



Relationship between hyperuricemia with deposition and sexual dysfunction in males and females

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Abstract

Purpose The association between gout, the most common crystal arthropathy, and sexual dysfunctions has often been investigated by studies in the last decades. Despite the presence of shared risk factors and comorbidities and the possible effects on sexual health of long-term gout complications, awareness of this association is severely lacking and the pathogenetic mechanisms have only partially been identified. In the present review, we aimed to investigate the current evidence regarding the potential mechanisms linking sexual dysfunctions and gout.

Methods A comprehensive literature search within PubMed was performed to provide a summary of currently available evidence regarding the association between gout and sexual dysfunctions.

Results Gout and sexual dysfunctions share several risk factors, including diabetes, chronic kidney disease, hypertension, metabolic syndrome, and peripheral vascular disease. Gout flares triggered by intense inflammatory responses feature severe pain and disability, resulting in worse sexual function, and some, but not all, treatments can also impair sexual health. Long-term gout complications can result in persistent pain and disability due to joint deformity, fractures, or nerve compression, with negative bearing on sexual function. The presence of low-grade inflammation impairs both sex steroids synthesis and endothelial function, further advancing sexual dysfunctions. The psychological burden of gout is another issue negatively affecting sexual health.

Conclusions According to currently available evidence, several biological and psychological mechanisms link sexual dysfunctions and gout. Addressing risk factors and providing adequate treatment could potentially have beneficial effects on both conditions. Appropriate clinical evaluation and multidisciplinary approach are recommended to improve patient care.

Keywords Gout · Hyperuricemia · Erectile dysfunction · Sexual dysfunction · Endothelial dysfunction · Disability

Introduction

Gout is a chronic form of arthritis caused by the inflammatory response to the deposition of monosodium urate (MSU) crystals in soft tissues and joints which occurs as a consequence of a number of factors having hyperuricemia as a central mechanism. Gout has been known for several centuries [1–3] and it has long been defined as the disease of kings or aristocrats, as in past times only wealthy individuals could afford purine-rich foods acting as potential triggers for gout, such as seafoods,

meat, and alcoholic beverages. To date, gout is the most prevalent inflammatory crystal arthropathy worldwide [4]; prevalence varies widely across countries in several studies, with an estimated prevalence of 3–4% in different countries [5–7], but an increasing worldwide trend has been observed in the last decades [8–10]. Gout is strongly associated with age, with an estimated 9% prevalence among adults over the age of 60 in the US [11], and with gender, being almost twice as frequent in men than in women [5]. Gout has a relapsing and remitting clinical course with intermittent episodes of acute crystal-associated inflammatory arthritis or bursitis. However, patients with gout are not fully symptom-free between acute attacks, and their quality of life is impaired during intercritical periods, as well as during flares, probably because of low-grade inflammation associated with tissue deposits of urate in addition to associated comorbidities such as obesity, diabetes mellitus, hypertension, hyperlipidaemia, and chronic renal

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disease [11]. In some patients, often after at least a decade of untreated gout, granulomatous tissue might develop around MSU crystal deposits, forming solid nodules which contribute to chronic pain: these nodules, called tophi (from the Latin word *tophus*, “tuff”, i.e., a volcanic rock), are pathognomonic of the disease, and can induce cartilage and bone remodeling, further contributing to the overall burden of the disease.

The association of gout with sexual dysfunction, exclusively in men, has been investigated by several studies in the last decades. This is hardly surprising, given that gout is a condition more commonly diagnosed in men and women’s sexual dysfunctions are studied far less investigated than in men [12]. Mainly, erectile dysfunction (ED), the persistent inability in obtaining and/or maintaining an erection adequate for sexual intercourse, is a common complaint, occurring in less than 10% in men younger than 40 years up to more than 70% in men over 70 years of age [13, 14]. ED has several known risk factors, both organic, such as endocrine, cardiovascular, neurological, metabolic, or iatrogenic [13, 15–19], and non-organic [20–22]. A strong association exists between gout and ED, largely owing to the shared comorbidities, risk factors, and pathophysiological mechanisms [23].

