Review

One year in review 2020: gout

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ABSTRACT

Gout is the most prevalent form of inflammatory arthritis, with a strong impact on individual health and healthcare systems. This article reviews clinical and experimental evidences about gout emerged throughout the 2019. Starting with an epidemiological analysis, the review explores new insights on genetic factors influencing the development of gout flare, pathogenetic mechanisms, risk factors for the disease and comorbidities. An overview on pharmacological therapies and recent knowledge on the impact of lifestyle and dietary habits are also included. Finally, the review contains a novel section on animal models, which reflects the renewed interest of researchers in the acute process triggered by monosodium urate crystals.

Introduction

The interest toward gout and hyperuricaemia has been increasing over the last years, probably in parallel with the evidences that have emerged from epidemiological studies, but also reflecting the increase of the categories of researchers attracted by these two conditions, which are ideal fields of translational medicine. Compared to the previous article (1), this one year in review 2020 includes a new section on animal models, which reflect the great interest that the inflammation caused by monosodium urate (MSU) crystals has stimulated in laboratory research.

However, despite their high quality, the scientific knowledge acquired has only partially improved the behaviour of physicians in daily practice. Thus, the diagnosis and especially the treatment of gout still remain still sub-optimal, and patients with gout continue to be the less adherent to therapies among the large spectrum of those affected by chronic rheumatic diseases (2, 3). To improve this attitude, a number of national and international scientific societies periodically propose new recommendations for both the diagnosis and management of gout, aiming to promote early interventions and to effectively improve adherence to therapies.

Epidemiology

Gout is the most prevalent form of inflammatory arthritis globally, with a strong impact on individual health and healthcare systems.

Recent analyses have reinforced the knowledge about the temporal and spatial variation of the occurrence of gout. A systematic analysis of the Global Burden of Disease Study confirmed the well-known geographical heterogeneity of gout prevalence, with a global age-standardised prevalence rates of 0.79% and 0.25% in 2017 in males and females, respectively (4). Of note, global trends of increasing prevalence and impact over time indicate a significant annual percent increase in age-standardised prevalence (males, 0.22%; females, 0.38%) and disability-adjusted life-years (males, 0.21%; females, 0.38%) for every year from 1990 to 2017. Such spatial and temporal heterogeneity is mainly explained by the variation in risk factor distributions, particularly obesity, suggesting that the possibility to interfere with this risk factor remains an unmet need in gout prevention.

The impact on healthcare systems is also rising, in contrast to what happens for hospitalisations in general. An ecological study performed using administrative databased in the UK from 2006 to 2017 demonstrated a strong increase in unplanned admissions for gout (+58.4%) over the study period, compared to an equally strong decrease (-50%) in admissions for RA in the same period (5).

Gout is associated with an excess of mortality, mainly due to cardiovascu-

Table I. Summary of the most important genes implicated in gout and hyperuricaemia identified in 2019.

Gene	Encoded protein	Function	Variants associated with gout and hyperuricaemia	ref.
ABCG2	ABCG2	Encode a xenobiotic and high-capacity urate membrane transporter expressed in the kidney, liver and gut.	rs2231142 (Q141K) rs372192400 (R147W) rs753759474) (T153M) rs752626614 (F373C) rs199854112 (T421A) rs769734146 (T434M) S476P rs750972998 (K360del) rs200894058 (S572R) rs34783571 (D620N) rs2231142 (V12M) rs72552713 (Q126*) rs4148155	8,12,19,20,23 18 18 18 18,19 18,19 18 18,19 18 18 19,23 21 12
CNTN5	Contactin 5	Member of the contactin family, which mediates cell surface interactions during the development of the nervous system.	rs7927466	7
HNF1A	HNF1 Homeobox A	Encode a transcription factor with strong expression in the liver, gut and kidney.	nd	11 15
HNF4A	Hepatocyte Nuclear Factor 4 Alpha	Encode a nuclear receptor and transcription factor that controls expression of many genes, including HNF1A and other overlapping target genes. Play a role in hepatic gluco-neogenesis and lipid metabolism	rs6031598 nd	9 11
LDHD	lactate dehydrogenase D	Involved in D-lactate, but not L-lactate catabolic process.	R370W	24
LINC01229	Long Intergenic Non-Protein Coding RNA 1229	Control of protein-coding gene expression.	nd	11
LINC01578	Long Intergenic Non-Protein Coding RNA 1578	Control of protein-coding gene expression.	rs8024067	9
MAFTRR	MAF Transcriptional Regulator RNA	Regulator of the development and differentiation of many organs and tissues, including the kidney	nd	11
MIR302F		microRNA deregulated in gastric cancer	rs9952962	7
MXD3-LMAN2	MAX dimerisation protein 3	Promote uncontrolled cell proliferation and tumorigenesis	rs11952102	9
NAP1L5	Nucleosome Assembly Protein 1 Like 5		Nucleosome assembly factor nd	12
NUDT9	Nudix hydrolase 9	ADP-ribose pyrophosphatase that catalyzes the hydrolysis of ADP-ribose to AMP and ribose-5-P	nd	12
PDZK1	PDZ domain containing 1	A scaffold protein that connects plasma membrane proteins and regulatory components, regulating their surface expression in epithelial cells apical domains. Coordinate regulatory processes for ion transport and second messenger cascades.	rs1471633	8
PKD2	Polycystin 2	Calcium permeable cation channel involved in calcium transport and signaling in renal epithelial cells.	nd	12
PNPLA3	Patatin Like Phospholipase Domain Containing 3	Mediate triacylglycerol hydrolysis in adipocyte	rs738409	9,10
PSORS1C1-PSORS1C2	Psoriasis Susceptibility 1 Candidate 1-2	Implicated in synovial inflammation and bone destruction in rheumatoid arthritis	rs16898823	9
SESN2	Sestrin 2	Regulate cell growth and survival and involved in cellular response to different stress conditions	rs74896528	9
SLC22A12	URAT1	Urate-anion exchanger expressed mainly in the kidney and localised in epithelial cells of the proximal tubule in the renal cortex	rs11231825 (H142H) rs505802	21 17
SLC22A13	OAT10	Urate reabsorption transporter on the apical side of the renal proximal tubular cells	rs117371763 (R377W)	16

Gene	Encoded protein	Function	Variants associated with gout and hyperuricaemia	ref.
SLC28A2	Solute Carrier Family 28 Member 2	Sodium-dependent and purine-selective transporter in kidney and other tissues.	rs2271437 rs16941238	22 22
SLC2A9	GLUT9	Urate transporter, which play a role in the urate reabsorption by proximal tubules	rs11942223	8
TM4SF4	Intestinal and Liver Tetraspan Membrane protein	Regulate the adhesive and proliferative status of intestinal epithelial cells and mediate density-dependent cell proliferation.	rs6774054	9
TMEM18	Transmembrane protein 18	Transcription repressor. Play a role in the central control of appetite and body weight regulation	rs10188118	9
ZNF724	Zinc Finger protein 724	Involved in transcriptional regulation.	rs12980365	7

nd: not discriminated.

lar (CV) causes. A population-based retrospective cohort study in Sweden compared the causes of death of 19,497 incident gout patients with matched controls (6). This study found that the overall excess of mortality of 23% and 15% in men and women was only partially explained by an increase in CVD (relative increase in mortality per cause 27%), but also by renal disease (78%), diseases of the digestive system (56%) and infections (20%), with a lower probability of dementia (-17%).

