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Review

The Evolving Landscape of Gout in the Female: A Narrative Review

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Abstract: Gout is at least 3 times more prevalent in men than in women. However, concurrent with rising total gout prevalence, complex factors, including comorbidities, diet and lifestyle, and aging, have promoted higher gout prevalence in females. This narrative review focuses on summarizing recent developments in the landscape of gout in women, and mechanisms involved. New knowledge on sex hormone effects on both urate-excreting and urate-reabsorbing transporters, and higher hypertension and chronic kidney disease prevalence in women compared to men, may help explain why gout incidence rises robustly after menopause in women to approach that in men. Racial and ethnic factors, risk profiles based on heritable genetic polymorphisms of urate transporters, and diet, body mass index, and lifestyle factors differ according to sex. In addition, sex differences in clinical phenotypes and outcomes of gout and non-gout illnesses include more frequent comorbidities, more pain and disability during gout flare, different perceptions of disease burden, and more frequent severe cutaneous hypersensitivity reaction to allopurinol in women. Significantly, women with gout also have poorer COVID-19 outcomes than do men. Collectively, such findings support the potential clinical benefits of tailoring gout and hyperuricemia treatment according to sex.

Keywords: gout; hyperuricemia; ABCG2; SLC2A9; urate transporter; alcohol; fructose; COVID-19; chronic kidney disease; hypertension

1. Introduction

Gout is a highly prevalent inflammatory joint disease that develops in individuals with hyperuricemia, with consequent tissue deposition of monosodium urate (MSU) crystals [1,2]. In the USA, the most recent published gout prevalence is estimated at 5.1% of adults, with ~12 million adults affected by the disease [3]. Urate, the end-product of purine metabolism, is normally excreted mainly (~70%) by the kidney and to a lesser degree (~30%) via transport into the gut. Multiple heritable and acquired factors that regulate urate transport in the kidney and the gut, and affect urate production, modulate urate homeostasis and promote hyperuricemia [4–8]. MSU crystal deposition is promoted by factors including altered articular tissue extracellular matrix homeostasis [9,10]. The crystals can trigger an inflammatory cascade mediated in large part by NLRP3 inflammasome activation and release of IL-1β [1,11], thereby resulting in acute flares of inflammatory arthritis superimposed on chronic synovitis [12,13]. A mixed granulomatous, fibrotic, chronic tissue inflammatory reaction to MSU crystal deposits mediates the formation of articular and subcutaneous tophi, and progression to erosive joint disease [12,14].

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Gout remains a male-predominant disease, with male-female sex ratio at least 3:1 [2,15–21]. However, the sex difference for prevalence narrows in association with a sharp rise of incident gout in women after menopause [22]. For example, the male to female ratio was only 2.3 in those over age of 70 years (yrs) in a study conducted in UK [23]. Since gout in women may be less well recognized clinically [24], gout is possibly under-reported in women. Regardless, at least ~5% of elderly women in the USA self-reported the diagnosis of gout [25]. Of all female gout patients, only 1-4.5% have premenopausal onset [23,26]. In these uncommon cases, renal dysfunction such as nephropathic effects induced by calcineurin inhibitors, and interstitial nephropathies due to analgesic abuse, lead nephropathy, and strong genetic risk factor(s) are typically the driving force in developing hyperuricemia and gout [27] .

Gout has increased in incidence over the last few decades in the USA, many other developed countries, and in many less well-developed nations [2,3,17,28]. Multiple studies [4,15,23,29–57] have detailed and illuminated the epidemiology and risk factors for gout in the female. This narrative review summarizes these and other recent developments, provides pathophysiologic perspectives, and addresses remaining questions in the landscape of gout in women. The literature cited emphasizes relevant manuscripts of the last 7 years, chosen from MEDLINE English language literature searches.

2. Mechanisms that decrease the gout and hyperuricemia sex ratio after menopause

2.1. Serum urate levels according to sex

Overall, serum urate is unequivocally lower in women than men [58]. For example, in the USA, mean serum urate in men recently was estimated at 6.04 mg/dL, compared to 4.79 mg/dL in women [59]. In a recent Austrian study, women with average age of 51 had serum urate 4.10 ± 1.15 mg/dL vs. 5.29 ±1.2 mg/dL in men with average age 41 [60]. Women gout patients develop gout at an older age than men patients, and women gout patients tend to have more comorbidities that promote hyperuricemia, most notably so for hypertension (HTN) and chronic kidney disease (CKD) [56]. Concordantly, the sex difference of serum urate lessens with increasing age, but especially so after menopause [61]. For example, in a study of 58,870 Korean women, the prevalence of hyperuricemia (defined as > 6.0 mg/dL in women) was 2.7% in the pre-menopause population and 6.7% in the post-menopause population [62].

A substantial limitation of many studies of serum urate in women at hyperuricemia is estimated based on standard deviations from the mean for serum urate in women, with "hyperuricemia" defined at a lower serum urate in women than men. In this regard, National Health and Nutrition Examination Survey (NHANES) data from 2015-2016 estimated prevalence of gout in men to be 5.2% [4.4-6.2%], and 2.7% [2.0-3.8%] in women [59]. In that study, when hyperuricemia was defined as >7.0 mg/dL, only 4.2% [3.3-5.3%] of women were hyperuricemic, compared to 20.2% [16.6-24.3%] in men. In our opinion, the conventional physiologic definition of hyperuricemia (greater than either 6-8 or 7.0 mg/dl), based on the predominant evidence for limited urate solubility in physiologic solution, should be applied universally to both sexes to support biologic rigor in studies in this field and to allow direct translatability to gout.

2.2. Effects of sex hormones on urate transporters

The forces driving male predominance in gout prevalence start with differences in androgen and estrogen sex hormone effects [63]. In this light, medical androgen deprivation therapy lowered serum urate in prostate cancer patients [64]. Moreover, testosterone administration in female to male trans-gender individuals significantly increases serum urate compared to baseline at 2 years [65]. Progesterone level was negatively correlated with serum urate level in premenopausal women whereas follicle stimulating hormone (FSH) positively correlated with serum urate level [66]. Differences in sex hormones lessen after menopause, and postmenopausal hormone replacement therapy in females decreases the risk of incident gout [45].

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The uricosuric effects of estradiol appear substantial. In this context, estrogen administration to male to female transgender people not undergoing orchiectomy is associated with decreased serum urate and increased renal urate fractional excretion [65]. Mechanistically, estrogen suppresses murine kidney protein levels of the urate-reabsorbing transporters such as urate transporters URAT1 and GLUT9 [67]. Estrogen downregulates GLUT9, at least partly, post-transcriptionally via estrogen receptor (ER)-beta induced proteasomal degradation [68].

Serum urate-regulating effects of sex hormones are not limited to renal tubule transporters (**Table 1**). A prime example is that estradiol upregulates intestinal ATP binding cassette subfamily G member 2 (ABCG2) expression through the phosphoinositide 3-kinase (PI3K)/Akt pathway [69]. ABCG2 is a renal and gut epithelial cell-expressed urate-excreting transporter. ABCG2 exerts major regulatory effects by the common ABCG2 variant Q141K encoded by *ABCG2*rs2231142 [70], on the heritable risks of hyperuricemia, gout, early-onset gout and tophaceous disease [71–82]. Much of the regulation of serum urate by ABCG2 occurs by effects on urate transport into the gut. Other extra-renal effects of urate transporters (eg, GLUT9, ABCC4) could also regulate urate metabolism and circulating urate levels in the intestine and/or liver [83,84].

Heritability of serum urate level is estimated to be 30-60%, with major effects of single nucleotide polymorphism (SNP)s in multiple urate transporter genes [7,85–87]. However, such contributions, reflected in the effect size of certain genes, differ according to sex. A prime example is SNPs in *SLC2A9* (e.g. rs7442295, rs734553), which have greater effect sizes in women, whereas *ABCG2* SNPs rs2231142 and rs2199936 have greater effect sizes in men [88,89].

Table 1. Effects of sex hormones on urate transporters.

