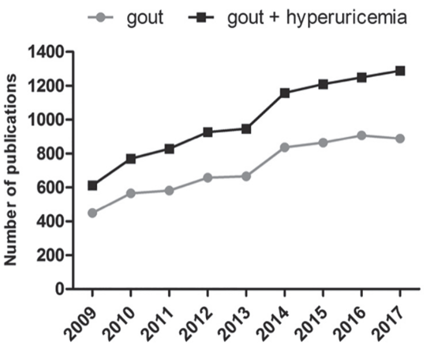

Fig. 1. The number of publications on gout and hyperuricaemia (PubMed) over the past 10 years (2018 not included).

In the largest GWAS in gout completed to date, preliminary data from 7,431 European patients with gout presented as an abstract at the American College of Rheumatology (ACR) meeting in 2017, which showed nine loci (*SLC2A9, ABCG2, GCKR, MLXIPL, SLC17A1–SLC17A4, SLC16A9, SLC22A12, PDZK1* and *TRIM46*) with genome-wide significance with an association with gout (27). All nine loci were associated with serum uric acid (sUA) levels in a previous European GWAS (28).

Common and rare variants

This year great efforts have been made in the attempt of elucidating genetic factors contributing to positively predict the risk of gout.

Based on the above-mentioned pathway analysis (29, 30), a novel gout-associated gene *SLC17A2* was identified and non-synonymous single nucleotide polymorphisms (SNPs) loci of *P2X7R* (an ATP receptor) regulate the occurrence and development of gout.

Since gout can be classified among the autoinflammatory diseases (31), some authors investigated autoinflammatory-related genes in gout patients. It was observed that *MEFV* variations affect the severity of gout (32). The GG genotype of *NLRP3* rs10754558 and the CGA haplotype of rs4612666, rs10754558, rs1539019 are all independent risk factors for gout.

Dong *et al*. (33) identified two novel urate transporter genes (*HNF4G* and *SLC17A4)* associated with gout. Other novel variants, candidates for gout susceptibility, are rs889472 in the *C-MAF* gene (34), four high-risk genotypes of *ALPK1* gene combined with *ABCG2, SLC2A9* and *ALC22A12* genes (35), and rs4148500 in the *ABCC4* gene (36). Yasukochi *et al*. (37) instead add rs55975541 in the *CDC42BPG* gene at the susceptibility locus for hyperuricaemia.

Clear evidence from Japanese and Czech re-sequencing studies (38, 39) indicate that genotyping the rare and common variants of *ABCG2*, a secretory transporter, is essential for evaluating the individual risk of gout. Moreover, non-synonymous allelic variants of *ABCG2*, among which rs2231142, were associated with an earlier onset of gout and the presence of gout history (38,39). In an Aotearoa New Zealand study (40), *ABCG2* SNPs (rs2231142 and rs10011796) were found to be associated with tophi in western Polynesian individuals with gout, independent of other risk factors as serum urate concentrations or disease duration.

Zambo *et al*. (41) discovered a relative frequent, novel rs148475733 mutation in *ABCG2* that reduced erythrocyte membrane protein expression, preserving transporter capability. Colchicine and other small molecule correctors were observed to restore *ABCG2* surface expression.

The common SNPs explained only part of the hereditability of gout. Copy number variants (CNVs), dosage imbalances of large segments of DNA, could play a role in genetic susceptibility to gout, as observed by Dong *et al*. (42). The authors identified three novel genes: *ABCF1* and *FCGR3A* with high copy number increased the risk of gout; and *IL17REL* with a low copy number acted as a protective factor for gout.

Overall, these findings emphasise the importance of sUA control in gout, and point out to some genetic bases for this disease.

Gene-environment interactions

Some recent studies have reported gene-environment interactions in the regulation of sUA levels or risk of gout. Beydoun *et al*. (43) highlighted the important contributions of sex-gene and gene-diet interactions in determining sUA. Dietary factors, such as legumes and alcohol intake, potentially interact with urate transporters genes in managing the risk of hyperuricaemia and gout. An interaction between alcohol and the SNP rs671 at *ALDH2* was described to handle serum urate levels in a Chinese Han male cohort (44). It was also observed that an interaction between the alcohol intake and the risk of gout in a New Zealand European cohort presenting rs780094 at *GCKR* and rs10821905 at *A1CF,* loci predominantly involved in glycolysis and lipid homeostasis (45).