Genetics

Recently, there has been a growing interest in the genetic factors influencing the development of gout flare from the hyperuricaemic state, with a focus on identifying the genes involved in initiating the inflammatory response to MSU crystals (Table I).

Researchers have identified two genetic loci (in *CNTN5* and *MIR302F*) and one potential locus (in *ZNF724*) associated with progression from hyperuricaemia to gout. The first-of-its-kind genome-wide association study (GWAS) compared patients with gout to individuals with asymptomatic hyperuricaemia, rather than patients with gout to normouricaemic individuals (as has been done in previous GWAS), to identify loci that influence the transition from hyperuricaemia to gout. Comparisons with results from previous GWAS suggested the existence of distinct mechanisms during the normouricaemia-to-hyperuricaemia and hyperuricaemia-to-gout transitions (7).

The role of serum urate in gout pathogenesis has focused interest on identifying genes implicated in the control of urate levels and fractional excretion of uric acid (FEUA), primarily by GWAS. In line with previous works – summarised in (3) – many of the identified loci include genes encoding renal and gut urate transporters. In people of New Zealand European ancestry, Narang reported effects of *SLC2A9* rs11942223 on FEUA variance, but not in the population of Polynesian ancestry (8). In a GWAS meta-analysis of Japanese subjects, Nakatochi *et al*. (9) identified eight novel loci associated with SUA: rs738409 of *PNPLA3* and rs74896528 of *SESN2* that were predicted to impair the function of the encoded proteins; *TMEM18* rs10188118, *TM4SF4* rs6774054, *MXD3-LMAN2* rs11952102, *PSORS1C1-PSORS1C2* rs16898823 and *HNF4A* rs6031598 that were related to cell metabolism or oxidative stress; and the unknown *LINC01578* rs8024067. *PNPLA3* risk allele (rs738409) was also reported inversely associated with gout in a phenome-wide association study (PheWAS) on non-alcoholic fatty liver disease (NAFLD) (10)

Leask and colleagues provided evidence that two prominent urate-association signals (SUA1 and SUA2) and MAF constitute a functional genomic regulatory domain that contributes to serum urate regulation (11). SUA1 and SUA2 are conserved between GWAS in European and Japanese sample sets and can be modulated by serum urate-associated variants. SUA1 variants alter the expression of *MAFTRR*, *LINC01229* and urate-relevant genes in *trans*. SUA2 rs4077450 and rs4077451 mark an enhancer element that functionally connects with LINC01229 and MAFTRR expression and recruit the transcription factor HNF4α.

Among Han Chinese residing in the Taiwanese population, novel loci have been reported in a recent GWAS by Lee *et al*. (12). Both *ABCG2* rs2231142 and rs4148155 were associated with gout due to the linkage disequilibrium. The authors also identified three genes, significantly associated with the risk of gout (*PKD2*, *NUDT9*, and *NAP1L5*). The latter two were reported for the first time.

Three GWAS with gout as the primary outcome using the UK Biobank database have also been conducted in recent years. The findings reported by Li and colleagues (13) from PheWAS analyses support a robust association between urate and a group of diseases including gout, hypertensive diseases, heart diseases, and metabolic disorders, due to the pleiotropic effects; however, the causal role of urate is only supported in gout. Gene-sex interactions for gout risk were identified by Narang *et al*. for *ABCG2* (rs2231142) and *PDZK1* (rs1471633), with male predominance of the serum urate-raising alleles (14). Unlike previous reports, the study did not identify sex-specific differences for serum urate in *SLC2A9* variants. The trans-ancestry GWAS meta-analysis by Tin *et al*. (15) reported that 3.5% of the UK Biobanker participants had a risk of gout comparable to a Mendelian disease effect size. Tissue and cell type-

specific enrichment analyses supported that the kidney and liver are the main target organs.

Comprehensive fine-mapping and colocalisation analyses identified potentially causal genes and variants, including *HNF1A* and *HNF4A*. The latter can transactivate transcription of *ABCG2* in a kidney cell line.

Accumulating evidence suggests that functional variants of already-characterised urate transporters affect SUA levels and susceptibility of gout.

In a Japanese cohort, the dysfunctional variant R377C (rs117371763) of organic anion transporter 10 (OAT10), encoded by *SLC22A13* gene, was found to be significantly associated with gout susceptibility and physiologically involved in supplying urate to the blood (16).

A Japanese study reported that the GG genotype of rs505802 in *SLC22A12* gene encoding URAT1 is independently associated with increased mortality via a mechanism unrelated to serum uric acid levels (17).

Among the urate transporters, the ABCG2 locus has demonstrated the strongest association with gout. A Czech study in a European gout/hyperuricaemia cohort examined nine rare exonic non-synonymous variants of *ABCG2*: R147W (rs372192400), T153M (rs753759474), F373C (rs752626614), T421A (rs199854112), T434M (rs769734146), S476P (not annotated), S572R (rs200894058), D620N (rs34783571), and a three-base deletion K360del (rs750972998) (18). Functional studies revealed that six of these rare variants were less functional or null. In the paediatric-onset cohort of Czech hyperuricaemic or gouty patients, two common non-synonymous variants (rs2231137 (V12M), rs2231142 (Q141K)) and three rare heterozygous non-synonymous variants (in-frame deletion rs750972998 (K360del), missense variant rs199854112 (T421A), and rs769734146 (T434M)) in *ABCG2* gene were detected (19). The ABCG2 dysfunction was a strong independent risk for paediatric-onset hyperuricaemia and/or gout.

Dysfunction in ABCG2 protein is particularly frequent in Caucasian population, mainly caused by the Q141K variant (rs2231142). Horváthová and colleagues reported that homozygotes for Q141K were younger hyperuricaemic and/or gout individuals, with earlier disease onset, lower BMI and C-reactive protein level, but a higher glomerular filtration rate (20). No association was observed with cytokine levels in the circulation.

In the Vietnamese population, polymorphisms in *ABCG2* and *SLC22A12* genes (rs72552713 and rs11231825) were likely associated with gout and serum uric acid and the T allele in both variants was associated with an increased risk of gout (21).

Zhou and colleagues' findings supported the associations of the *SLC28A2* gene with the SUA level, the hyperuricaemic phenotype and gout in Han Chinese patients (22). The intron variant rs16941238 showed the most significant associations with SUA level and hyperuricaemia and the exonic variant rs2271437 was significantly associated with gout. In the same population, it has been observed that *ABCG2* rs2231142 (V12M) may predict the risk of specific kidney comorbidities for primary gout patients in the male population, but not the allopurinol response (23).

A linkage analysis performed in a Bedouin-Israeli family affected by autosomal recessive gout with hyperuricaemia identified as disease causative a single homozygous variant R370W in *LDHD* gene, encoding d-lactate dehydrogenase (24). This result suggested that elevated levels of d-lactate could play a role in the exchange for uric acid reabsorption culminated in hyperuricaemia and gout.

In view of the autoinflammatory nature of the disease, Salehzadeh *et al*. investigated any correlation between *MEFV* gene mutations and gouty arthritis (25); however, the study did not provide asupport for a major role of *MEFV* mutation.