Urate Transporter or Transport Modulator (function)[references]	**Tissue Expression**	**Estrogen effects**	**Progesterone effects**	**Testosterone effects**
SLC22A12/URAT1 (reabsorption) [67,90]	RA	↓		↑
SLC2A9/GLUT9 (reabsorption)[63,68,91]	RB, RA	↓		↓
ABCG2 (secretion) [67,69,83]	RB, RA I H	↓ ↑ ↓	(-)	
SLC22A6/OAT1 (excretion) [92]	RB	↑		↓
SLC22A7/ OAT2 (secretion) [93]	RB	↑		↓
ABCC2/MRP2 [84]	I, H	↑ (males) (-) (female)		↓(male) (-) (female)
SMCT1, SMCT2 (modulators of URAT1 function) [67,90]	RA	(-)	↓	↑
SGLT2 (modulator of SLC2A9 and URAT1 function) [94]	RA	↑		↑

Abbreviations: sodium monocarboxylate cotransporter (SMCT), monocarboxylate transporter (MCT), renal basolateral (RB), renal apical (RA) intestinal(I), hepatic(H), organic anion transporter (OAT).

2.3. Sex hormones in purine metabolism

Purine metabolism in women with gout is similar to that in men with primary gout, including decreased renal clearance and fractional excretion of urate, hypoxanthine, and xanthine and increased mean plasma urate, hypoxanthine, and xanthine levels [95]. However, plasma xanthine oxidoreductase (XOR) activity, measured in patients with coronary artery spasm, was reported to be

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significantly lower in women [96]. The difference could be due to estradiol and other sex hormones. In this context, estradiol stereoisomers prevented hypoxia-induced increase in XOR enzymatic activity at a posttranscriptional level by a receptor-independent mechanism in cultured microvascular endothelial cells [97]. In addition, the genes of two major enzymes in purine metabolism – hypoxanthine-guanine phosphoribosyltransferase (HPRT) and phosphoribosylpyrophosphate synthetase – are on the X chromosome and associated with X-linked inborn errors of purine metabolism (also phosphoribosylpyrophosphate synthetase superactivity and HPRT deficiency including Lesch-Nyhan disease) [98,99]. Generally, female heterozygote carriers do not develop symptoms unless their normal alleles are inactivated due to skewed X chromosome inactivation, while males with pathogenic variants generally are affected.

XOR and urate transporter activity in the prostate is an obvious distinction between the sexes. A positive correlation was discovered between XOR activity and prostate specific antigen levels in the serum in prostate cancer patients [100]. Human single cell RNA sequencing data showed that XOR is expressed in prostatic basal and urothelial cells, and urate concentration is robust in the murine prostate [101]. However, patients who underwent prostatectomy alone for cancer showed a non-significant change in serum urate, though there was a decrease in those patients with hyperuricaemia [64]. Notably, post-castration for prostate cancer, serum urate falls in a transitory way [102], and androgen deprivation therapy lowers serum urate in prostate cancer patients [64]. Hence, the role of the prostate by itself in sex differences for serum urate requires further investigation.

3. Sex differences in risk factors for gout

3.1. Age, race, ethnicity demographic factors

Age is a well-established risk factor for gout [103–105], and female gout patients are older than males on average, and the hazard ratio for incident gout with every one-year increase is higher in women than men [106,107]. Black women have a higher risk for developing gout than white women [54], suggesting the role of ethnicity as a risk factor. In accordance with this, a nation-wide study showed that emergency department visit (relative ratio 5.91[5.79-6.03] and hospitalization (relative ratio 4.80[4.45-5.17] was strikingly higher in Black than White women [108]. However, a recent study using NHANES 2007-2016 showed that the effect of ethnicity diminished or became attenuated after adjusting for potential confounders including low income, low education [15]. Therefore, associated diet, social determinants, and clinical factors rather than ethnicity *per se* appear to contribute to higher incident gout risk in Black women.

Notably, prevalence of hypertension in Black men in the USA in 2017-2020 was 57.5% and was 58.4% in females compared to 48.9% in White males and 42.6% in White females [109]. Moreover, the prevalence of gout in those of East and South Asian descent residing in the USA has steeply increased, and numerically exceeded all other ethnicities in 2017-2018 period [3]. However, gout prevalence in women was comparable among ethnicities, whereas gout prevalence of Asian men was the highest of all studied ethnicities and races after adjustment for social and clinical factors [3].

3.2. Diet, Obesity, Alcohol, Smoking

Risk factors for gout include obesity, alcohol consumption, high fructose consumption [103], and foods such as meat and seafood [110]. Though alcohol consumption in female gout patients is higher than in controls, effects of alcohol on the risk of gout in women are lower than in men [53]. In this context, a recent Japanese study found that alcohol consumption is a risk factor for hyperuricemia or gout in men but not in women. Furthermore, in the same study, smoking increased the risk for gout only in women [46].

Female gout patients have a higher frequency of obesity compared to male patients. In one study, the risk of gout was reported to be higher in females with body mass index (BMI) ≥27kg/m^2 (adjusted relative risk [RR] 1.30 in men and 2.15 in women) [111]. In another study using linear Mendelian randomization (MR), one standard deviation higher BMI increased the incidence rate for

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gout (incidence rate ratio [IRR]=1.73, 95% confidence interval [CI] [1.56-1.92]) in men and women. That said, BMI was found to be a stronger risk factor for gout in women compared to men (*P*=0.0043). Nonlinear effects of BMI were identified for gout in men, and for gout in women, but nonlinearity for gout was more pronounced in men compared to women (*P*=0.03) [112]. This reflects a stronger causal effect of BMI on gout in leaner people.

Associations with gout of food, lifestyle factors, and of genetic predisposition in genome-wide association studies (GWAS) [7,48,80,86,87,113–121] have prompted study of relative contributions to incident gout of non-modifiable genetic and modifiable risk factors [122]. Two previous studies, which included male subjects (50%, ~75%, respectively), showed relatively small contribution of dietary factors to serum urate level [123,124]. In a prospective cohort study limited to female subjects, subjects with a less healthy diet (low Dietary Approaches to Stop Hypertension [DASH] score) had higher risk of incident gout than those with a healthy diet, but this was much more prominent in those with an increased genetic predisposition (high genetic risk score [GRS]) [43]. Significantly, 51% of the excess risk of incident gout was attributable to the additive gene–diet interaction in the cohorts studied [74].

3.3. Comorbidities

Table 2 summarizes gout comorbidities as risk factors for gout development comparing sex differences where available. Gout comorbidities that promote hyperuricemia include hypertension, metabolic syndrome/insulin resistance, obesity, type 2 diabetes mellitus (T2DM), CKD, and heart failure (HF) [125]. Observational studies suggest that the incidence of gout is increased in hypertensive patients in both men and women [6,56]. However, MR studies have had conflicting results. Analysis of the Taiwan biobank found that the liability of hypertension doesn't have a causal effect on gout [126]. On the other hand, a genetic analysis of over million European ancestors found that systolic blood pressure and pulse pressure had a causal effect on serum urate and gout, but sex-specific effects were not identified [127]. Observational studies showed that HF or hypertension are more common in female gout patients [21,128]. This may be a result of the higher frequency of urate-elevating diuretic use in female gout patients. In this regard, a MR study found no consistent evidence for the causal effect of HF on serum urate levels [129].

T2DM is more prevalent in female gout patients [53], and female gout patients are at higher risk than males for developing T2DM [39]. However, T2DM itself was not a causal factor of incident gout in two MR studies [130,131], though there is evidence by MR for a causal role of insulin resistance for hyperuricemia and gout [132]. Metabolic factors related with T2DM such as hyperinsulinemia, obesity, hypertriglyceridemia are strongly linked to hyperuricemia and gout [133,134]. Indeed, hyperinsulinemia was reported to reduce renal fractional excretion of urate via uncharacterized mechanisms [135]. A recent study found genetic interaction between *SLC2A9* and its variants with human insulin, insulin receptor and insulin receptor substrate-1 loci, which was most evident in women [136]. Notably, *SLC2A9* genetic variants are more prominently associated with female gout, and *SLC2A9*-encoded GLUT9 may be involved in hyperinsulinemia associated with obesity and metabolic syndrome, which are more prevalent in female gout and promote hyperuricemia and gout.