Mitochondrial dysgenesis in gout

Mitochondrial DNA (mtDNA) represents a relatively new chapter in the genetics implied in gout pathogenesis. The mtDNA is a double-stranded, circular molecule contains 37 genes coding for two rRNAs, 22 tRNAs and 13 subunits of enzyme complexes of the oxidative phosphorylation system. Gosling *et al*. (46) investigated the role of mtDNA variation and copy number in the risk of gout in New Zealand Māori and Pacific people. The authors found that both heteroplasmy and reduced mtDNA copy number did associate with gout. Mitochondrial conformation differences, white blood cell population differences or reduced mitochondrial biogenesis and mitophagy could potentially explain the reduced mtDNA copy number.

Consistent with a role for mitochondrial dysgenesis in gout, the SNP rs45520937 in *PPARGC1B*, an anti-inflammatory mediator gene, is associated with gout and increased MSU-stimulated NLRP3 activation and IL-1β secretion in Twainese Chinese gout patients (47). A published abstract reported that this allele is also associated with increased risk of gout in people of Polynesian ancestry (48).

Epigenetics in gout

A growing body of evidence has implicated epigenetic factors, in particular, altered patterns of DNA methylation and microRNA (miRNA), in the pathogenesis of gout.

Given the important roles of miRNAs as negative post-transcriptional gene regulators in inflammatory diseases, including gout, Zhou *et al*. (49) analysed the expression profiles of miR-

NA regulating the pathogenesis of acute gout. The authors observed that miR-488 and miR-920 significantly decreased in patients with gout and, if overexpressed, could significantly inhibit the gene and protein expression of pro-inflammatory cytokines. These findings propose miRNAs as regulators in the development of gout.

This year, primary insights have been provided on changes in DNA methylation in gout patients. Hypomethylation at the promoter region of the gout-risk gene *NRBP1* can lead to enhanced gene expression both *in vitro* and *in vivo*, contributing to the development of gout (50). Li *et al*. (51) marked in Chinese Han population with gout a significant association between *CCL2* promoter hypomethylation and the risk of the disease. Hypermetilation of uromodolin (*UMOD*) observed in gout patients might reduce the gene expression, leading to an augmented risk of gout (52).

These investigations on mitochondrial dysgenesis and epigenetics pave the way to new lines of research to improve the knowledge of the genetic basis of gout.

Pathogenesis and natural history

The key aspect of the pathogenesis of gout is the elevated sUA concentrations, leading to the formation of MSU crystals (53). Once crystals are deposited into a joint, they can initiate an inflammatory cascade causing acute gout. However, although hyperuricaemia is a key risk factor for gout, not all people with elevated sUA develop the disease. Moreover, gout patients can have intermittent flares despite the persistence of MSU crystals deposition. Therefore, other factors may contribute to trigger inflammation.

In recent years, a great attention has been paid to the mechanisms involved in the development of gout (Fig. 2). Using a pathway analysis strategy, Dong *et al*. (54) found two transmembrane transporter activity-related pathways that regulated sUA level and the development of gout, influenced by gender and BMI. There is also indirect evidence of a role for the ATP-P2X7R signaling pathway in the pathogenesis of gout. Tao *et al*. (30) indeed observed an increased IL-1β secretion as a result of MSU crystals and ATP interaction in patients with non-synonymous polymorphisms in the ATP receptor gene *P2X7R*.

Metabolic components could be additional factors that synergise with MSU crystals to elicit inflammation. Zang *et al*. (55) identified clear metabolic changes in lipid, amino acids and energy metabolic pathways between patients with hyperuricaemia and those with gout. The combination of these alterations may indicate a continuous development from hyperuricaemia to gout.

Furthermore, genetic factors can be implicated in the gout progression. Indeed, the identification of two novel gout-associated loci (*NIPAL1* and *FAM35A*) in a 2017 GWAS suggested the involvement of the distal nephron in gout progression (24). In addition, the carriers of urate-associated genes not coding for urate transporters (*i.e. GCKR* and *TRIM46*) were found to influence the development of gout, suggesting that the differences in biological function of these genes may be a reason for different progression of hyperuricaemia into