Epigenetic regulation

Since a possible mechanism for the development of gout involves the dopaminergic system (26), an epigenetic mechanism of the major enzyme of catecholamine neurotransmitters (COMT) in gout was described (27). The authors showed that *COMT* methylation levels were significantly lower in gout patients than in controls and correlate with the risk of gout in males.

Epigenetic modifiers appear to be linked to the MSU-induced inflammatory response in gout. In a recent study, Cleophas *et al*. showed that romidepsin, a histone deacetylase (HDAC) 1/2 inhibitor, decreased *in vitro* cytokine production in response to MSU crystal stimulation (28). HDAC inhibition by romidepsin controlled inflammation by increasing the expression of SOCS1, targeting inflammatory molecules for proteasomal degradation.

Pathogenetic mechanisms

In the last year, several new studies have been performed to advance knowledge in the molecules and mechanisms underlying MSU crystal-induced inflammation (Fig. 1).

NLRP3 inflammasome pathway activation

A prerequisite for gout development is hyperuricaemia that can promote MSU crystal formation and deposit. It is known that urate crystal formation induces inflammation by activation of different pathways, and in particular of the NLRP3 inflammasome. A recent interesting study demonstrated that in the presence of high urate concentration, human cartilage homogenates increase MSU crystallisation, promoting the formation of smaller crystals (29).

It has been suggested that also the liquid form at high concentrations can contribute to innate immune activation acting as a DAMP, through a priming effect and induces pro-inflammatory cytokine production (30). In contrast with the latter hypothesis, it has been reported that MSU crystals, but not uric acid, induces mRNA expression and release of pro-inflammatory cytokines, including IL-1β, in human whole blood cultures (31); thus suggesting that urate crystallisation elicits pro-inflammatory response and is essential for NLRP3 signalling activation. In agreement with this, some studies have evidenced that, even though stimulation of human monocytes with soluble uric acid increased the production of reactive oxygen species (ROS), this is not asso-

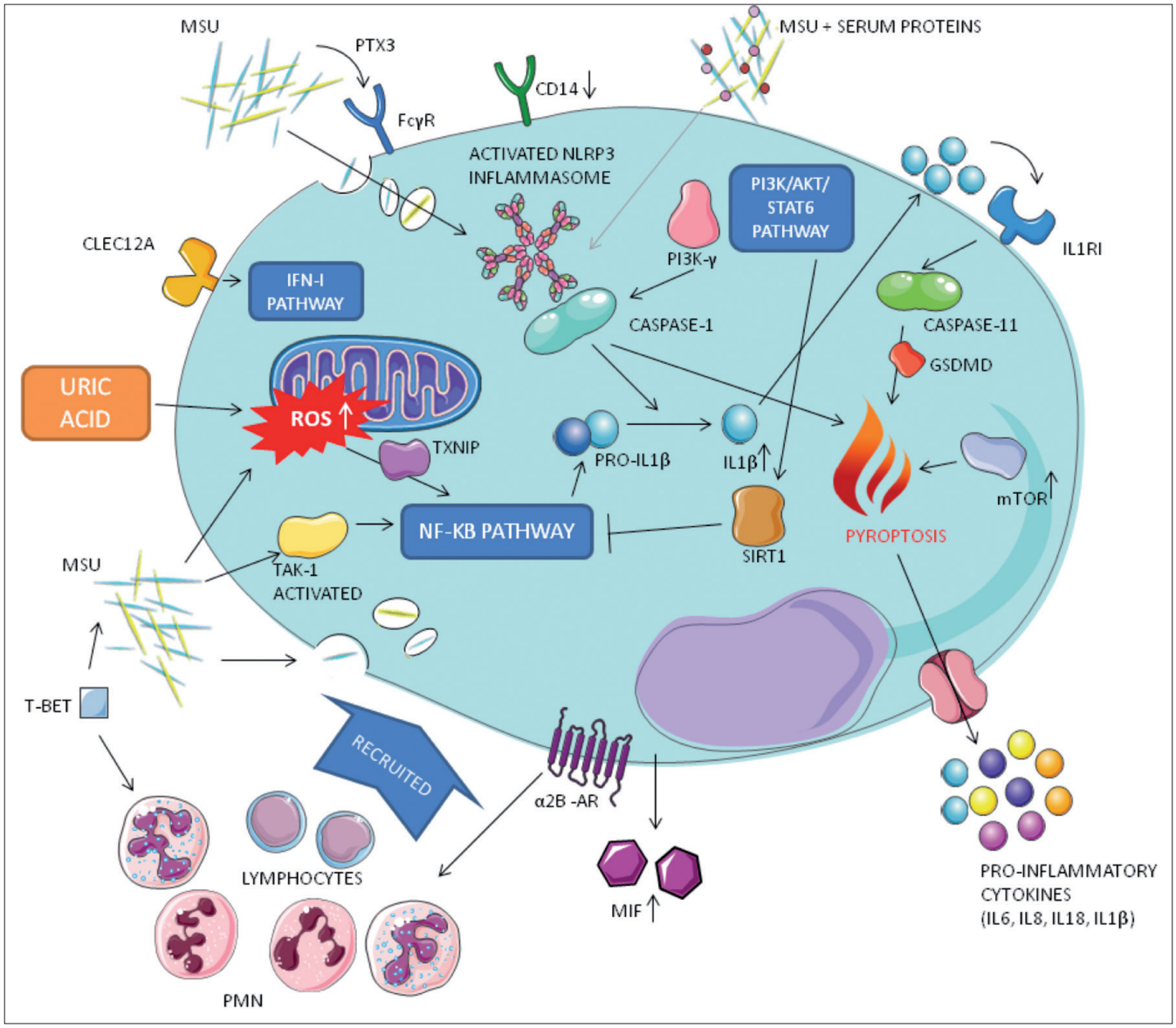

Fig. 1. New insights into mechanisms underlying MSU crystal-induced inflammation.
AKT: protein kinase B; α2B-AR: α2B-adrenergic receptor; CLEC12A: C-type lectin domain family 12 member A; FcγR: Fc-gamma receptor; GSDMD: gasdermin D; IFN-I: type I interferon; IL: interleukin; IL1R1: interleukin 1 receptor type I; MIF: macrophage migration inhibitory factor; MSU: monosodium urate crystals; mTOR: mammalian target of rapamycin; NF-κB: nuclear factor kappa B; NLRP3: NACHT-LRRPYD-containing protein-3; PI3K: phosphoinositide 3-kinase; PMN: polymorphonuclear cells; PTX3: pentraxin 3; ROS: reactive oxygen species; SIRT1: sirtuin 1; STAT6: signal transducer and activator of transcription 6; T-bet: T-box expressed in T cells; TAK1: tumour growth factor-β(TGF-β)-activated kinase 1; TXNIP: thioredoxin-interacting protein. This figure was created using Servier Medical Art images, licensed under a Creative Commons.

ciated with changes in NLRP3 inflammasome component expression and IL-1β production (32, 33). Therefore, other factors may be involved in these processes.

In different studies, the ROS-NLRP3 inflammasome axis was shown to play a role in MSU crystal-induced inflammatory response but the precise mechanism remains unknown. In this context, it has been demonstrated that the interaction of thioredoxin-interacting protein (TXNIP), a modulator of cellular redox state, and NLRP3 inflammasome through intracellular translocation of TXNIP from the nucleus to mitochondria leads to the activation of NF-κB signalling (34).