CKD is a clearly associated with hyperuricemia and sharply elevates the risk of incident gout [137]. CKD is more prevalent in women overall [138], and in female gout patients compared to male patients. When the 3-year cumulative incidence of gout was addressed stratified by the level of eGFR, men showed a higher incidence of gout across all the levels of eGFR than women [139]. However, this likely reflects the higher prevalence of gout in men, rather than CKD contributing more to gout development in men. Indeed, with adjustment for confounding factors, CKD was associated with gout with HR of 1.88 (1.13 to 3.13) among men and 2.31 (1.25 to 4.24) in women [140], a result which should not be interpreted as a greater prevalence of CKD in gout. In women, owing to the overlapping 95% CIs.

Osteoarthritis (OA) is associated with gout, and the pathogenic link appears to extend beyond shared risk factors (e.g. age, obesity), to involve effects of degenerative changes in cartilage and altered boundary lubricants in joints with OA [141,142]. In this context, we recently reported incident,

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erosive gouty arthritis without hyperuricemia in a young adult female with attenuated serum lubricin levels [10]. Decrease in lubricin promotes synovitis, and this study implicated TLR2 ligands in suppressing fibroblast-like synoviocyte lubricin levels. Moreover, lubricin, at concentrations present in normal joint fluids, was found to markedly suppress MSU crystal precipitation [10]. Lubricin also blunted the capacity of IL-1b to induce xanthine oxidase and elevated urate in synovial resident macrophages [10]. Lubricin is reduced in OA joints, which suggests a link between increased risk of postmenopausal women for developing gout and OA. In addition, type II collagen, which is released from OA articular cartilage, can increase MSU crystallization *in vitro* [143] and enhance inflammatory responses to MSU crystals [144]. Prevalence of OA is higher in aged women. In nodal hand OA, which is more common in females, gout is commonly superimposed on distal interphalangeal joint OA [145]. Notably, OA patients with gout are at higher risk of total knee replacement surgery [146]. However, a MR study found no causal association between OA and gout [147]. Therefore, the link between OA and gout is likely not mediated by genetic association. Instead, changes in the articular cartilage surface and other changes in joint biology in OA (eg. low grade synovitis, decreased synovial lubricin production [148,149], decrease in hyaluronan production that also can dampen gouty inflammation [150], as well as increased type II collagen release from damaged cartilage) likely predispose to intra-articular MSU crystal deposition and could impact intra-articular xanthine oxidase and urate production in the joint [151].

Table 2. Sex differences of gout comorbidities as risk factors for gout development.

Comorbidities	Prevalence in gout patients	Causal effect on gout (observed in MR or cohort studies)
HTN [126,130]	Higher in females	Inconsistent
T2DM[130,131].	Higher in females	Causal effect identified for insulin resistance but not T2DM *per se*
Obesity[133,134]	Higher in females	Positive causal effect Higher in females
CKD [137–140]	Higher in females	Positive causal effect Higher in females
HF[21,50,129]	Higher in females	Causal effects not identified to date
OA [147]	Not specifically reported	Causal effects suggested to be due to changes in lubricin, hyaluronan, and the cartilage extracellular matrix in OA

Abbreviations: Mendelian randomization (MR), hypertension (HTN), type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), heart failure (HF), osteoarthritis (OA).

3.4. Genetic studies

Genetic factors clearly influence serum urate level and gout [152]. Genome wide association studies (GWAS) have revealed genetic variants associated with hyperuricemia, with effect sizes differing according to sex [7,71,89,118,153]. Two recent studies addressed genetic risk for gout using polygenic risk score (PRS), with female gout patients included. A gout PRS, calculated in large European and Polynesian cohorts, was associated with earlier age at gout onset and tophaceous disease in men but not in women [113]. In another study, a PRS for gout was determined in 59,472 Taiwanese and Chinese female gout patients stratified by age to take the influence of menopause into account. Six variants located in *SLC2A9*, *C5orf22*, *CNTNAP2* and *GLRX5* were significant predictors of female gout with age ≥ 50yrs. For those under age 50 years, only the variant rs147750368 (*SPANXN1*) on chromosome X was found [48]. Results suggested that even women bearing gout risk

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gene variant alleles do not commonly develop gout until they are older, and that the genetic variants underlie a lower portion of incident gout in females compared to males.

4. Differences in age and clinical characteristics of gout in females

The different clinical characteristics of female compared to male gout include onset of gout almost a decade later in women than men [6,56]. The onset age difference is associated with menopause, and loss of aforementioned sex hormone protective effects. Female gout patients overall have more comorbidities associated with aging such as hypertension, T2DM and CKD. The higher prevalence of hypertension is not only related to more diuretic use, but also impaired renal dysfunction which is more prevalent in female gout patients. Female gout patients also have higher BMI, though they consume less alcohol than men [47,50,56,57]. Sites of clinically manifest gouty arthritis differ in women. The typical presentation of arthritis in the first toe metatarsophalangeal joint (podagra) is less frequent in females, who also tend to have oligoarticular presentation affecting other sites such as small hand joints and the ankle [56]. Furthermore, gout can be superimposed on existing OA which often leads to delayed diagnosis. Also, the degree of severity of many comorbidities in women that overshadow gout can contribute to delayed diagnosis. Mean serum urate level at diagnosis is higher in female gout patients (8.91± 2.19mg/dL in women vs. 8.24 ± 1.85mg/dL in men)[50].

A study from the Netherlands reported characteristics of 161 female and 793 male gout patients [50], specifically comparing patients with age ≥ 55yrs to explore effects of sex hormones. Most of the differences were attenuated in the ≥ 55yrs group, and after menopause the gout phenotype was more similar with that of men.

Strikingly, women but not men with gout had increased risk of COVID-19 infection and higher COVID-19 related death [154]. The higher risk for death of women with gout remained significant after adjusting for 16 other diseases, for BMI, and for age though it is possible that this adjustment did not fully account for the underlying metabolic in women with gout. Nevertheless, female gout itself, rather than gout-associated comorbidities, could be an independent risk factor for Covid-19, and potentially via differences in immunity and inflammation in women.

5. Potential sex differences in gouty inflammation

Gouty inflammation is primarily driven by innate immunity [11], which serves as the first line of defense against pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Potential factors affecting inflammatory response that may contribute to clinical differences between female and male gout are summarized in Table 3. Importantly, sex hormones can affect the immune system by changing the tissue milieu that immune cells encounter [155]. Innate immunity also can be influenced by intrinsic (host) and extrinsic (environmental) factors such as age and certain comorbidities [156]. As cited above, women are substantially older than men when diagnosed with gout and have distinctions in sites of arthritis favoring degenerative hand arthritis, and less frequent polyarticular gouty arthritis flares [56].

Table 3. Potential factors affecting inflammatory response that could contribute to sex differences in gout.

Potential factor	Effect on immune response
Transcription [155,157]	● Responses to cytokine, type I interferon signaling in immune cells ● Gene expression regulated by transcription factors ERα and ERβ
Mitochondria [158,159]	● Female mitochondria have higher antioxidant capacity with lower ROS production, which is related to less NLRP3 activation in gout. ● Estrogen increases PGC1α and NRF1/2, leading to upregulation of TFAM, TFB1M/TFB2M, and SOD2, thereby alleviating

	mitochondrial dysfunction.
	● Decreased activation of AMPK signaling due to decreased estrogen aggravates mitochondrial dysfunction that is related to gouty inflammation.

Abbreviations: estrogen receptor (ER), reactive oxygen species (ROS), PPAR-γ coactivator-1α (PGC1α), nuclear respiratory factor (NRF), mitochondrial transcription factor A (TFAM), mitochondrial transcription factor B1 and B2 (TFB1M/TFB2M), manganese sodium dismutase (SOD2), AMP-activated protein kinase (AMPK).

Sex hormones including estrogen, progesterone, and testosterone directly impact the inflammatory capacity and functions of immune cells [155]. Comparison of female and male transcriptomes in whole blood has revealed a sex-specific immune transcriptome, and genes influenced by sex have been associated with responses to cytokines, type I interferon signaling and rheumatoid arthritis [157].