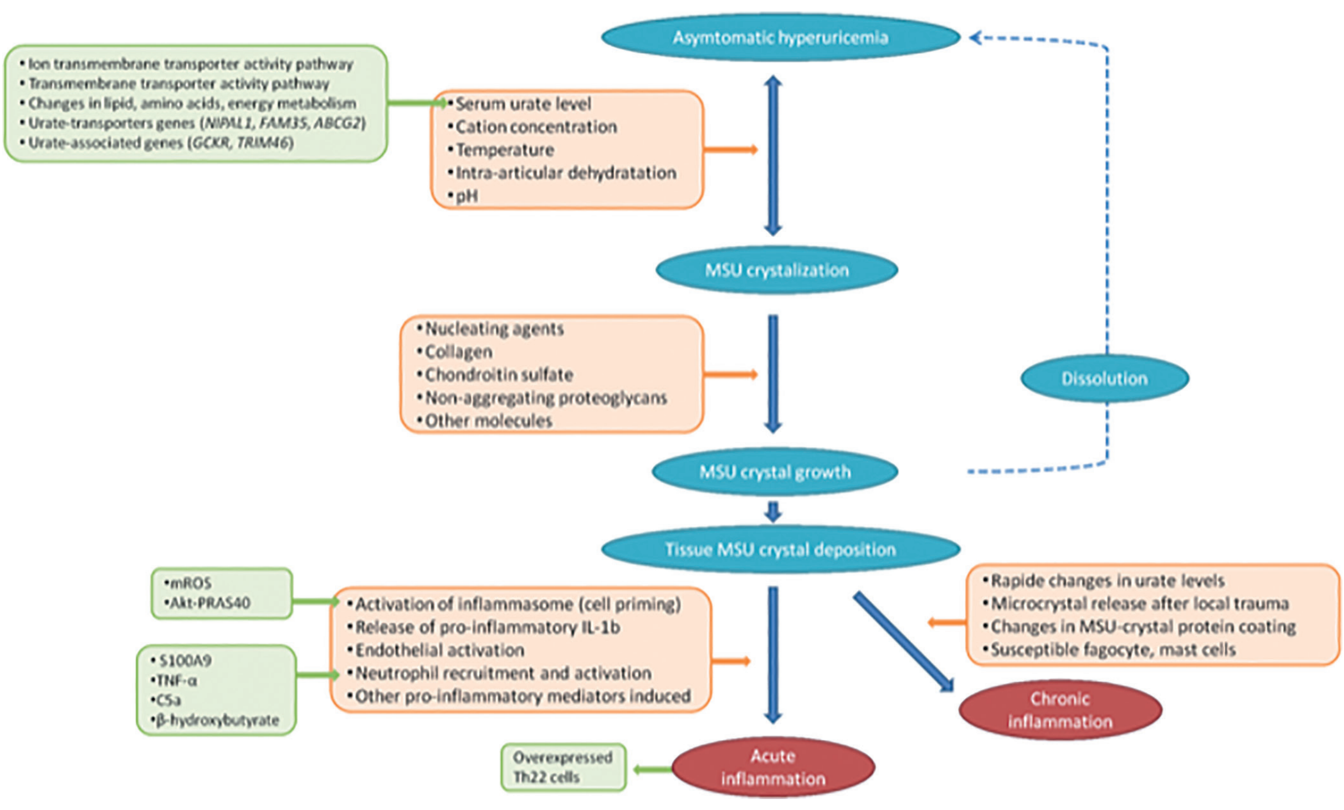

Fig. 2. Schematic mechanisms of MSU crystal formation and crystal-induced inflammation. In the green boxes (far left), the latest insights into gout pathogenesis. (Modified from Choi *et al*., 2005 (131).

gout (33). Hyperuricaemia and gouty inflammation can be further elicited by *ABCG2* gene via augmented IL-8 release in endothelial cells (56).
By performing proteomics analysis, a member of the beta tubulin family (*TBB4A* gene) was found to be significantly associated with primary gout and potentially involved in gout pathogenesis (57).

Cell priming
IL-1β-mediated inflammation is a well-known key aspect of gout, mediated by MSU crystals triggering the NLRP3 inflammasome complex. Two steps are necessary to engage the inflammasome: cells priming and inflammasome activation (58). In the past year, different factors were reported to mediate initially the priming of monocytes and mast cells, and then of neutrophils in gout. Crisan *et al.* (59) have investigated how the uric acid-induced priming of monocytes determined an augmented IL-1 production. The Akt/PRAS40 autophagy pathway was proposed to drive the monocytes activation. Using a zebrafish model, Hall *et al.* (60) provided a novel metabolic mechanistic insight into acute gout showing that macrophage activation in response to MSU crystals required mitochondrial reactive oxygen species (ROS) generated through fatty acid oxidation.
Novel factors have been proposed instead to affect neutrophils priming. Rousseau *et al.* (61) suggested that the extracellular S100A9 potentiated the neutrophils priming in response to MSU crystals and in a context of sterile inflammation. In a similar sterile environment, TNF-α may also contribute to prime neutrophils promoting uric acid-mediated IL-1β secretion (62). In a mouse model, Khameneh *et al.* (63) identified the complement component C5a produced by MSU crystals as one of the key regulators of IL-1β secretion and neutrophil recruitment at the site of inflammation. A possible effect on priming of neutrophils has been suggested also for β-hydroxybutyrate, a ketone body known to suppress inflammasome activation in response to MSU crystals (64).