Another study evidences that NLRP3 dependent IL-1β release is regulated by PI3Kγ-induced caspase-1 activation. In fact, absence or inhibition of PI3Kγ reduced IL-1β levels, neutrophil recruitment and articular hypernociception after injection of MSU crystals in the tibiofemoral joint of wild type mice (35).

Then, caspase-1 activation with the subsequent release of IL-1β may induce the expression of caspase-11 in an IL-1 receptor manner in macrophages, thus promoting neutrophil directional trafficking and neutrophil extracellular trap (NET) formation during the acute phase (36).

Recently, it has been reported that activation of both caspase-1 and caspase-11 induces pyroptosis via Gasdermin D (GSDMD), a protein which is able to generate membrane pores, allowing the

release of intracellular contents. An *in vitro* study demonstrates that GSDMD is rapidly activated by MSU crystals in murine macrophages but is dispensable for IL-1β release and cell death. Indeed, even though cleavage of GSDMD into its active pore-forming N-domain was detected in both cell lysate and supernatant after MSU crystal stimulation, GSDMD genetic deletion had no impact on IL-1β secretion, propidiumiodide (PI) uptake and lactate dehydrogenase (LDH) release (37).

Alternative pathway activation and cell involvement

It is known that pyroptosis and inflammation are also partially regulated by the mammalian target of Rapamycin (mTOR). An *ex vivo* study demonstrates that peripheral blood mononuclear cells from patients with gout have high expression of mTOR pathway, and monocytes are the most prominent expressers. These observations are accompanied by *in vitro* experiments showing MSU crystal-induced upregulation of mTOR pathways gene expression, IL-1β, IL-6, IL-8, IL-18 release and cell death in monocytes, which are reduced in the presence of mTOR inhibitors rapamicyn and metformin (38).

Monocytes have also been shown to increase the production of macrophage migration inhibitory factor (MIF) after stimulation with MSU crystals *in vitro*. MIF is a proinflammatory, chemotactic and destructive cytokine that induces neutrophil recruitment in gouty joints (39).

Instead, *in vitro* stimulation of macrophages reveals that MSU crystals may arrest tumour growth factor-β (TGF-β)-activated kinase 1 (TAK1) in an active state conformation that results in a sustained protein activation and identifies a role of TAK1 in this type of inflammation (40).

In addition, in-depth immunophenotyping was used to identify circulating Treg (defined as $CD4^+CD25^+Foxp3^+$), Th17 (defined as $CD4^+IL\text{-}17^+$) cells and joint-infiltrated inflammatory monocytes (defined as $B220^-GR1^{high}F480^{high-}CD115^+$) in a mouse model of gouty inflammation (41).

Phagocytosis

Synoviocytes may also participate in the activation of inflammatory processes induced by MSU crystals. It has been hypothesised that crystal uptake through phagocytosis may induce morphostructural changes in synoviocytes and formation of secretory vesicles containing IL-6, TNF-α, IL-8, CCL2, nerve growth factor (NGF) and hepatocyte growth factor (HGF). Moreover, IL-β production enhances in a time-dependent manner and may be associated with the time in which phagocytosis increases (42).

Interestingly, phagocytosis seems to be facilitated by pentraxin 3 (PTX3), an acute phase protein which increases in the plasma and synovial fluid of patients with acute gout and in periarticular tissues of mice after injection of MSU crystals. Indeed, *in vitro* treatment of monocytes with PTX3 promotes MSU crystal phagocytosis via the pentraxin receptor FcγR and results in an increase in caspase-1 activation and IL-1β production (43).

In parallel, phagocytosis has also been shown to be regulated by transcription factor T-bet, a cell transcription factor which plays a role in adaptive and innate immune systems. Experiments in different *in vivo* gout models evidence that T-bet deficiency reduces MSU crystal phagocytosis, leukocyte recruitment, IL-1β, IL-17 and IL-23 levels and mice paw swelling (44).

Receptors

Other than phagocytosis and NLRP3 activation, the engagement of specific receptors also may take a part in the MSU crystal-induced inflammatory reaction. A recent study in neutrophils identified a potential role of the α2B-adrenergic receptor (α_{2B}-AR) in the recruitment of this type of cell. Using α_{2B}-AR-overexpressing mice, increased neutrophil infiltration after MSU crystal intraperitoneal injection and an enhanced migratory ability of the same cells in *in vitro* experiments are observed. In contrast, α_{2B}-AR overexpression does not affect IL-1β production by macrophages (45).

The opposite effects on MSU crystal-mediated inflammatory reaction has been demonstrated by the involvement of inhibitory receptors, such as Clec12A. This is a C-type lectin receptor for the detection of cell death that limits pro-inflammatory pathways induced by MSU crystals (46). Additionally, it was found that Clec12A amplifies type I interferon (IFN-I) responses *in vitro* and *in vivo*, thus enhancing protective immunity during DAMP-sensing and sterile inflammation (47).

It is known that inhibitory mechanisms contribute to the processes of inflammatory resolution that occur spontaneously in gout, and are, at least in part, associated to downregulation of specific proteins. CD14, a glycosylphosphatidylinositol (GPI)-anchored receptor that plays a pivotal role for MSU crystal uptake, caspase-1 activation, and IL-1β production, is reduced in mRNA and protein levels in PBMC from both gout patients and healthy volunteers after stimulation with MSU crystals (48).

Spontaneous resolution

Many other mechanisms have been proposed to explain the self-limiting nature of gout attack. For instance, modification of protein coating on the crystal surface has been largely studied by several authors in the literature. Recently, *in vitro* experiments using primary macrophages and THP1 monocytes have shown that adsorption of serum proteins and BSA on MSU crystals reduces their capacity to induce IL-1β and ATP secretions, and disturbance of mitochondrial membrane depolarisation activation (49).

Finally, amelioration of MSU crystal-induced inflammation response by Sirt1 activation was observed in a murine gout model. Sirt1 is a member of the sirtuin family that mediates deacetylation of many target proteins suppressing inflammatory processes. In gouty mice, Sirt1 attenuates the tendency of macrophages to polarise toward the pro-inflammatory M1 phenotype via the PI3K/Akt/STAT6 pathway (50).

Experimental models

Compared to other inflammatory diseases, few animal models of human gout are currently in use and among them, rodent models are preferred in order to

investigate pathogenesis and to test efficacy of new compounds in preclinical studies for new therapies (Table II).

Rodents do not develop gout spontaneously and have lower serum urate concentration than humans. This is due to the presence of uricase enzyme in the liver which degrades urate in allantoin, further excreted at renal level. Two main strategies are used to reproduce gout in mice or rats: the genetic modification of animals to obtain mice knocked out for one or more molecular component involved in gouty inflammatory pathways, or the injection of exogenous MSU crystals to induce a condition resembling a human gout attack. While MSU-induced experimental gout-like inflammation is very useful to test the efficacy of new compounds in preclinical studies, genetically modified murine strains are utilised to dissect gene expression involved in gouty disease.