Despite its prevalence and its association with sexual dysfunctions, gout is rarely considered during clinical assessment by sexual health specialists. Surprisingly, even the most recent guidelines on male sexual dysfunction, issued by the European Association of Urology in 2021 [24], only briefly mention gout as a possible risk factor for ED. On the other hand, female sexual dysfunctions (FSD) are also highly prevalent, with an estimated 38–63% prevalence. While female arousal deficiencies and hypolubrications share with ED several pathophysiological mechanisms and risk factors, they are much less studied [25, 26], and this lack of knowledge seems even worse when attempting to link gout with FSDs. However, as addressing the association between sexual dysfunctions and gout might represent a strategy to improve both conditions and quality of life, with sexual health acting as a leverage to improve compliance to treatment, we aim in this review to evaluate the available evidence regarding the potential mechanisms leading to the development of sexual dysfunctions in the clinical setting of gout, to highlight the relevance of this highly prevalent, yet largely underestimated condition for the endocrinologist and rheumatologist, as well as for the sexual medicine specialist.

Materials and methods

A literature search was performed between June and July 2021 for original reports, literature reviews, meta-analyses, and systematic reviews pertaining to hyperuricemia with deposition and sexual dysfunctions using PubMed and

Google Scholar. The search string used was: *gout and sexual dysfunction*. Titles and abstracts were screened to identify possibly relevant and suitable papers for the present research. Only studies in English or Italian with full text available were included, with no limits concerning date of publication. From the initial results, two of the authors (AS and EAJ) expanded our research looking through the references of all papers found during initial query, and subsequently performed other searches in order to find additional evidence for selected topics (e.g., *gout and erectile dysfunction*, *gout and premature ejaculation*, *gout and desire*, *gout and arousal*, *IL-1 β and erectile dysfunction*, *gout and female sexual dysfunction*, and *IL-1 β and anorgasmia*).

Results

Pathophysiology of gout

Gout results from a disorder of purine catabolism, which leads to the accumulation of serum uric acid (UA), which in turn leads in some, but not all, individuals to the formation and deposition of MSU crystals. The pathogenesis of gout has been thoroughly investigated: while lifestyle factors still largely contribute to the pathogenesis of the disease, with dietary factors accounting for about 12% of cases [27], several other factors have been identified, such as genetic factors, relevant comorbidities, and the use of some medications [11]. During evolution, humans have developed genetic mutations leading to a non-functional form of uricase, the enzyme which in other mammals (as well as in several other species) allows the catalyzation of UA to 5-hydroxyisourate and finally to allantoin [27]. Therefore, these mutations put humans, as well as other primates, at risk of developing hyperuricemia. While hyperuricemia is a potentially harmful condition by itself, being associated with oxidative stress, it is also the predisposing condition for the development of gout flares, i.e., bouts of acute inflammation induced by deposition of MSU crystals in the joints and in soft tissue. MSU crystals deposit when serum UA levels increase over the solubility threshold of 6.8 mg/dl, can cause inflammation and severe pain, limiting the mobility of affected subjects and negatively affecting their quality of life (QoL) [27]. In some conditions, the solubility threshold changes according to temperature and/or pH [28, 29], therefore leading to the deposit of MSU crystals also at lower UA concentrations. While gout flares usually self-resolve in less than two weeks [11], gout is an intermitting disease, with asymptomatic periods of “intercritical gout” in which crystals persist in affected tissues, despite the absence of a suggestive clinical phenotype. In the acute phase, gout flares feature a strong neutrophilic reaction in the affected tissues: macrophages triggered by MSU crystals activate the NOD-, LRR-, and

pyrin domain-containing protein 3 (NLRP3) inflammasome [30], which in turn leads to an inflammatory cascade through the activation of caspase-1, the synthesis and release of interleukin (IL)-1 β , and the subsequent production of other inflammatory chemokines such as IL-6 and IL-8 [31, 32]. These chemokines are still present in intercritical periods, although at much lower concentrations, suggesting that low-grade inflammation persists following the resolution of the gout flare [33].

While theoretically the equation “hyperuricemia = crystal deposit” might seem a simple and concise explanation for the pathogenetic mechanism, the clinical scenario is often quite different. Only a minority of patients with serum UA levels over solubility threshold actually develop crystals [34–36], suggesting that while hyperuricemia is a prerequisite, other factors, currently unknown, might be involved in crystal deposition. This finding is also relevant for the clinical management of gout: not only routine screening for hyperuricemia is not recommended in the general population [37], but on top of that, most currently available treatments are not approved for use in asymptomatic individuals [38], being rather suggested only for patients with a confirmed diagnosis of gout and the presence of tophi, two or more acute gout flares every year, and/or kidney involvement (either chronic kidney disease or urolithiasis) [39, 40].