Neutrophil extracellular traps
The pathogenesis of gouty arthritis involves initial activation of monocytes and mast cells followed by neutrophils. Interestingly, neutrophils have also a major role in the resolution of acute gout, through the formation of neutrophil extracellular traps (NETs), an extracellular DNA network associated with histones and PMN granule proteins. In 2017, Sil *et al.* (65) proved a new mechanism by which macrophages and macrophage-derived IL-1β affect neutrophils function enhancing MSU-induced NET formation. This could contribute to the inflammation in gout. Further research provided insights into the mechanisms of MSU-induced NETs. MSU crystals induce NETs formation through a distinctive pathway, which resulted in a nuclease-resistant, actin-enriched DNA coating of crystals (66). This aggregation may contribute to the persistence of tophi and explain the spontaneous resolution of acute flares of gout. Substances that inhibit the purinergic P2Y receptor, such as suramin, PPADS and MRS2578 can limit MSU-induced NET formation (67).

Adaptive immune cells
The pathological process of gout involved not only innate immune response but also adaptive immune processes. Luo *et al.* (68) for the first time reported that peripheral T-helper (Th) 22 and Th17 cells were overexpressed in patients with acute gout and decreased gradually during the disease progression. Plasma IL-22, derived from Th22 cells, were also upregulated in acute gout, suggesting a possible role in the gouty inflammation.
Overall, while deposition of sUA is the established *primum movens* in the pathogenesis of gout, current research is investigating other factors surrounding sUA deposition and contributing to inflammation.

Diagnosis
Early diagnosis is important in order to control gout and prevent joint damage. Several specific tools have been developed to reveal deposits of MSU crystals; however, many of these techniques are often expensive and not available easily, thus leaving the clinician reliant on the patient history and presentation.

Synovial fluid analysis
Even if different diagnostic strategies have been proposed in last years, the identification of MSU crystals in synovial fluid (SF) or tophus by polarised microscopy remains the gold standard method with specificity of 100% (69). The finding of needle-like shape crystals with strong negative birefringence allows the immediate diagnosis of gout both in undiagnosed patients and in those with other established joint diseases (70). A recent study on the evaluation of the current performance of the crystal identification by professionals involved in examining SF in routine care has revealed that MSU are the best recognisable crystals, and that they were correctly identified by 81% of all participants (71). Moreover, experiments carried out in order to increase the sensitivity of polarised light microscopy have reported that, unlike calcium pyrophosphate (CPP) crystals, MSU are well recognised even without SF centrifugation (72). Despite the high reliability of the microscopic analysis, results from the GEMA-2 transversal study on practice have evidenced that gout diagnosis based on the observation of MSU crystals on the microscope has made in only 31% of cases (73). The relative invasiveness and difficulty of small joint SF aspiration are considered to be the mean reasons for the continuous search of a replacement procedure for gout diagnosis. To this purpose, important advances have been realised in last decade in imaging methods.

Conventional radiography
X-ray is still considered a fast method to evaluate joint damage in clinical practice, but it is of little help for diagnosis in early stages of the disease. A gout-modified Sharp/van der Heidje scoring method (SvdH-mG) has been established to assess radiographic joint damage (74). A recent study that investigated the construct validity of radiographic damage of the feet in gout, has shown that erosions scored using the SvdH-mG were associated with physical function, but not with overall physical health (75).

Ultrasound

In 2015, the ACR and the European League Against Rheumatism (EULAR) recognised the value of ultrasound (US) and dual-energy computed tomography (DECT) as scoring items for gout classification (76). Musculoskeletal ultrasound (MSUS) has demonstrated good sensitivity and specificity in diagnosing crystal-related arthropathies (77-80). Standardisation and validation of MSUS in the diagnosis and monitoring of gout is a current task of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) MSUS group in order to improve the use of this technique in clinical practice (81, 82).

A very interesting review by Naredo and Iagnocco provides an overview of the last year's literature on validation and diagnostic performance of MSUS in crystal arthritis (16). More recently, further studies have reported new insights into this field.

The value of ultrasonographic features of crystal deposition in the diagnosis of gout have been confirmed in a study carried out on 89 consecutively enrolled patients with acute arthritis. The sensitivity and specificity of the double contour sign were 42% and 92%, respectively; those of the intra-articular aggregates were 58% and 92%, respectively; and those of tophi were 40% and 100%, respectively (83).