The acute gout model is generated by injecting MSU crystals into the hind legs. Injection of MSU crystals can be performed sub-cutaneously under the plantar surface, or intra-articularly in the ankle or knee in the tibio-femoral cavity (41). After a few hours, MSU treatment induces assessable swelling and oedema at the site of injection that generally is self-limiting and resolves within 48-72 hours from induction.

The air pouch model of gout and crystal-induced peritonitis are experimental models that mimic gout without the involvement of joint tissues (51). The first resembles morphologically the joint synovial cavity and is induced by injecting MSU crystals in a pouch previously generated by insufflating sterile air subcutaneously in the dorsum of the mouse, whereas crystal-induced peritonitis is induced by the injection of MSU crystals directly into the peritoneal cavity (45). The activation of the NOD-like receptor NLRP3 and the assembly of inflammasome with a rapid increase of IL-1β occur in all animal models of gout developed using exogenous MSU crystals. The massive expression of pro-inflammatory cytokines such as CXCl-1, CXCL-2, IL-6, TNF-α, the activation of resident macrophages at the site of injection and massive neutrophil recruitment in a dose-dependent manner accurately reproduces the inflammatory scenario of gout flare in human patients (52, 53).

As regards hyperuricaemic mice, several models are available but none of these can reproduce an arthritic gout attack or induce deposition of MSU crystals at joint level (54, 55). The main issue with these mice is related to the shortened life span and viability due to early and massive deposition of urate crystals in the kidney with subsequent severe nephropathy and renal failure (56)

Over the past years, few genetically modified rodent strains have been developed to dissect gene expression involved in gout.

Caution and collagues, knocking out *caspase 11* gene in mice, showed the absence of macrophages activation and neutrophilic extracellular traps formation in joint tissues after MSU injection. Furthermore, in the absence of caspase 11, almost every pro-inflammatory cytokine usually involved in gout was unexpressed. These observations highlight caspase 11 as a prospective therapeutical target for gout (57).

Sirt-1 is a nicotine adenine dinucleotide dependent deacetylase involved in the normal tissue turnover. Observing an elevated expression of SIRT-1 in PBMCs of patients with acute gout but not in presence of tophi or chronic synovitis, Liu and colleagues injected MSU crystals in the knee of mice *SIRT-1* $^{+/-}$ and observed a more severe form of arthritis than in WT. Interestingly, *SIRT-1* $^{+/-}$ are more gout-prone mice due to impaired M2 polarisation of macrophages that indicates that SIRT-1, activating the PI3K/Akt/STAT6 pathway, may play a pivotal role in self-limiting inflammation typical of gout attack (50).

Obesity, chronic kidney disease, hypertension, type 2 diabetes, dyslipidaemia are risk factors that can increase the incidence of gout. Despite the impact of concomitant diseases, no *in vivo* experimental models have been developed that allow investigation into the role of co-morbidities in gout.

Only recently and in order to investigate the role of leptin, a cytokine-like hormone with a key role in regulating satiety and hunger as a cross-link between gout and obesity, it was described how the obese mouse strain B6 $^{ob/ob}$, knocked out for leptin, is protected with respect wild type mice, when treated with MSU crystals in the footpad. Instead, the administration of leptin in mice knocked out for this regulative factor reverted this condition, inducing strong joint involvement, activating NLRP3 and enhancing the expression of IL-1β and IL-6 (58).

Uro knockdown flies represent the first model of gout and hyperuricaemia-related diseases established in *Drosophila Melanogaster.* The model is based on the reduced expression of *Uro* gene, the orthologue of the urate oxidase gene in humans and primates. *Uro* knockdown flies have elevated uric acid in haemolymph and spontaneous deposition of MSU in several tissues. Interestingly, urate deposition can be modulated by different dietary conditions and is strictly dependent on the insulin-like signalling pathway (59).

In conclusion, although questionable, animal models of gout remain an irreplaceable research tool to understand the pathogenesis of gout and, the recent development of experimental gout in flies could amplify the usefulness of *in vivo* studies in gout and crystal-induced inflammation related diseases.

Gout risk factors and comorbidities

Important progress has been made in recent years in understanding risk factors for gout, in particular, the importance of obesity, lifestyle factors, comorbidities and iatrogenic factors. However, some novelties have emerged from the literature also for classical risk factors and comorbidities.

Among dietary factors, sugar-sweetened beverages (SSBs) are associated with hyperuricaemia and gout. A meta-analysis focused on the potential impact of other important food sources of fructose-containing sugars on the risk of incident gout and hyperuricaemia (60). The meta-analysis included 3 prospective cohort studies and showed a positive association between fruit juice (RR=1.77, 95% CI 1.20–2.61; very low certainty) and SSB (RR=2.08, 95% CI 1.40–3.08; moderate certainty), while there was no significant as-

Table II. Preclinical studies of efficacy tested in gout animal models.

Substance	Model	Actions	ref.
Luteolin and Luteolin-4'-O'-Glucoside	mouse, injection of MSU crystals in the foot pad	IL-1 β, TNF-α, NALP3, ↓	98
Oridonin	WT and NALP3 KO mouse, MSU-induced peritonitis and knee arthritis	arthritis, IL-1β ↓	99
Epigallocatechin-3-gallate (EGCG)	mouse, injection of MSU crystals in the foot pad	NALP3 ↓	100
Rhizoma smilacis glabrae extract	mouse, MSU crystal injection in the ankle	arthritis, IL-1β ↓	101
Puerariae lobatae Radix carbon dots	mouse, MSU crystal injection in the knee	arthritis, IL-1β ↓	102
Y-27632	mouse, MSU crystal-induced peritonitis	Rho-associated kinase (ROCK) activity _	103
Salidroside	mouse, MSU crystal injection in the knee	COX 2 ↓	104
Extract of Taiwanese green propolis	mouse, MSU crystal-induced peritonitis	NLRP3 and IL-1β precursor (pro-IL-1β) ↓	105
Resveratrol	mouse, MSU crystal injection in the knee	TAK-1, NFkB pathway ↓	106
Inhibitors of PI3K-γ (AS605240) or PI3Kδ (GSK045)	mouse, MSU crystal injection in the knee	myeloperoxidase activity, IL-1β↓	107
Recombinant IL-33	mouse, MSU crystal-induced peritonitis	IL-1β ↓	108
Madecassoside	DBA1 diabetic mouse, MSU crystal-induced peritonitis and injection in the knee	IL-1 β, IL-6 TNF-α, NALP3 ↓	109
Chrysanthemum indicum extract	mouse, MSU crystal-induced peritonitis	pro-inflammatory cytokines, neutrophils recruitment↓	110
LV-sFRP2-shRNA	mouse, MSU crystal injection in the knee	L4 and L5 dorsal root ganglio neurostimulation ↓, pain ↓	111
IL-17A Neutralising Antibody	mouse, MSU crystal injection in the knee	leukocyte infiltration↓ pro-inflammatory cytokines↓	112
Artemisinin	mouse, injection of MSU crystals in the foot pad and ankle	IL-1 β, IL-6 TNF-α, NALP3, NFkB ↓	113
Sirt1 agonist (Resveratrol) and peroxisome proliferator-activated receptor γ (PPARγ) inhibitor (T0070907)	mouse, injection of MSU crystals in the foot pad	leukocyte infiltration, pro-inflammatory cytokines↓	114
Curcumin	mouse, injection of MSU crystals in the foot pad and ankle	inflammation, mitochondrial damage ↓	115
N-Butyrylated hyaluronic acid	rat, MSU crystal injection in the knee	IL-1β, IL-8, IFN-γ, joint swelling ↓	116
Pulchinenoside b4	rat, MSU crystal injection in the knee	arachidonic acid, sphingolipid, glycerophospholipid, arthritis ↓	117

sociation between fruit intake and gout (RR 0.85, 95% CI 0.63–1.14; (very low certainty).