Postmenopausal women have less pronounced sex-specific differences in gene expression, suggesting a role for estrogen in maintaining sex dimorphism in the blood transcriptome [157]. Estrogen receptors, ERα and ERβ, function as transcription factors by binding to estrogen response elements in gene promoters and regulating transcription in the presence of estrogen [155]. Low levels of estradiol increase the pro-inflammatory capacity of macrophages and monocytes in both humans and mice. Sex-specific open chromatin regions have been identified in murine macrophages, indicating a sex dimorphic immune epigenome, and menopause is linked with epigenetic changes [155].

The innate immune response can be influenced by mitochondria. Moreover, mitochondrial dysfunction, a central driver of aging, has been implicated in not only the pathogenesis and pathophysiology of gout, but also cardiovascular, metabolic and renal comorbidities such as HTN, obesity, type 2 diabetes, and CKD [155,158–160]. Firstly, mitochondria are involved in signal transduction of downstream of pattern recognition receptors (PRRs). Intracellular signaling pathways of several PRRs physically interact with mitochondria and act as modulators of their function [158]. For instance, Toll-like receptors trigger the recruitment of mitochondria to macrophage phagosomes, where they release reactive oxygen species (ROS). Secondly, when mitochondrial damage occurs (such as an increase in mitochondrial membrane permeability), mitochondrial DNA (mtDNA) can be released into the cytosol or extracellular space. This mtDNA can be recognized as a DAMP by PRRs, leading to the initiation of a proinflammatory response. Third, mitochondrial signals, including from oxidative stress, are linked to NLRP3 inflammasome activation [161]. Fourth, mitochondrial sex dimorphisms are evident [158,159], supported by the distinct male and female sex hormones in regulating mitochondrial energy, oxidative phosphorylation, and Ca2+ homeostasis [158,159]. Effects of estrogen on mitochondrial function can vary depending on the tissue and context. In most tissues, particularly heart, kidney and skeletal muscle, female mitochondria have been reported to have upregulated antioxidant capacity, respiratory function, and mitochondrial biogenesis capacity, with lower ROS production than male mitochondria [158,159].

In humans, estrogen treatment reverses the mitochondrial dysfunction associated with menopause by increasing expression of PPAR-γ coactivator-1α (PGC1α), a master regulator of mitochondrial biogenesis and a coactivator of nuclear respiratory factor (NRF)1/NRF2. This leads to upregulation of expression of mtDNA-specific transcription factors including mitochondrial transcription factor A (TFAM), mitochondrial transcription factor B1 and B2 (TFB1M and TFB2M), as well as expression of the antioxidant enzyme glutathione peroxidase and manganese sodium dismutase (SOD2) [158]. Estrogen plays a significant role in heart and kidney protection in premenopausal women by modulating renal mitochondrial bioenergetics during acute kidney injury, hypertension, and T2DM [158]. Decreased activation in certain female tissues of AMP-activated protein kinase (AMPKa1) and SIRT1, which are crucial regulators of mitochondrial biogenesis and gouty inflammation [162] may be significant.

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6. Treatment responses in females with gout

Most gout clinical trials have been conducted with a vast majority (~9:1 or more) of male patients, with only few studies that address efficacy of gout medications in females [47]. However, post-hoc analyses suggest that ULT treatment response does not differ between the sexes [55]. That said, gout is associated with a moderately higher risk of fracture [40,163], and postmenopausal women have elevated risk of osteoporotic fracture. A recent study indicated that ULT that achieves serum urate target reduces the risk of fracture in gout patients [164]. Therefore, postmenopausal gout patients with osteoporosis might benefit from treat-to-target ULT. In a recent questionnaire-based study that addressed illness perception on gout according to sex, women felt more disabled and pain score was higher in acute gout flares [165]. Furthermore, allopurinol hypersensitivity syndrome incidence is higher in female gout patients, which may be partially related to a greater CKD population [166,167]. Also, it should be noted there are limitations in choosing anti-inflammatory drugs (e.g. non-steroidal anti-inflammatory drugs) for acute flares [47]. Collectively, pharmacologic treatment should take into account the special considerations for female gout along with the different non pharmacologic approaches (eg. impact of lifestyle modifications).

7. Special consideration in treatment of female gout: pregnancy, breastfeeding

Normal pregnancy increases serum urate level. Although, relatively small number of female gout patients are at their reproductive ages, pregnancy or breastfeeding limits the treatment options for these patients [168,169]. For acute flares, clinicians generally use corticosteroids, colchicine and/or NSAIDs. However, in pregnancy, NSAID use is not recommended in the third trimester, as it can result in premature closure of ductus arteriosus of the fetus. Certain corticosteroids (e.g. dexamethasone) can cross the placenta and also are not recommended. Colchicine is generally not recommended due to unknown effects on the fetus; that said, safe use of colchicine during pregnancy in patients with familial Mediterranean fever has been reported [170]. Regarding the use of ULT, xanthine oxidase inhibitors including allopurinol and febuxostat cannot be employed during pregnancy due to potential teratogenicity [169]. Pegloticase safety data do not exist in pregnancy in humans. Taken together, there are no unequivocally safe drugs to decrease serum urate level during pregnancy.

For breastfeeding and gout acute flare, NSAIDs and corticosteroids can be used. With regard to ULT, allopurinol can be used while breastfeeding, but it is secreted into breastmilk, and the infant should be closely monitored for possible adverse reaction such as hypersensitivity or cytopenia [171]. There are no reported data on using febuxostat in breastfeeding women.

8. Conclusions

Gout is common in females, though it remains concentrated among postmenopausal women. A primary driver for the rise of gout prevalence in women after menopause is loss of female sex hormone effects on serum urate level. However, it remains unclear what effects other than decreased estrogen-mediated uricosuria are contributory, with one possibility being altered gut urate transport. Understanding mechanisms of observed sex differences in progression and susceptibility to gout in males and females may help tailor more effective treatment. Multiple factors, exemplified by genetics, sex hormones, comorbidities, lifestyle, and distinct inflammation responses appear to contribute to differences in gout according to sex. For example, polymorphism in the gut and renal urate excretory transporter ABCG2 is more strongly associated with serum urate in men than women, whereas *SLC2A9* polymorphisms are more strongly associated with serum urate in women than men. Obesity is more frequently linked with gout in females and compounds genetic susceptibility factors. Alcohol consumption is less related to risk of gout in women.

Though men and postmenopausal women tend to have similar profiles of primary gout, comorbidity studies have mostly been small and conclusions for sex differences in gout have been inconsistent. OA is a risk factor for gout, and articular cartilage surface and other changes in articular biology in OA (e.g. low grade synovitis, decreased lubricin, type II collagen release from damaged

cartilage) [xx] could predispose to MSU crystal deposition. In this light, OA is more common in older women than men. Certain comorbidities that cause hyperuricemia (e.g. hypertension, CKD) also are more prevalent in female gout, but only so in younger patients. Hence, younger patients who have a lower serum urate level due to protective effects of estrogen commonly develop gout when they develop urate-elevating comorbidities, and many such comorbidities are more common in female gout patients. Though post hoc analyses show no difference in the treatment response between women and men with gouty arthritis, females appear to report more pain and disability during gout flares. The higher frequency of CKD and of severe cutaneous hypersensitivity reaction to allopurinol could narrow urate-lowering therapy options in women. Lastly, women with gout have significantly poorer COVID-19 outcomes than do men with gout. This finding was unexpected, in part because men generally have significantly worse Covid-19 outcomes compared to women.