When considering the diagnostic performance for all stages of gout, US has demonstrated a good accuracy with high specificity. A meta-analysis performed by Lee and Song in 11 studies, which included 938 patients and 788 controls, showed that the pooled sensitivity and specificity of US were 65.1% and 89%, respectively (84).

Although there are several published studies that have shown the capability of US to detect abnormalities in gouty patients compared with controls, which and how many sites should be investigated for an optimal, short and easy to perform US test in the diagnosis of gout are still in debate. Recently, a screening of two sites (knee and first MTP) for the same lesions has been recently proposed (85).

US sensitivity is high in late gout, but limited without tophi and in early stages of the disease (78). However, a prospective controlled study in 60 patients with MSU crystal-proven gout proposed a four-joint investigation as a screening test for early gout classification. The results showed that ultrasonographic signs for tophi in both first metatarsophalangeal joints and double contour in both ankles contributed to the final model for early gout diagnosis. Sensitivity and specificity were 84% and 81%, respectively (86).

US seems able also to differentiate the acute phase of gout from the intercritical periods using colour Doppler imaging. Wang *et al*. demonstrated that the colour Doppler signal grade in the acute phase of gout was higher than that in the intercritical phase. In addition, the combination of colour Doppler US and shear wave elastography (SWE) increased the receiver operating characteristic curve (AUROC), sensitivity and accuracy significantly in comparison with colour Doppler US alone (87).

Dual-energy computed tomography

Dual-energy computed tomography (DECT) is a modified computed tomography using two x-ray beams instead of one, which allows differentiating deposits in soft tissue on the basis of on their relative absorption of x-rays at different photon energy levels. Currently, the costs and the ionising radiation exposure to the patients limit its use in clinical practice.

Recent systematic literature review and meta-analysis concluded that DECT has relatively high diagnostic accuracy for gout, particularly for intra- or extra-articular tophaceous gout. It can be a second-line imaging modality of choice in patients with uncertain diagnosis (88, 89). Analysis of eight studies by Lee and Song revealed a pooled specificity of 93.7% and a pooled sensitivity of 84.7% from a total 510 patients with gout and 268 controls (90). A meta-analysis performed by Yu *et al*. including seven studies reported a lower specificity (90%) but a higher sensitivity (88%) (91). Moreover, it has been reported that DECT could be a useful tool to identify MSU crystals deposits also in patients with asymptomatic hyperuricaemia. A cross-sectional study showed that 15% of asymptomatic patients with high sUA levels had subclinical MSU crystal deposits on foot/ankle DECT scans (92).

DECT is also able to evaluate changes in urate deposition volume and bone damage, demonstrating a high concordance with anatomical pathology (93-95).

Some studies comparing findings of US with DECT in patients with suspected acute gout reported that the percentage of gouty deposits detected by DECT was significantly higher than that detected by US, especially in the extraarticular spaces (96, 97). However, it was observed that DECT underestimated the size of the tophi when compared with US and the inability of DECT to detect inflammation was confirmed (94, 98).

Finally, it has been demonstrated that DECT has limited diagnostic sensitivity for gout with a short disease duration, especially in the first onset patients. A study in 221 patients found that the sensitivity was 35.71, 61.54, and 92.86% in the first onset, less than a 24-month period, and more than a 24-month period, respectively (99).

Lifestyle and diet

Over the last decade, the role of diet in gout has received a strong attention by the scientific community. It has been clear that diet is partially responsible of sUA level fluctuations in the blood (43), and patients with gout are recommended to reduce foods that cause an increase of sUA such as high purine-rich foods, alcoholic and sweetened beverages. In general, patients with gout are encouraged to adopt a Mediterranean lifestyle. However, although the EULAR 2016 guidelines state that every individual with gout should receive advice regarding lifestyle, the task force recognised that lifestyle and dietary modification, at present, should be considered to have little effect on urate concentrations (100).

Despite this, research on lifestyle and diet in the pathogenesis and prevention of gout is active.