Although gout is strongly associated with CVD, it is not clear whether treating gout to target (sUA <6mg/dl or <0.36 mmol/L) modifies the CV risk of these patients. An observational study from Spain included 1,193 patients with gout and analysed the crude and adjusted relationship between failing to achieve the target and mortality (61). After adjustment for age, sex, CV risk factors, previous CV events, observation period and baseline sUA concentration, a sUA of ≥0.36 mmol/L was associated with elevated overall mortality (HR=2.33, 95% CI 1.60–3.41) and CV mortality (HR=2.05, 95% CI 1.21–3.45). This study support sULT as a potential modifier of the increased risk of CVD morbidity and mortality in patients with hyperuricaemia of gout.

Another classical association between gout and renal diseases is still matter of debate, particularly for the reciprocal relationship between chronic kidney disease (CKD) and hyperuricaemia *versus* renal damage due to hyperuricaemia. A retrospective matched cohort study, including 68,897 patients with gout and matched controls from the UK, showed that patients with gout had an increased risk of developing advanced CKD, including end-stage renal disease (adjHR 1.29; 95% CI 1.23–1.35; and adjHR, 2.13 95% CI 1.73–2.6, respectively) (62). However, whether controlling gout is protective against CKD progression in gout remains to be demonstrated.

Novel gout-associated comorbidities

Several new comorbid associations of gout have been described in recent years. Beyond the established association between gout and CVD, evidence has emerged that gout increases the risk of other vascular and non-vascular disorders.

Previous studies found association between gout with an increased risk of development of atrial fibrillation (AF),

Table III. Novel candidate associations between comorbidities and gout.

Author	Country	Study design	Participants	Comorbidity	Key results
Li (7)	China	Prospective cohort	123,238	Atrial fibrillation	1st quintile: 1 (reference) 5th quintile: adjHR 1.91 (1.32–2.76)
Sultan (8)	UK	Retrospective matched cohort (1:1)	62,234 gout 62,234 controls	Venous thromboembolism (VTE)	adjHR 1.25 (1.15–1.35)
Blagojevic-Bucknall (9)	UK	Retrospective matched cohort (1:4)	15,879 OSA 63,296 controls	Obstructive sleep apnea (OSA)	Overall adjHR 1.42 (1.29-1.56) *By BMI category* Normal: adjHR 1.76 (1.22-2.53) Overweight: adjHR 1.27 (1.06-1.54) Obese: adjHR 1.40 (1.21-1.61)
Luo (10)	UK, USA, Taiwan, Korea	Meta-analysis	355,761 (85,067 with gout)	Erectile dysfunction	Pooled RR 1.20 (1.10 -1.31)
Zong (11)	AUS, China, Korea, Italy, Taiwan, UK, USA	Meta-analysis	909,803	Osteoporosis and fractures	*All studies* Any fracture RR 0.98 (0.85–1.11) Osteoporotic fractures RR 1.02 (0.90–1.14) *Hyperuricaemia subgroup* Any fracture RR 0.80 (0.66–0.96) Osteoporotic fractures RR 0.84 (0.68–1.03) *Gout subgroup* Any fracture RR 1.17 (1.04–1.31) Osteoporotic fractures RR 1.13 (1.00–1.26)
Singh (12)	USA	Retrospective cohort (Medicare)	94,133 with gout >65y rs 1.63 million controls >65 yrs	Parkinson's disease	*Overall* adjHR 1.14 (1.07, 1.21) *By age category* 65–75 adjHR 1.27 (1.16, 1.39) 75–85 adjHR 1.07 (0.97, 1.16) > 85 adjHR 0.97 (0.79, 1.20),
Singh (13)	USA	Retrospective cohort (Medicare)	1.73 million >65 yrs	Giant cell arteritis (GCA)	Gout: adjHR 1.81 (1.55, 2.12)
Singh (14)	USA	Retrospective cohort (Medicare)	1.73 million >65 yrs	Sjogren's syndrome	Gout: adjHR 1.48 (1.25, 1.77)
Xie (15)	N/A	Meta-analysis	8 studies	Cancer	*Overall* RR 1.19 (1.12–1.25) *Stratified by gender* Males: RR = 1.15 (1.06–1.25) Females: RR = 1.29 (1.20–1.40)

probably due to hyperuricaemia and chronic inflammation. A recent cohort study focused on the relationship over time between hyperuricaemia, systemic inflammation (C-reactive protein - CRP) and incidence of atrial fibrillation, including 123,238 patients followed biannually for 6 years (63). The relationship between cumulative average SUA or CRP and the occurrence of AF showed that those subjects with extreme values (highest quintile) of SUA levels had a 91% higher probability of developing AF over time, even after adjusting for several potential confounders (related to demographic characteristics, lifestyles and BMI, comorbidities, treatments). Similar results were obtained for SUA in the subgroup of patients with gout and for CRP in the entire cohort.

Increasing evidence supports an increased occurrence of venous thromboembolism (VTE) in patients with gout. A population-based study from the UK, linking data from CPRD and Hospital Episode Statistics, retrospectively follow up a matched cohort of 62,234 incident gout, assessing the risk of VTE over time (64). A crude increase of 38% of the VTE risk was observed I patients with gout, and an increase of 25% was still significant even after adjusting for sociodemographic factors, comorbidities, medications, and lifestyle factors. The highest risk increase was found in the subgroup of patients with less than 50 years (HR 1.79 (1.30–2.48)). Though the relative increase of the risk does not justify prophylaxis, active surveillance might be helpful.

An association between gout and obstructive sleep apnoea (OSA) has also been demonstrated. The plausibility of such association is related to the relationship between hypoxia and the turnover of nucleotides, increasing the generation of purines, which can lead to hyperuricaemia. A matched cohort study using the UK Clinical Practice Research Datalink (CPRD) data from 1990 to 2015 including 15,879 patients with OSA and 63,296 controls, followed for a mean of 5.8 years, revealed that the OAS is an independent risk factor for gout (65). After adjusting for age, sex, BMI, alcohol consumption,

comorbidities, diuretic use and incident risk of gout was 42% more in a follow-up period of up to 10 years in the UK CPRD. This excess of risk of developing gout in OSA patients was even higher in patients with normal BMI (76%).

Recent studies have shown that gout is associated with an increased risk of erectile dysfunction. A meta-analysis of the published studies from 2010 and 2019, identified 8 studies (3 cross-sectional and 5 cohort studies, 85,067 patients with gout), comparing the risk of erectile dysfunction in patients with gout compared to different control populations (66). The meta-analysis estimates a mean increase of 20% of the probability of having or developing erectile dysfunction in patients with gout.