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References

1. Dalbeth, N., et al., *Gout.* Lancet, 2021. **397**(10287): p. 1843-1855.
2. Dehlin, M., L. Jacobsson, and E. Roddy, *Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors.* Nat Rev Rheumatol, 2020. **16**(7): p. 380-390.
3. Yokose, C., et al., *Trends in Prevalence of Gout Among US Asian Adults, 2011-2018.* JAMA Netw Open, 2023. **6**(4): p. e239501.
4. Yokose, C., et al., *Adherence to 2020 to 2025 Dietary Guidelines for Americans and the Risk of New-Onset Female Gout.* JAMA Intern Med, 2022. **182**(3): p. 254-264.
5. Dehlin, M., et al., *Lifestyle factors and comorbidities in gout patients compared to the general population in Western Sweden: results from a questionnaire study.* Scandinavian Journal of Rheumatology, 2022. **51**(5): p. 390-393.
6. Drivelegka, P., et al., *Comorbidity in gout at the time of first diagnosis: sex differences that may have implications for dosing of urate lowering therapy.* Arthritis Res Ther, 2018. **20**(1): p. 108.
7. Tin, A., et al., *Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels.* Nat Genet, 2019. **51**(10): p. 1459-1474.
8. Major, T.J., et al., *An update on the genetics of hyperuricaemia and gout.* Nat Rev Rheumatol, 2018. **14**(6): p. 341-353.
9. Xu, H., et al., *Type II collagen facilitates gouty arthritis by regulating MSU crystallisation and inflammatory cell recruitment.* Ann Rheum Dis, 2023. **82**(3): p. 416-427.
10. Elsaid, K., et al., *Amplification of Inflammation by Lubricin Deficiency Implicated in Incident, Erosive Gout Independent of Hyperuricemia.* Arthritis Rheumatol, 2023. **75**(5): p. 794-805.
11. Martinon, F. and L.H. Glimcher, *Gout: new insights into an old disease.* J Clin Invest, 2006. **116**(8): p. 2073-5.
12. Narang, R.K. and N. Dalbeth, *Pathophysiology of Gout.* Semin Nephrol, 2020. **40**(6): p. 550-563.
13. Dalbeth, N., et al., *Effects of Febuxostat in Early Gout: A Randomized, Double-Blind, Placebo-Controlled Study.* Arthritis Rheumatol, 2017. **69**(12): p. 2386-2395.
14. Chhana, A. and N. Dalbeth, *The gouty tophus: a review.* Curr Rheumatol Rep, 2015. **17**(3): p. 19.
15. McCormick, N., et al., *Racial and Sex Disparities in Gout Prevalence Among US Adults.* JAMA Network Open, 2022. **5**(8): p. e2226804-e2226804.
16. Pathmanathan, K., et al., *The prevalence of gout and hyperuricaemia in Australia: An updated systematic review.* Semin Arthritis Rheum, 2021. **51**(1): p. 121-128.
17. Park, J.S., et al., *Trends of Gout Prevalence in South Korea Based on Medical Utilization: A National Health Insurance Service Database (2002~2015).* Journal of Rheumatic Diseases, 2020. **27**(3): p. 174-181.

18. Pisaniello, H.L., et al., *Gout prevalence and predictors of urate-lowering therapy use: results from a population-based study.* Arthritis Res Ther, 2018. **20**(1): p. 143.
19. Kim, J.W., et al., *Prevalence and incidence of gout in Korea: data from the national health claims database 2007-2015.* Rheumatol Int, 2017. **37**(9): p. 1499-1506.
20. Ting, K., et al., *Prevalence and associations of gout and hyperuricaemia: results from an Australian population-based study.* Intern Med J, 2016. **46**(5): p. 566-73.
21. Wändell, P., A.C. Carlsson, and G. Ljunggren, *Gout and its comorbidities in the total population of Stockholm.* Prev Med, 2015. **81**: p. 387-91.
22. Kuo, C.-F., et al., *Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study.* Annals of the Rheumatic Diseases, 2015. **74**(4): p. 661.
23. Cea Soriano, L., et al., *Contemporary epidemiology of gout in the UK general population.* Arthritis Res Ther, 2011. **13**(2): p. R39.
24. Guillén, A.G., et al., *Gender and Ethnic Inequities in Gout Burden and Management.* Rheum Dis Clin North Am, 2020. **46**(4): p. 693-703.
25. Burke, B.T., et al., *Gout in Older Adults: The Atherosclerosis Risk in Communities Study.* J Gerontol A Biol Sci Med Sci, 2016. **71**(4): p. 536-42.
26. Safiri, S., et al., *Prevalence, Incidence, and Years Lived With Disability Due to Gout and Its Attributable Risk Factors for 195 Countries and Territories 1990–2017: A Systematic Analysis of the Global Burden of Disease Study 2017.* Arthritis & Rheumatology, 2020. **72**(11): p. 1916-1927.
27. Khurshid, L., et al., *Gout in Premenopausal Women and in Pregnancy – A Case-Based Review.* Indian Journal of Rheumatology, 2020. **15**(3).
28. Zhang, J., et al., *Global, regional and national burdens of gout in the young population from 1990 to 2019: a population-based study.* RMD Open, 2023. **9**(2).
29. Choi, H.K. and G. Curhan, *Coffee, tea, and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey.* Arthritis Rheum, 2007. **57**(5): p. 816-21.
30. Choi, J.W., et al., *Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey.* Arthritis Rheum, 2008. **59**(1): p. 109-16.
31. Hak, A.E. and H.K. Choi, *Menopause, postmenopausal hormone use and serum uric acid levels in US women--the Third National Health and Nutrition Examination Survey.* Arthritis Res Ther, 2008. **10**(5): p. R116.
32. Choi, H.K. and G. Curhan, *Coffee consumption and risk of incident gout in women: the Nurses' Health Study.* Am J Clin Nutr, 2010. **92**(4): p. 922-7.
33. Choi, H.K., W. Willett, and G. Curhan, *Fructose-rich beverages and risk of gout in women.* Jama, 2010. **304**(20): p. 2270-8.
34. De Vera, M.A., et al., *Independent impact of gout on the risk of acute myocardial infarction among elderly women: a population-based study.* Ann Rheum Dis, 2010. **69**(6): p. 1162-4.
35. Zhu, Y., B.J. Pandya, and H.K. Choi, *Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008.* Am J Med, 2012. **125**(7): p. 679-687.e1.
36. Bao, Y., et al., *Lack of gene-diuretic interactions on the risk of incident gout: the Nurses' Health Study and Health Professionals Follow-up Study.* Ann Rheum Dis, 2015. **74**(7): p. 1394-8.
37. Merola, J.F., et al., *Psoriasis, psoriatic arthritis and risk of gout in US men and women.* Ann Rheum Dis, 2015. **74**(8): p. 1495-500.
38. Juraschek, S.P., et al., *Effects of the Dietary Approaches to Stop Hypertension (DASH) Diet and Sodium Intake on Serum Uric Acid.* Arthritis Rheumatol, 2016. **68**(12): p. 3002-3009.
39. Rho, Y.H., et al., *Independent impact of gout on the risk of diabetes mellitus among women and men: a population-based, BMI-matched cohort study.* Ann Rheum Dis, 2016. **75**(1): p. 91-5.
40. Paik, J.M., et al., *Gout and Risk of Fracture in Women: A Prospective Cohort Study.* Arthritis Rheumatol, 2017. **69**(2): p. 422-428.
41. McCormick, N., et al., *Racial and Sex Disparities in Gout Prevalence Among US Adults.* JAMA Netw Open, 2022. **5**(8): p. e2226804.
42. McCormick, N., et al., *Impact of adiposity on risk of female gout among those genetically predisposed: sex-specific prospective cohort study findings over >32 years.* Ann Rheum Dis, 2022. **81**(4): p. 556-563.
43. Lin, K., et al., *Interactions Between Genetic Risk and Diet Influencing Risk of Incident Female Gout: Discovery and Replication Analysis of Four Prospective Cohorts.* Arthritis Rheumatol, 2023. **75**(6): p. 1028-1038.
44. Xie, D., et al., *Gout and Excess Risk of Severe SARS-CoV-2 Infection Among Vaccinated Individuals: A General Population Study.* Arthritis Rheumatol, 2023. **75**(1): p. 122-132.
45. Hak, A.E., et al., *Menopause, postmenopausal hormone use and risk of incident gout.* Ann Rheum Dis, 2010. **69**(7): p. 1305-9.
46. Teramura, S., et al., *Risk Factors for Hyperuricemia or Gout in Men and Women: The Circulatory Risk in Communities Study (CIRCS).* J Atheroscler Thromb, 2023.
47. Patel, A.V. and A.L. Gaffo, *Managing Gout in Women: Current Perspectives.* J Inflamm Res, 2022. **15**: p. 1591-1598.