Clinical management of gout

Luckily for gout patients, much has changed since the times when the Holy Roman Emperor Charles V, also known as King Charles I of Spain, became unable to even hold a quill at just 37 years of age due to gout [41]. For a long time, dietary interventions have been considered as the only prevention strategy: as hyperuricemia is the single most important predictor for the development of gout and its progression to more severe forms, purine-rich diets, acting as potential triggers by increase serum UA levels, should be avoided. However, the potential mechanisms through which such diets can lead to gout are way more complex, and at present there is little evidence to support dietary management as a viable stand-alone treatment. Several medications have been made available in the last decades and have largely been used in all phases of the disease. Broadly speaking, clinical management of gout is enacted at different levels: prevention of newly diagnosed (incident) gout; resolution of gout flares; prevention of subsequent flares and progression to advanced, tophaceous gout; and treatment of advanced forms. Clinical management closely mirrors the progression of the disease, from asymptomatic hyperuricemia to crystal deposition, recurrent gout flares, and formation of tophi.

Urate-lowering therapy (ULT) is recommended as the treatment of choice for long-term management of gout, to reduce serum UA levels and therefore induce to dissolution

of MSU crystals. Xanthine-oxidase inhibitors have long been considered as the mainstay of treatment for gout: these drugs include allopurinol, approved in 1966 by the FDA, and the more recent febuxostat, approved in 2009, which has shown increased efficacy in regards to lowering serum UA levels [42, 43]. Uricosuric drugs and recombinant uricase are also available and can be used as second- or third-line treatments, respectively.

Several medications aimed to contain pain can be used both for the management of acute pain and for prophylaxis of the increase flare rate upon ULT initiation. Corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred treatment: these drugs are comparable in terms of efficacy [44], and choice should be dictated by the patient’s comorbidities. Colchicine, a drug used for treatment of gout since centuries, can be used for the management and prophylaxis of gout flares: while potentially having beneficial effects on cardiovascular outcomes in gout patients, colchicine is difficult to manage, as possible interactions with other drugs and conditions can affect its pharmacokinetic and pharmacodynamic properties [45]. Notably, colchicine use during pregnancy has also been associated with an increased risk of Down syndrome [46] and should thus be discouraged in pregnant women. IL-1 inhibitors have also been considered [47], as shutting down inflammatory response mediated by IL-1 β could potentially have beneficial effects for the management of gout flares [31, 32]. Several trials have been performed using these drugs [48, 49]: at present, in patients with frequent flares and contraindications to colchicine, NSAIDs, and corticosteroid (oral and injectable), IL-1 blockers should be considered for treating flares.

In the most severe cases, surgical treatment of gout has also been proposed [50], mostly for resolution of infections, compression, and persisting pain. Being a risky procedure with limited applications, guidelines do not recommend surgery, and it is therefore unsurprising that no randomized controlled trials have ever been performed to compare its efficacy to medical treatment [50]. However, in extremely severe cases, surgery might potentially be the last-ditch attempt before undergoing amputation—a procedure which is necessary in almost 1 in 2300 gout patients, only slightly less than diabetes [51].

Ongoing issues with ULT

The timing of ULT initiation is controversial [34, 35, 52]: while potentially useful to keep UA levels under the solubility threshold, guidelines currently do not support starting ULT before the first gout flares or more severe complications [38], despite the extremely likely decade-long silent hyperuricemia which can allow deposition of MSU crystals. Several reasons can contribute to this delay in treatment initiation: screening for asymptomatic hyperuricemia

is not recommended in the general population [37], only a minority of individuals with biochemical confirmation of hyperuricemia develop gout [36], and ULT is not exempt from side effects [53, 54]. However, as deposition of MSU crystals may occur even before the first gout flares in completely asymptomatic individuals [35], the best timing for ULT initiation is still an open question for clinical management of hyperuricemic patients. Another potential issue lies in the possibility of initiating ULT during a gout flare: some studies suggest that ULT used as soon as possible during the acute phase of the disease might improve compliance and yield better outcomes [55, 56], whereas others suggest that the early treatment might lead to more frequent flares [57]. Even existing guidelines disagree in these regards [58–60]; a meta-analysis study found no significant effect of initiation of ULT during a gout flare on pain severity and flare duration, although high heterogeneity and the low number of studies included did not allow drawing definite conclusions [61]. There is solid evidence, suggesting that gout flares frequently develop during the first several months of ULT, owing to dissolution of small tophi in intra-articular spaces resulting in release of needle-shaped crystals, which can in turn promote inflammation: to prevent this risk, it is generally suggested to start with a low dose and progressively titrate up to the full dose [62] while also providing anti-inflammatory prophylaxis with low-dose colchicine, corticosteroids, or NSAIDs [44].