Several studies have looked at associations between gout and osteoporosis and fractures, with contrasting results. A systematic review and meta-analysis of observational studies investigated the associations of hyperuricaemia, gout, and ULT with the risk of fractures (67). Up to January 2019, 14 eligible studies were included, for a total of 909 803 participants and 64 047 incident fractures. The main meta-analysis suggested that hyperuricaemia and gout are not associated with any type of fracture (relative risk [RR], 0.98, 95% CI 0.85–1.11; p=0.71) or osteoporotic fractures (RR, 1.02, 95% CI 0.90–1.14). Secondary analyses suggested heterogeneity between hyperuricaemia alone and gout, with a marginal increase of the risk in gout and a slight decrease in hyperuricaemia. A further exploratory result showed by meta-regression a U-shaped relationship between sUA and the risk of fracture with the lowest risk in normal values and higher risk both in hypo- and hyperuricaemia.

A cluster of studies on claims databases, including older people in the US, explored the association between gout and three different diseases typical of the elderly: Parkinson's disease, giant cell arteritis and Sjögren's syndrome (68-70). All these analyses showed positive associations ranging from 14% for Parkinson's disease to 81% for giant cell arteritis. In the absence of a strong rationale for these associations, these results, though interesting, require further validation.

Even the association with cancer remains controversial. A meta-analysis including 6 observational studies of patients with gout and controls found a significantly overall increase in cancer risk (RR=1.19; 95% CI, 1.12–1.25), both in males (RR=1.15; 95% CI, 1.06–1.25) and females (RR=1.29; 95% CI, 1.20–1.40) (71). The increased risk was significant for respiratory, digestive, and urinary systems in males and digestive and urinary systems in females. Again, due to the lack of biological plausibility, these results should be taken with caution.

Epidemiological results emphasise the fact that patients with gout hide major medical complexities and the need to improve the assessment and management of a wider spectrum of comorbidities, even beyond joints and cardiovascular system.

Diagnosis and therapy

In an attempt to improve the approach to gout, many scientific societies continue to propose new recommendations and/or guidelines (72-78). As expected, more attention has been dedicated to the management rather than to the diagnosis, in keeping with the assumption that the main problem for the suboptimal approach to gout is the poor adherence to the therapy (79). As regard the diagnosis, in comparison with previous ones, the recent 2018 EULAR recommendations propose new significant suggestions (75). Although the gold standard for the diagnosis is still MSU crystal detection in SF, more consideration is given to the value of clinical aspects, especially when SF analysis is difficult or not feasible (75). Following the advice of EULAR experts, a clinical diagnosis of gout may be supported by the following suggestive features: "monoarticular involvement of a foot (especially the first MTP) or ankle joint; previous similar acute arthritis episodes; rapid onset of severe pain and swelling (at its worst in <24 hours); erythema; male gender and associated cardiovascular diseases and hyperuricaemia". The presence of comorbidities in a diagnostic context underlines the importance of carefully assessing the patient in view of future management.

A new entry as a reliable tool in the diagnostic consideration is ultrasound scanning (US), which allows the detection of characteristic features of gout, such as the double contour (DC) sign at cartilage surfaces, highly specific for urate deposits in joints (80). This technique is now widely accepted in the context of musculoskeletal diseases and offers a number of advantages, including the low cost, the absence of radiation and the possibility to be performed by the same rheumatologist during the visit allowing them, if necessary, to obtain SF from joints difficult to access. Furthermore, US may also be useful to differentiate gout from calcium pyrophosphate deposition disease and to assess bone remodelling and monitor disease responsiveness (81, 82).

The inclusion of US in the very limited list of performing diagnostic tools for gout, in addition to MSU crystal detection in the SF, may come across as an attempt to emphasise the indispensability of specialists, in particular rheumatologists, in the definition of the diagnosis. However, in reality, it should be seen as an opportunity for GPs or non-specialised physicians to obtain a correct diagnosis in most cases, as early as possible.

More extensive and numerous are the new recommendations for the management of gout proposed by different international and national societies. Although some are very different from each other, all strongly share the need to appropriately inform and educate patients and also, between the lines, physicians, assuming that the unfamiliarity with gout is rather common. In keeping with this, a recent Italian survey involving GPs, specialists, pharmacists and patients, found that the insufficient knowledge about the causes of gout was quite similar in all these categories and mainly attributed to the diet (83). Furthermore, the majority of GPs interviewed were unaware of the SUA target in the therapy of gout (83). Accordingly, many studies have demonstrated that the treatment goal is generally reached by less than half patients with gout and only a minority of patients had

Table IV. Significant differences between some relevant national and/or international sets of recommendations for the management of gout.

Recommendation	EULAR 2016	BSR 2017	SIR 2019	SFR 2020	ACR 2020
ACUTE FLARES					
First line therapy	Colchicine NSAIDs Corticosteroids	NSAIDs Colchicine Corticosteroids	Colchicine NSAIDs Corticosteroids	Colchicine NSAIDs Corticosteroids	Colchicine NSAIDs Corticosteroids
Second line therapy	IL-1 inhibitor	IL-1 inhibitor	IL-1 inhibitor	IL-1 inhibitor	IL-1 inhibitor
PROPHYLAXIS					
First line therapy	Colchicine	Colchicine	Colchicine	Colchicine	Colchicine NSAIDs Steroids
Duration	6 months	6 months	6 months	at least 6 months	3-6 months
URATE LOWERING THERAPY					
Gold standard (SUA target level)	<6 mg/dl (360 μm/L)	<5 mg (300 μm/L)	<6 mg/dl (360 μm/L)	<6 mg/dl (360 μm/L) and if possible 5 mg (300 μm/L)	<6 mg/dl (360 μm/L)
Indication for initiating ULT	Recurrent flares, tophi, urate arthropathy, renal stones	Diagnosis of gout	Recurrent flares, tophi, urate arthropathy, renal stones	Diagnosis of gout	≥1 subcutaneous tophi, evidence of radiographic damage attributable to gout; frequent gout flares (≥2 annually)
Close to the diagnosis	Young age (<40 yrs), very high SUA level (>8 mg/dl) (480 μmol/L) and/or comorbidities	Particularly advised in patients with: recurrent attacks (≥2 in 12 months); tophi; chronic gouty arthritis; joint damage; renal impairment; urolithiasis; diuretic therapy use; primary gout starting at young age;	Very high SUA level (>8 mg/dl) (480 μmol/L) and/or comorbidities	Always	Conditionally recommended when comorbid moderate-to-severe CKD, SUA >9 mg/dl or urolithiasis
Commencement during acute phase	Non-specified	Discouraged	Discouraged	Permitted	Recommended
First line ULT	Allopurinol	Allopurinol	Allopurinol	Allopurinol	Allopurinol
Starting dose (mg/day)	100	50-100	100	50-100	100
Maximum dose (mg/day)	800	900	800	ND	800
Second line ULT	Febuxostat	Febuxostat	Febuxostat	Febuxostat	Febuxostat
Uricosurics	In patients resistant or intolerant to XOI (in combination)	In patients resistant or intolerant to XOI (in combination)	In patients resistant or intolerant to XOI (in combination)	Not recommended	Conditionally recommended

EULAR: European League Against Rheumatism; BSR: British Society of Rheumatology; SIR: Italian Society for Rheumatology; SFR: French Society of Rheumatology; ACR: American College of Rheumatology; SUA: serum uric acid; XOI: xanthine oxidase inhibitors; ULT: urate lowering therapy; CKD: chronic kidney disease.