 doi:10.20944/preprints202311.0298.v1

48. Lin, C.Y., et al., *Genetic contributions to female gout and hyperuricemia using genome-wide association study and polygenic risk score analyses.* Rheumatology (Oxford), 2022.
49. Eun, Y., et al., *Association between female reproductive factors and gout: a nationwide population-based cohort study of 1 million postmenopausal women.* Arthritis Research & Therapy, 2021. **23**(1): p. 304.
50. te Kampe, R., et al., *Sex differences in the clinical profile among patients with gout: cross-sectional analyses of an observational study.* The Journal of Rheumatology, 2020: p. jrheum.200113.
51. Huang, X.-B., et al., *Prevalence and associated factors of hyperuricemia among urban adults aged 35–79 years in southwestern China: a community-based cross-sectional study.* Scientific Reports, 2020. **10**(1): p. 15683.
52. Evans, P.L., et al., *Gender-specific risk factors for gout: a systematic review of cohort studies.* Adv Rheumatol, 2019. **59**(1): p. 24.
53. Harrold, L.R., et al., *Sex differences in gout characteristics: tailoring care for women and men.* BMC Musculoskelet Disord, 2017. **18**(1): p. 108.
54. Singh, J.A., *Racial and gender disparities among patients with gout.* Curr Rheumatol Rep, 2013. **15**(2): p. 307.
55. Chohan, S., et al., *Women with gout: efficacy and safety of urate-lowering with febuxostat and allopurinol.* Arthritis Care Res (Hoboken), 2012. **64**(2): p. 256-61.
56. Dirken-Heukensfeldt, K.J., et al., *"Clinical features of women with gout arthritis." A systematic review.* Clin Rheumatol, 2010. **29**(6): p. 575-82.
57. McClory, J. and N. Said, *Gout in women.* Med Health R I, 2009. **92**(11): p. 363-4, 368.
58. Maiuolo, J., et al., *Regulation of uric acid metabolism and excretion.* International Journal of Cardiology, 2016. **213**: p. 8-14.
59. Chen-Xu, M., et al., *Contemporary Prevalence of Gout and Hyperuricemia in the United States and Decadal Trends: The National Health and Nutrition Examination Survey, 2007-2016.* Arthritis Rheumatol, 2019. **71**(6): p. 991-999.
60. Zitt, E., et al., *Sex- and age-specific variations, temporal trends and metabolic determinants of serum uric acid concentrations in a large population-based Austrian cohort.* Sci Rep, 2020. **10**(1): p. 7578.
61. Haeckel, R., et al., *Age- and sex-dependent reference intervals for uric acid estimated by the truncated minimum chi-square (TMC) approach, a new indirect method.* Journal of Laboratory Medicine, 2020. **44**(3): p. 157-163.
62. Cho, S.K., et al., *The Prevalence of Hyperuricemia Sharply Increases from the Late Menopausal Transition Stage in Middle-Aged Women.* J Clin Med, 2019. **8**(3).
63. Nicholls, A., M.L. Snaith, and J.T. Scott, *Effect of Oestrogen Therapy on Plasma and Urinary Levels of Uric Acid.* British Medical Journal, 1973. **1**(5851): p. 449.
64. Park, J.W., et al., *Influence of androgen deprivation therapy on serum urate levels in patients with prostate cancer: A retrospective observational study.* PLoS One, 2018. **13**(12): p. e0209049.
65. Yahyaoui, R., et al., *Effect of Long-Term Administration of Cross-Sex Hormone Therapy on Serum and Urinary Uric Acid in Transsexual Persons.* The Journal of Clinical Endocrinology & Metabolism, 2008. **93**(6): p. 2230-2233.
66. Mumford, S.L., et al., *Serum uric acid in relation to endogenous reproductive hormones during the menstrual cycle: findings from the BioCycle study.* Human Reproduction, 2013. **28**(7): p. 1853-1862.
67. Takiue, Y., et al., *The effect of female hormones upon urate transport systems in the mouse kidney.* Nucleosides Nucleotides Nucleic Acids, 2011. **30**(2): p. 113-9.
68. Zeng, M., et al., *Estrogen receptor β signaling induces autophagy and downregulates Glut9 expression.* Nucleosides Nucleotides Nucleic Acids, 2014. **33**(7): p. 455-65.
69. Liu, L., et al., *Estradiol regulates intestinal ABCG2 to promote urate excretion via the PI3K/Akt pathway.* Nutr Metab (Lond), 2021. **18**(1): p. 63.
70. Yu, K.-H., et al., *A comprehensive analysis of the association of common variants of ABCG2 with gout.* Scientific Reports, 2017. **7**(1): p. 9988.
71. Dong, Z., et al., *Association between ABCG2 Q141K polymorphism and gout risk affected by ethnicity and gender: a systematic review and meta-analysis.* Int J Rheum Dis, 2015. **18**(4): p. 382-91.
72. Wrigley, R., et al., *Pleiotropic effect of the ABCG2 gene in gout: involvement in serum urate levels and progression from hyperuricemia to gout.* Arthritis Res Ther, 2020. **22**(1): p. 45.
73. Woodward, O.M., et al., *Gout-causing Q141K mutation in ABCG2 leads to instability of the nucleotide-binding domain and can be corrected with small molecules.* Proc Natl Acad Sci U S A, 2013. **110**(13): p. 5223-8.
74. Woodward, O.M., *ABCG2: the molecular mechanisms of urate secretion and gout.* Am J Physiol Renal Physiol, 2015. **309**(6): p. F485-8.
75. Stiburkova, B., et al., *Functional non-synonymous variants of ABCG2 and gout risk.* Rheumatology (Oxford), 2017. **56**(11): p. 1982-1992.
76. Qiu, Y., et al., *The ABCG2 gene Q141K polymorphism contributes to an increased risk of gout: a meta-analysis of 2185 cases.* Mod Rheumatol, 2014. **24**(5): p. 829-34.
77. Petru, L., et al., *Genetic background of uric acid metabolism in a patient with severe chronic tophaceous gout.* Clin Chim Acta, 2016. **460**: p. 46-9.
78. Matsuo, H., et al., *Identification of ABCG2 dysfunction as a major factor contributing to gout.* Nucleosides Nucleotides Nucleic Acids, 2011. **30**(12): p. 1098-104.