Experimental evidence

Growing evidence supports the anti-inflammatory and anti-hyperuricaemic

effects of plant-derived components in crystal-induced inflammation. Among these, polyphenols and fibres have been the most studied in the last decade, and interesting additional works have been published during the last year.
One of these showed how short-chain fatty acids (SCFAs), resulting from the metabolism of fibres, are capable to inhibit the inflammatory response to MSU crystals in mice (101). In this work the Authors observed that mice fed a high fibre diet 2 weeks before injection of MSU crystals into the knee joint had a faster resolution of the inflammatory response with respect to mice fed a low fibre diet. In particular, they showed that treatment with the SCFA acetate reduced the levels of chemokine CXCL1 decreasing neutrophil accumulation at late stages after injection of MSU crystals. Using a mouse model of MSU crystal-induced inflammation in the peritoneum, they also demonstrated that acetate increased the percentage of apoptotic neutrophils and the levels in the knee tissue of two anti-inflammatory cytokines (TGF-β and IL-10), processes which are essential for the resolution of inflammation.
The production of β-hydroxybutyrate (BHB), a ketone body induced by fatty acid oxidation or fibre fermentation, has also been shown to exert some promising effects (64). Using human bone-marrow-derived macrophages, a mouse model of peritonitis induced by intraperitoneal injection of MSU crystals and a gout model induced in rats by intra-articular injection of MSU crystals in the knee, Goldberg et colleagues reported that BHB prevents IL-1β production through the inhibition of the signals that control both the priming and assembly of NLRP3 inflammasome (64).
The beneficial effects of polyphenols in gout has been recently reviewed (102, 103). These plant-derived natural compounds have been shown to modulate multiple inflammatory pathways. In gout, polyphenols may exert a dual role. They act whether on sUA levels by decreasing the activity of xantine oxidase or diminishing inflammation through the inhibition of NF-B transcriptional factor and inflammasome activation. To this regard, a flavonoid (hesperidin) has been tested in articular inflammation induced by MSU crystals in mice demonstrating some effects on hyperalgesia, joint oedema, and recruitment of leukocytes induced by crystals (104). The inhibitory effect of polyphenols on IL-1β production has been confirmed in the animal model by intraperitoneal administration of *Artemisia Princeps* extract, a chlorogenic acid-rich medicinal herb used in Asian countries, before injection of MSU crystals (105).

Clinical evidence

Several clinical studies have focused on the detrimental effects of some dietary components on the risk of gout and progression of disease.
Recent data evaluating the associations of sUA with a genetic risk score, diet and sex, showed that gene-diet interactions are important in determining sUA levels. Dietary factors which have been found to interact with genetic risk to alter sUA levels included legumes (in the overall population), red meat (among women) and vitamin C (among men) (43).
A national cohort study conducted on gout patient profile, demonstrated that patterns of dietary intake are markedly different in men and woman, with a striking difference in the intake of alcohol (men consume greater quantities of alcohol as compared to women). Based on this study, dietary triggers represent more frequently risk factors for men than for women (106).
Among food components that strongly affect uricaemia and that are associated with higher risk to develop gout, a particular attention has been focused on fructose (107). High fructose intake, in fact, causes consumption and degradation of adenosine nucleosides (AMP/ATP hydrolysis) resulting in uric acid accumulation in the circulation. Furthermore, many fructose-induced inflammatory effects have been associated to inflammasome activation (108).
With regards to alcohol consumption, a recent nationwide population-based cohort study revealed a strong association between alcohol-related diseases and alcohol-dependence syndrome and gout occurrence (109). Alcohol has been the most frequent self-reported triggers of acute gout attack by a survey of community-derived people with gout (110).
Accumulating clinical evidence suggests that hyperuricaemia is strongly associated with insulin resistance and abnormal glucose metabolism. Furthermore, higher levels of sUA have been shown to be independently associated with higher blood pressure and hypertension prevalence (111).
Adherence to the DASH (dietary approaches to stop hypertension) diet might contribute to decrease sUA levels (112). This diet essentially promotes the intake of vegetables, fruit, whole grains, nuts, fish, low-fat products, and recommend limiting foods that are high in saturated fat and sugar-sweetened beverages and sweets. In a recent-published large prospective cohort study, the DASH diet has been associated with a lower risk of gout in men with respect to the western diet (113).
The effect on the diminution of sUA levels has been shown to arise within 30 days of diet initiation and is maintained at 90 days (114). The reduction in sUA levels from the DASH diet has been demonstrated to be greater among participants with higher baseline sUA (>6 mg/dL) (115).
As far as the relation between gout and obesity is concerned, a recent study reviewed the effects of weight loss for overweight gout patients in terms of sUA, achieving sUA target and gout attacks.
Although the moderate quality of evidence, this study showed the beneficial effects of weight loss on sUA and gout attacks at medium-term/long-term follow-up, while weight loss from bariatric surgery has shown to increase temporarily sUA levels and gout attacks at short-term (116).
A retrospective study investigating the role of sleeve gastrectomy in reducing the frequency of acute attacks in patients with gout, showed that a low-purine diet had a greater effect on decreasing the sUA levels with compared with a normal-purine diet. Furthermore, the frequency in gouty attacks and allopurinol use were completely abolished after 12 months in the group of patients following a low-purine diet (117). Indeed, reducing protein intake has been shown to be associated with a reduced risk of gout (118).