at least one SUA measurement before and after ULT initiation (84, 85). This approach is not surprising since it can also be found in other chronic diseases such as diabetes, hypertension and hyperlipidaemia, and first defined by Lawrence Phillips "clinical inertia". This term seems appropriate to describe what happens in gout and accordingly, it was subsequently adopted to interpret the inadequate approach of GPs to this disease (86-88). In an attempt to improve this poor behaviour, some important national scientific societies, in particular the British Society of Rheumatology (BSR), the French Society of Rheumatology (SFR) and the Italian Society of Rheumatology (SIR) have particularly detailed and subsequently emphasised the major points that GPs and specialists should bear in mind to improve patients' adherence (73, 74, 77). However, as regards other recommendations, the differences between the various guidelines are sometimes relevant and can confuse both patients and physicians (Table II) (89). In fact, even if elaborated by national societies, most recommendations are published in English and generally with open access, thus they are easily available for the patients, who increasingly explore the web to obtain confirmation of what has been said by their doctors. As regards the treatment of acute flares, almost all guidelines recommend that drugs for the first line therapy should be NSAIDs, colchicine or corticosteroids (oral or intra-articular), with the choice depending on patient preference, renal function and comorbidities, while for the prophylaxis, the most indicated is

colchicine. However, in daily practice, it is difficult to assume that a drug suitable for long-time treatment (at least 6 months), should not be the preferred for a much shorter period, such as the acute flare. All guidelines agree on the use of IL-1 inhibitors in second line treatment. Another matter of discrepancy is the opportunity to commence the treatment with ULT during the acute phase of gout. While the EULAR guidelines did not give specific guidance, this is encouraged by ACR (78), permitted by SFR and discouraged by SIR and BSR guidelines (73, 74, 77). As regards the indication for initiating ULT, SFR recommendations clearly and simply state that it should be started when the diagnosis for gout is made (Table I) (77). This is in contrast with almost all other guidelines for which the diagnosis of gout alone is not enough to initiate, since the presence of other elements is required such as the number of recurrent flares, age, SUA levels, renal stones and/or other comorbidities which, in addition, may vary from each other and thus may complicate the approach (Table II) (72-74, 78). There is general agreement for allopurinol as first line and febuxostat as second line ULT, respectively. For both these drugs, is recommended starting at low doses, which will be increased progressively until the treatment goal is reached, having the target levels at 6 mg/dl (360 μmol/L) for almost all guidelines, with the exception of BSR, which indicate 5 mg/dl (300 μmol/L). While almost all documents generically recommend paying attention to renal function, the SFR carefully establish the dose of allopurinol on the basis of eGFR. As regards febuxostat, although most guidelines indicate that it should be in the second line, they suggest considering it in patients with impaired renal function. Another unusual aspect is that uricosurics which are indicated by EULAR, BSR and Italian Society of Rheumatology (SIR) in patients resistant or intolerant to XOI, usually in combination, while they are not recommended for the SFR and are conditionally recommended by the ACR. Furthermore, it should be underlined that availability of uricosurics varies greatly among different countries and in addition, it is increasingly limited (Table II). This may represent another matter of confusion for non-specialists, who, for educational purposes, were taught that reduced excretion of uric acid rather than increased synthesis is mainly responsible for the pathogenesis of hyperuricaemia. In contrast, for therapeutic purposes, it is recommended using the inhibitor of the synthesis when uricosurics are not or are conditionally recommended.

Lifestyle and diet

A remarkable number of research articles have been published throughout 2019 on the role of lifestyle in gout and its management.

It has been recognised that lifestyle influences both the risk of gout and the capacity to control the disease. Indeed, diet and physical activity play a role not just in the diminution of serum uric acid but also insulin resistance, metabolic syndrome and diabetes, which are known to be associated to the disease.

A recent Swedish population study showed that anthropometric measures, including body mass index and waist circumference, are able to predict the incidence of gout (90). This is of particular interest given that the increased inflammation associated with fat tissue further increases the risk of cardiovascular and other metabolic disorders.

In this regard, it has been observed that educational resources for patients offer a potential help for patients to improve their knowledge and manage their disease.

A web-based platform has recently been used in gout patients as a practical and educational tool to improving their knowledge on the disease. This study demonstrated that walking through an interactive website allows patients to identify actionable changes including the decision to continue lifelong urate-lowering therapy, complying with periodic monitoring of serum urate, and making dietary changes (91).

A mobile app for patients with gout has also been applied in an RCT study to examine participant improvements in self-care behaviour (92). This app included information about gout and its causes, lifestyle tips for preventing flares and treatment options. Interestingly, it provided information about common triggers of the disease. This app was compared with a control dietary app developed for hypertension and that educated patients on diet and foods to consume or to avoid. After 2 weeks, participants found the gout app more engaging than the dietary app. Although no difference in self-care was found, the gout app group demonstrated stronger illness perceptions.

These two 2019-published studies underline how working with patients' education might help in gout management and have an impact on flare development.

A recent French prospective cohort study, set up to investigate the features of patients with gout and their management, showed that general practitioners and private-practice rheumatologists usually propose insufficient non-pharmacologic measures for gout management. Furthermore, physicians identified fewer modifiable risk factors of hyperuricaemia than those actually present in their patients, revealing their poor knowledge about recognised international recommendations on gout (93). Another interesting aspect of this study concerns the identification of different patient compliance profiles that could help physicians to personalise the management of patients with gout.

As far as new investigations on the role of diet in gout are concerned, some studies carried out in 2019 on polyunsaturated fatty acid (PUFA) and plant-derived substances have reinforced the concept that diet can play a role in the risk of recurrent gout flares (94). Zhangh *et al*. found that n3 PUFA-rich fish consumption was significantly associated with lower risk of recurrent gout attacks (95). In particular, they found that n3 PUFA-rich fish consumed in the 48 hours preceding a gout flare period, was associated to a 23% lower risk of recurrent flare.

The association between a vegetarian diet and gout has been examined through a prospective study conducted on two devoted Buddhists cohorts in Taiwan (96). This study showed that vegetarians had the lowest uric acid concentrations followed by vegans and

non-vegetarians. In addition, vegetarians experienced a lower risk of gout at the end of the study period. This effect was evident also after adjustment for hyperuricaemia, demonstrating anti-inflammatory benefits and the preventive role of plant-derived compounds, unsaturated fat and fibre with regard to crystal-induced inflammation (97).

Overall, papers published in 2019 confirm the importance of lifestyle and dietary habit in the management of gout and highlight how the involvement of patients through web-based platforms or apps might increase patients' awareness of the disease and comorbidities and their adherence to pharmacological treatment.

Conclusion

Among the most interesting aspects which have influenced the outline of this review, there is the remarkable increase in the number of high-quality papers published on hyperuricaemia and gout over these last two years. This trend is encouraging because it is sustained not only by basic research but also by clinical studies, including recommendations. In this respect, in comparison to former papers, it is possible to observe significant progress regarding the need to improve the education of primary care physicians who are, in addition, increasingly involved also in the research projects. These new acquirements are so relevant that we have decided to include in this review also some recent articles, even though they were published in 2020.

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