79. Matsuo, H., et al., *ABCG2/BCRP dysfunction as a major cause of gout.* Nucleosides Nucleotides Nucleic Acids, 2011. **30**(12): p. 1117-28.
80. Hoque, K.M., et al., *The ABCG2 Q141K hyperuricemia and gout associated variant illuminates the physiology of human urate excretion.* Nat Commun, 2020. **11**(1): p. 2767.
81. Higashino, T., et al., *Multiple common and rare variants of ABCG2 cause gout.* RMD Open, 2017. **3**(2): p. e000464.
82. Cleophas, M.C., et al., *ABCG2 polymorphisms in gout: insights into disease susceptibility and treatment approaches.* Pharmgenomics Pers Med, 2017. **10**: p. 129-142.
83. Eclov, R.J., et al., *In Vivo Hepatic Enhancer Elements in the Human ABCG2 Locus.* Drug Metab Dispos, 2017. **45**(2): p. 208-215.
84. Simon, F.R., et al., *Hormonal regulation of hepatic multidrug resistance-associated protein 2 (Abcc2) primarily involves the pattern of growth hormone secretion.* American Journal of Physiology-Gastrointestinal and Liver Physiology, 2006. **290**(4): p. G595-G608.
85. Le, M.T., et al., *SLC2A9--a fructose transporter identified as a novel uric acid transporter.* Nephrol Dial Transplant, 2008. **23**(9): p. 2746-9.
86. Yang, Q., et al., *Genome-wide search for genes affecting serum uric acid levels: the Framingham Heart Study.* Metabolism, 2005. **54**(11): p. 1435-41.
87. Wang, W., et al., *Heritability and Genome-Wide Association Analyses of Serum Uric Acid in Middle and Old-Aged Chinese Twins.* Front Endocrinol (Lausanne), 2018. **9**: p. 75.
88. Kolz, M., et al., *Meta-Analysis of 28,141 Individuals Identifies Common Variants within Five New Loci That Influence Uric Acid Concentrations.* PLOS Genetics, 2009. **5**(6): p. e1000504.
89. Döring, A., et al., *SLC2A9 influences uric acid concentrations with pronounced sex-specific effects.* Nat Genet, 2008. **40**(4): p. 430-6.
90. Hosoyamada, M., et al., *The effect of testosterone upon the urate reabsorptive transport system in mouse kidney.* Nucleosides Nucleotides Nucleic Acids, 2010. **29**(7): p. 574-9.
91. Takiue, Y., et al., *The Effect of Female Hormones Upon Urate Transport Systems in the Mouse Kidney.* Nucleosides, Nucleotides & Nucleic Acids, 2011. **30**: p. 113 - 119.
92. Euteneuer, A.M., et al., *Estrogen receptor α (ERα) indirectly induces transcription of human renal organic anion transporter 1 (OAT1).* Physiol Rep, 2019. **7**(21): p. e14229.
93. Ljubojević, M., et al., *Renal expression of organic anion transporter OAT2 in rats and mice is regulated by sex hormones.* Am J Physiol Renal Physiol, 2007. **292**(1): p. F361-72.
94. Sabolić, I., et al., *Expression of Na+-d-glucose cotransporter SGLT2 in rodents is kidney-specific and exhibits sex and species differences.* American Journal of Physiology-Cell Physiology, 2012. **302**(8): p. C1174-C1188.
95. Puig, J.G., et al., *Purine metabolism in women with primary gout.* Am J Med, 1994. **97**(4): p. 332-8.
96. Watanabe, K., et al., *Gender Differences in the Impact of Plasma Xanthine Oxidoreductase Activity on Coronary Artery Spasm.* J Clin Med, 2021. **10**(23).
97. Budhiraja, R., et al., *Estrogen modulates xanthine dehydrogenase/xanthine oxidase activity by a receptor-independent mechanism.* Antioxid Redox Signal, 2003. **5**(6): p. 705-11.
98. Torres, R.J. and J.G. Puig, *Hypoxanthine-guanine phosophoribosyltransferase (HPRT) deficiency: Lesch-Nyhan syndrome.* Orphanet J Rare Dis, 2007. **2**: p. 48.
99. de Brouwer, A.P.M. and J. Christodoulou, *Phosphoribosylpyrophosphate Synthetase Superactivity*, in *GeneReviews(®)*, M.P. Adam, et al., Editors. 1993, University of Washington, Seattle Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.: Seattle (WA).
100. Veljković, A., et al., *Xanthine Oxidase/Dehydrogenase Activity as a Source of Oxidative Stress in Prostate Cancer Tissue.* Diagnostics (Basel), 2020. **10**(9).
101. Urquiaga M, L.M., Sumpter N, Maxwell B, Lewis S, Kelley E, Merriman T., *The Prostate Plays a Role in Serum Urate Levels and the Risk of Gout in Men [abstract].* Arthritis and Rheumatology 2022. **74**.
102. Darlington, L.G., et al., *Changes in urate metabolism after castration of patients suffering from carcinoma of the prostate.* Adv Exp Med Biol, 1991. **309a**: p. 235-8.
103. MacFarlane, L.A. and S.C. Kim, *Gout: a review of nonmodifiable and modifiable risk factors.* Rheum Dis Clin North Am, 2014. **40**(4): p. 581-604.
104. Singh, J.A., S.G. Reddy, and J. Kundukulam, *Risk factors for gout and prevention: a systematic review of the literature.* Curr Opin Rheumatol, 2011. **23**(2): p. 192-202.
105. Saag, K.G. and H. Choi, *Epidemiology, risk factors, and lifestyle modifications for gout.* Arthritis Research & Therapy, 2006. **8**(1): p. S2.
106. Chen, J.-H., et al., *Gender-specific risk factors for incident gout: a prospective cohort study.* Clinical Rheumatology, 2012. **31**(2): p. 239-245.
107. Chen, J.-H., et al., *Impact of obesity and hypertriglyceridemia on gout development with or without hyperuricemia: A prospective study.* Arthritis Care & Research, 2013. **65**(1): p. 133-140.
108. Yokose, C., et al., *Nationwide racial/ethnic disparities in US emergency department visits and hospitalizations for gout.* Rheumatology (Oxford), 2023. **62**(6): p. 2247-2251.

109. Tsao, C.W., et al., *Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association.* Circulation, 2023. **147**(8): p. e93-e621.
110. Choi, H.K., et al., *Purine-rich foods, dairy and protein intake, and the risk of gout in men.* N Engl J Med, 2004. **350**(11): p. 1093-103.
111. Chen, J.H., et al., *Gender-specific risk factors for incident gout: a prospective cohort study.* Clin Rheumatol, 2012. **31**(2): p. 239-45.
112. Karlsson, T., et al., *Body Mass Index and the Risk of Rheumatic Disease: Linear and Nonlinear Mendelian Randomization Analyses.* Arthritis & Rheumatology, 2023. **n/a**(n/a).
113. Sumpter, N.A., et al., *Association of Gout Polygenic Risk Score with Age at Disease Onset and Tophaceous Disease in European and Polynesian Men with Gout.* Arthritis & Rheumatology, 2022. **n/a**(n/a).
114. Lukkunaprasit, T., et al., *The association between genetic polymorphisms in ABCG2 and SLC2A9 and urate: an updated systematic review and meta-analysis.* BMC Medical Genetics, 2020. **21**(1): p. 210.
115. Narang, R.K., et al., *Interactions between serum urate-associated genetic variants and sex on gout risk: analysis of the UK Biobank.* Arthritis Res Ther, 2019. **21**(1): p. 13.
116. Kawamura, Y., et al., *Genome-wide association study revealed novel loci which aggravate asymptomatic hyperuricaemia into gout.* Annals of the Rheumatic Diseases, 2019. **78**(10): p. 1430.
117. Yang, B., et al., *A genome-wide association study identifies common variants influencing serum uric acid concentrations in a Chinese population.* BMC Medical Genomics, 2014. **7**(1): p. 10.
118. Köttgen, A., et al., *Genome-wide association analyses identify 18 new loci associated with serum urate concentrations.* Nat Genet, 2013. **45**(2): p. 145-54.
119. Reginato, A.M., et al., *The genetics of hyperuricaemia and gout.* Nat Rev Rheumatol, 2012. **8**(10): p. 610-21.
120. Choi, H.K., Y. Zhu, and D.B. Mount, *Genetics of gout.* Curr Opin Rheumatol, 2010. **22**(2): p. 144-51.
121. Vitart, V., et al., *SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout.* Nature Genetics, 2008. **40**(4): p. 437-442.
122. Dalbeth, N., *Gene-Diet Interactions: Beyond Duelling Views of Gout Pathogenesis.* Arthritis Rheumatol, 2023. **75**(6): p. 869-871.
123. Topless, R.K.G., et al., *The comparative effect of exposure to various risk factors on the risk of hyperuricaemia: diet has a weak causal effect.* Arthritis Research & Therapy, 2021. **23**(1): p. 75.
124. Major, T.J., et al., *Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts.* BMJ, 2018. **363**: p. k3951.
125. Choi, H.K., N. McCormick, and C. Yokose, *Excess comorbidities in gout: the causal paradigm and pleiotropic approaches to care.* Nat Rev Rheumatol, 2022. **18**(2): p. 97-111.
126. Lai, B., et al., *Assessing the causal relationships between gout and hypertension: a bidirectional Mendelian randomisation study with coarsened exposures.* Arthritis Research & Therapy, 2022. **24**(1): p. 243.
127. Yang, Y., et al., *The role of obesity, type 2 diabetes, and metabolic factors in gout: A Mendelian randomization study.* Front Endocrinol (Lausanne), 2022. **13**: p. 917056.
128. Wändell, P., A.C. Carlsson, and G. Ljunggren, *Gout and its comorbidities in the total population of Stockholm.* Preventive Medicine, 2015. **81**: p. 387-391.
129. Yang, F., T. Hu, and H. Cui, *Serum urate and heart failure: a bidirectional Mendelian randomization study.* Eur J Prev Cardiol, 2022. **29**(11): p. 1570-1578.
130. Yang, Y., et al., *The role of obesity, type 2 diabetes, and metabolic factors in gout: A Mendelian randomization study.* Frontiers in Endocrinology, 2022. **13**.
131. Wijnands, J.M.A., et al., *Individuals With Type 2 Diabetes Mellitus Are at an Increased Risk of Gout But This Is Not Due to Diabetes: A Population-Based Cohort Study.* Medicine, 2015. **94**(32).
132. McCormick, N., et al., *Assessing the Causal Relationships Between Insulin Resistance and Hyperuricemia and Gout Using Bidirectional Mendelian Randomization.* Arthritis Rheumatol, 2021. **73**(11): p. 2096-2104.
133. Sumpter, N.A., et al., *Comorbidities in gout and hyperuricemia: causality or epiphenomena?* Curr Opin Rheumatol, 2020. **32**(2): p. 126-133.
134. Eun, Y., et al., *Altered Risk of Incident Gout According to Changes in Metabolic Syndrome Status: A Nationwide, Population-Based Cohort Study of 1.29 Million Young Men.* Arthritis & Rheumatology, 2023. **75**(5): p. 806-815.
135. Perez-Ruiz, F., et al., *Renal clearance of uric acid is linked to insulin resistance and lower excretion of sodium in gout patients.* Rheumatol Int, 2015. **35**(9): p. 1519-24.
136. Mandal, A.K., et al., *Genetic and Physiological Effects of Insulin on Human Urate Homeostasis.* Front Physiol, 2021. **12**: p. 713710.
137. Juraschek, S.P., et al., *Association of kidney disease with prevalent gout in the United States in 1988–1994 and 2007–2010.* Seminars in Arthritis and Rheumatism, 2013. **42**(6): p. 551-561.
138. García, G.G., et al., *Sex and gender differences in chronic kidney disease and access to care around the globe.* Seminars in Nephrology, 2022. **42**(2): p. 101-113.
139. Tan, V.S., et al., *The 3-Year Incidence of Gout in Elderly Patients with CKD.* Clin J Am Soc Nephrol, 2017. **12**(4): p. 577-584.