Pharmacological treatment

Pharmacological treatment of gout is possible: crystal formation may be prevented and reversible, and therefore it can be controlled by reducing sUA levels below the limits of solubility, with a safety threshold of 6 mg/dL (100). However, compliance is crucial for a correct management of gout in clinical practice (100). The EULAR 2016 guidelines state that lowering therapy (ULT) should be considered from the first presentation of gout (the first acute attack), as well as recommended in the presence of recurrent acute attacks, tophi, gouty arthropathy and/or kidney stones and maintained over time (100). At present, xanthine oxidase inhibitors (XOI) – namely allopurinol as first line of therapy and febuxostat as second line of therapy – are recommended as ULTs (29]). They act by inhibiting the production of UA. More recently, Lesinurad (Zurampic®) entered clinical practice (1). This urocosuric agent is an oral selective inhibitor of URAT1 and OAT4 renal transporters, which increases renal UA excretion and lowers sUA levels by inhibiting UA reabsorption. Compared with other uricosuric agents, lesinurad exhibits minimal drug-drug interactions and side effects (119). Current EULAR guidelines recommend a second-line combination therapy with a XOI and a uricosuric agent in gouty patients who do not achieve sUA target with XOI monotherapy, given the complementary mechanism of action of these molecules (100).

Several pieces of evidence on the three above-mentioned molecules have been conducted and finalised in the last year. We present here the most relevant studies on allopurinol, febuxostat and lesinurad in 2017 and 2018.

Allopurinol

Three studies on allopurinol are, in our opinion, particularly worth mentioning. Stamp *et al.* conducted a randomised, controlled trial to determine the efficacy and safety of allopurinol dose escalation using a treat-to-target sUA approach (120). Patients with gout receiving creatinine clearance (CrCL)-based allopurinol dose for ≥1 month and sUA ≥6 mg/dL were randomly assigned to continue current dose (control; n=93) or allopurinol dose escalation for 12 months (n=90): in this latter group, allopurinol was increased monthly until sUA was <6 mg/dL. Mean changes in sUA at the final visit were -0.34 mg/dL in controls and -1.5 mg/dL with dose escalation (p<0.001); 32% of controls and 69% in the dose escalation showed sUA <6 mg/dL. These findings were overall confirmed during the extension phase of this study (121), thus suggesting that about 70% of people with gout, including those with kidney impairment, may achieve and maintain target sUA with allopurinol dose escalation in clinical practice.

Remarkably, a large study by Lin *et al.*, conducted on a Taiwanese National Database (n=8047), showed that treatment with >270 defined daily doses (DDDs) of allopurinol over the follow-up period was associated with a reduced risk of coronary artery disease (CAD), thus confirming the importance of sUA reduction in the management of cardiovascular (CV) risk in gouty patients (122). Indeed, recent evidence further confirms the high CV risk in gouty patients, and stresses the need for a proper estimation of CV risk and the establishment of prevention strategies (123).

Febuxostat

Febuxostat is a well-established second-line therapy for gout. In 2017, a randomised study by Dalbeth *et al.* investigated febuxostat treatment versus placebo on joint damage in 314 hyperuricaemic subjects with early gout (one or two gout flares) (124). Overall, treatment with febuxostat did not lead to any change in joint erosion over a 2-year period. However, treatment with febuxostat significantly improved the synovitis score at month 24 compared with placebo, decreased the overall incidence of gout flares (29.3% *vs.* 41.4%; p<0.05), and improved sUA control (62.8% *vs.* 5.7%; p<0.001).

In a landmark multicentre, randomised, double-blind study, published in the *New England Journal of Medicine*, White *et al.* compared the CV outcomes associated with febuxostat therapy with those associated with allopurinol in gouty patients with concomitant major CV disease (125). The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or unstable angina with urgent revascularisation. At a median follow-up of 32 months, a primary endpoint event occurred in 335 patients (10.8%) with febuxostat and in 321 patients (10.4%) in the allopurinol group (hazard ratio: 1.03; upper limit of the one-sided 98.5% confidence interval [CI]: 1.23; p=0.002 for non-inferiority). However, all-cause and cardiovascular mortality were higher with febuxostat (hazard ratio for death from any cause: 1.22 [95% CI: 1.01–1.47]; hazard ratio for CV death: 1.34 [95% CI: 1.03–1.73]). The authors concluded that in patients with gout and major CV concomitant conditions, febuxostat is non-inferior to allopurinol with respect to rates of adverse cardiovascular events; however, all-cause mortality and cardiovascular mortality are higher with febuxostat.