140. Weiqi, W., B. Vidula Manish, and K. Eswar, *Chronic kidney disease as a risk factor for incident gout among men and women: retrospective cohort study using data from the Framingham Heart Study.* BMJ Open, 2015. **5**(4): p. e006843.
141. Ma, C.A. and Y.Y. Leung, *Exploring the Link between Uric Acid and Osteoarthritis.* Front Med (Lausanne), 2017. **4**: p. 225.
142. Xu, H., et al., *Contributions of joint damage-related events to gout pathogenesis: new insights from laboratory research.* Ann Rheum Dis, 2023.
143. Chhana, A., et al., *Human Cartilage Homogenates Influence the Crystallization of Monosodium Urate and Inflammatory Response to Monosodium Urate Crystals: A Potential Link Between Osteoarthritis and Gout.* Arthritis Rheumatol, 2019. **71**(12): p. 2090-2099.
144. HanLin, X., et al., *Type II collagen facilitates gouty arthritis by regulating MSU crystallisation and inflammatory cell recruitment.* Annals of the Rheumatic Diseases, 2023. **82**(3): p. 416.
145. Neogi, T., S. Krasnokutsky, and M.H. Pillinger, *Urate and osteoarthritis: Evidence for a reciprocal relationship.* Joint Bone Spine, 2019. **86**(5): p. 576-582.
146. Teng, G.G., et al., *Gout and risk of knee replacement for severe knee osteoarthritis in the Singapore Chinese Health Study.* Osteoarthritis and Cartilage, 2017. **25**(12): p. 1962-1968.
147. Chen, D., et al., *Assessing causality between osteoarthritis with urate levels and gout: a bidirectional Mendelian randomization study.* Osteoarthritis Cartilage, 2022. **30**(4): p. 551-558.
148. HanLin, X., et al., *Contributions of joint damage-related events to gout pathogenesis: new insights from laboratory research.* Annals of the Rheumatic Diseases, 2023: p. ard-2023-224679.
149. Elsaid, K., et al., *Amplification of Inflammation by Lubricin Deficiency Implicated in Incident, Erosive Gout Independent of Hyperuricemia.* Arthritis Rheumatol, 2022.
150. Li, L., et al., *N-Butyrylated hyaluronic acid ameliorates gout and hyperuricemia in animal models.* Pharm Biol, 2019. **57**(1): p. 717-728.
151. Nasi, S., et al., *Xanthine Oxidoreductase Is Involved in Chondrocyte Mineralization and Expressed in Osteoarthritic Damaged Cartilage.* Front Cell Dev Biol, 2021. **9**: p. 612440.
152. Tin, A., et al., *Target genes, variants, tissues and transcriptional pathways influencing human serum urate levels.* Nature Genetics, 2019. **51**(10): p. 1459-1474.
153. Dehghan, A., et al., *Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study.* Lancet, 2008. **372**(9654): p. 1953-61.
154. Topless, R.K., et al., *Gout and the risk of COVID-19 diagnosis and death in the UK Biobank: a population-based study.* Lancet Rheumatol, 2022. **4**(4): p. e274-e281.
155. Shepherd, R., et al., *Sexual Dimorphism in Innate Immunity: The Role of Sex Hormones and Epigenetics.* Frontiers in Immunology, 2021. **11**.
156. Li, Y., et al., *Clinical Characteristics of Early-Onset Gout in Outpatient Setting.* ACR Open Rheumatol, 2019. **1**(7): p. 397-402.
157. Jansen, R., et al., *Sex differences in the human peripheral blood transcriptome.* BMC Genomics, 2014. **15**(1): p. 33.
158. Sultanova, R.F., et al., *Sex differences in renal mitochondrial function: a hormone-gous opportunity for research.* Am J Physiol Renal Physiol, 2020. **319**(6): p. F1117-f1124.
159. Gerdts, E. and V. Regitz-Zagrosek, *Sex differences in cardiometabolic disorders.* Nat Med, 2019. **25**(11): p. 1657-1666.
160. Gosling, A.L., et al., *Mitochondrial genetic variation and gout in Māori and Pacific people living in Aotearoa New Zealand.* Ann Rheum Dis, 2018. **77**(4): p. 571-578.
161. Abderrazak, A., et al., *NLRP3 inflammasome: From a danger signal sensor to a regulatory node of oxidative stress and inflammatory diseases.* Redox Biology, 2015. **4**: p. 296-307.
162. McWherter, C., et al., *Arhalofenate acid inhibits monosodium urate crystal-induced inflammatory responses through activation of AMP-activated protein kinase (AMPK) signaling.* Arthritis Research & Therapy, 2018. **20**(1): p. 204.
163. Zong, Q., et al., *Associations of hyperuricemia, gout, and UA-lowering therapy with the risk of fractures: A meta-analysis of observational studies.* Joint Bone Spine, 2019. **86**(4): p. 419-427.
164. Wei, J., et al., *Lowering Serum Urate With Urate-Lowering Therapy to Target and Incident Fracture Among People With Gout.* Arthritis Rheumatol, 2023.
165. Bergsten, U., et al., *Gender differences in illness perceptions and disease management in patients with gout, results from a questionnaire study in Western Sweden.* BMC Musculoskeletal Disorders, 2023. **24**(1): p. 300.
166. Sato, T., et al., *Real-world evidence of population differences in allopurinol-related severe cutaneous adverse reactions in East Asians: A population-based cohort study.* Clin Transl Sci, 2021. **14**(3): p. 1002-1014.
167. Yang, C.-Y., et al., *Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan.* JAMA Internal Medicine, 2015. **175**(9): p. 1550-1557.
168. Pierre, K., et al., *Gout in Pregnancy: A Rare Phenomenon.* Cureus, 2020. **12**(11): p. e11697.
169. van Veen, T.R. and S. Haeri, *Gout in pregnancy: a case report and review of the literature.* Gynecol Obstet Invest, 2015. **79**(4): p. 217-21.

 doi:10.20944/preprints202311.0298.v1

170. Colchicine: 1998 Update.
171. Anderson, P.O., *Treatment of Gout During Breastfeeding.* Breastfeeding Medicine, 2021. **16**(11): p. 848-850.