Last, an open-label, phase II trial tested the combination of febuxostat and arhalofenate, an uricosuric agent with anti-flare activity (126), showing that this combination lowered sUA to a greater extent when compared with either drug alone, thus confirming the feasibility of combination-based regimens in the pharmacological treatment of gout.

Lesinurad

At the beginning of 2017, Saag *et al.* published the results of the CLEAR 1 study, a 12-month, multicentre, randomised, double-blind, placebo-controlled phase III trial, conducted to investigate lesinurad (200 or 400 mg/day orally) added to allopurinol versus allopurinol alone in patients with sUA levels >6.0 mg/dl and previously treated with allopurinol (127). In total, 603 patients were enrolled. Lesinurad at doses of 200 mg or 400 mg added to allopurinol increased the proportions of patients who achieved serum UA target levels by month 6 compared with subjects on allopurinol alone (54.2%, 59.2%, and 27.9%, respectively, p<0.0001), without any relevant safety warning. The authors of that study concluded that lesinurad added to allopurinol provided greater benefit than allopurinol alone in reducing sUA levels and therefore may represent a new treatment option for patients needing additional urate-lowering therapy. These findings were overall replicated in the CLEAR 2 study, with the same design as the previous trial (128). In total, 610 patients were enrolled. Lesinurad at both doses, added to allopurinol, significantly increased proportions of patients achieving sUA target *versus* allopurinol alone by month 6 (55.4%, 66.5% and 23.3%, respectively, $p<0.0001$). At present, lesinurad is marketed at 200 mg/day dose. Lesinurad has also been tested in combination with febuxostat by a phase III randomised clinical trial in patients with tophaceous gout (129). In total, 324 patients with sUA ≥8.0 mg/dl (≥6.0 mg/dl with urate-lowering therapy) and ≥1 measurable target tophus received febuxostat 80 mg/day for 3 weeks before being randomly assigned to either lesinurad (200 or 400 mg/day) or placebo in addition to febuxostat. The primary endpoint was the proportion of patients achieving a sUA level of <5.0 mg/dl by month 6. Overall, significantly more patients achieved the sUA target by month 6 with the addition of lesinurad 400 mg (76.1%; $p<0.0001$), but not 200 mg (56.6%; $p=0.13$), compared with febuxostat monotherapy (46.8%). However, lesinurad 200 mg plus febuxostat was superior to febuxostat alone at all other study visits except month 6 (months 1, 2, 3, 4, 5, 8, 10, and 12, *p*-values ranging from 0.0002 to 0.0281). Notably, in the subgroup of patients with sUA levels >5.0 mg/dl at baseline, following 3 weeks of febuxostat treatment, the proportion of patients who achieved a sUA level <5.0 mg/dl was greater in lesinurad plus febuxostat group than in the febuxostat alone group at all time points assessed (44% *vs*. 24% at 6 months). This result is of particular importance as the subgroup of non-responder patients represents the target population for lesinurad combination therapy with febuxostat. No safety concerns were identified. On these bases, lesinurad in combination with XOI can be considered a very promising option for the treatment of gout in patients not controlled by XOI therapy alone.

Lastly, a 6-month phase III clinical trial followed by an extension phase has investigated the efficacy and safety of lesinurad monotherapy at a dose of 400 mg/day, higher than the one approved for clinical practice in 214 gouty patients who were intolerant to XOI and have sUA levels ≥6.5 mg/dl (130). The primary endpoint was the proportion of patients with sUA <6.0 mg/dl by month 6. Patients who completed the study were eligible for an open-label extension study of lesinurad at the same dosage. Overall, significantly more patients achieved the primary endpoint with lesinurad than placebo (29.9 *vs*. 1.9%; $p<0.0001$). However, treatment-emergent adverse events were higher with lesinurad (77.6 *vs*. 65.4%), particularly at the renal level. During the extension phase, treatment with lesinurad resulted in rapid and sustained sUA lowering that persisted for up to 18 months. No new safety signals were reported during the extension phase.

Conclusion

Although gout can be regarded as the most easily treatable inflammatory arthritis, it is often very poorly managed in clinical practice. Therefore, improved involvement of patients, institution of tailored management strategies and the prompt establishment of treatment – prolonged over the long-term are crucial.

The last year and a half has documented exciting news in the basic knowledge, diagnostic tools, and treatment strategies for gout. We hope that research will further disclosed new pieces of well-grounded evidence, making clinicians more and more capable to assist patients in their long journey with gout.

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