As serum UA levels are the most important predictors of gout, it stands to reason that all efforts, both concerning lifestyle and drug treatment, should be made at maintaining concentrations below a 6 mg/dl “safe” target concentration, or even below 5 mg/dl for tophaceous disease [40, 60] once diagnosis is made. However, the current misbelief that gout is a condition requiring treatment only during acute phase is shared by doctors and patients alike, resulting in a decreased compliance to treatment—which, in turn, can result in recurrence of the disease. On the contrary, considering the complexity of a multifocal therapy, which integrates pharmacological treatment with dietary requirements and a number of lifestyle changes, the adherence of the patient plays a pivotal role for the clinical outcomes and for the final therapeutical success, together with correct doctor/nurse/patient communication and with the overall quality of gout care in primary care and hospital practice [63–65].

Despite that, medication adherence remains suboptimal and the poor compliance has been proven by several international studies [66–72]; therefore, strategies aimed at improving patient and clinician education are necessary. To achieve this goal, it is important to highlight the potential risks coming from untreated gout, among which sexual dysfunction, to identify possible leverages to promote patient awareness. Additionally, as the lack of physician monitoring is another largely unresolved issue [64], it is necessary to “re-think”

gout as a condition not only relevant for the endocrinologist and for the rheumatologist, but also for other healthcare professionals, with sexual medicine experts being among the most likely candidates for this task.

Hyperuricemia, gout, and sexual dysfunction: shared risk factors

The issue of sexual dysfunctions occurring in the context of gout and hyperuricemia has been largely investigated in the last decades. Indeed, two recent meta-analysis studies have highlighted a significantly higher risk of developing erectile dysfunction among patients with gout, also following adjustment for age and comorbidities [73, 74]. Indeed, another study showed increased rates of erectile dysfunction not only following diagnosis of gout, but even in the year previous to diagnosis [75]. This evidence is suggestive of some common pathogenetic mechanisms among the two different conditions [23]. The role of hyperuricemia as a potential cardiovascular risk factor should not be overlooked, as UA can promote the development of hypertension, atherosclerosis, fibrillation, and heart failure [76]: however, a recent meta-analysis study has highlighted that hyperuricemia, while potentially independently contributing to endothelial dysfunction, is more likely to be a reliable marker of systemic dysmetabolic disorders which might negatively affect erectile function [77]. Obesity, diabetes mellitus (and “diabesity”), chronic kidney disease, hypertension, metabolic syndrome, hypovitaminosis D, use of diuretics, and peripheral vascular disease are known risk factors and comorbidities for gout [78–82], which can potentially act on an already established state of asymptomatic hyperuricemia, promoting progression to clinical disease. These comorbidities, however, are also well known to sexual medicine experts: obesity, insulin resistance, hypertension, and the use of diuretics are known risk factors for the development of sexual dysfunctions in both men [13, 15, 17, 83–85] and women [83, 84, 86–89]. Several mechanisms have been hypothesized to explain the association between sexual dysfunctions and obesity, among which endothelial dysfunction: insulin resistance, another hallmark feature of metabolic syndrome, further inhibits synthesis of nitric oxide (NO) and NO-induced vasodilation [90, 91]. These factors are known to affect sexual response in men, by reducing blood flow to the cavernosal arteries and therefore impairing erectile function; in women, similar mechanisms resulting in increased clitoral vascular resistance have been hypothesized as a possible mechanism bridging female sexual dysfunction and obesity [89]. Diabesity is a risk factor for both ED and major cardiovascular events, where daily 100 mg of aspirin is very frequently used for secondary prevention of the latter and perhaps of the former [92]. However, it should be mentioned that aspirin is able to induce in some predisposed

subjects a typical gout crisis [93]. Glomerulosclerosis secondary to hypertension is another potential risk factor for the development of hyperuricemia and gout; diuretics used in the treatment of hypertension can also contribute by altering kidney filtration of UA, although evidence in these regards is not conclusive [94].

It is therefore clear that gout and sexual dysfunctions are closely linked to each other: prevention strategies enacted to reduce either condition can also lead to beneficial effects for the other. This is even more important in patients already diagnosed with gout, who require careful management to prevent the onset of severe complications (Fig. 1). Interestingly, the sexual impact of gout seems tremendously more dramatic with respect to that of the “simple” hyperuricemia. While a few doubts could be cast in the relationship between ED and gout, the independent association between hyperuricemia and erectile function has recently been questioned [95]. In fact, although hyperuricemia can potentially contribute to oxidative stress, it is unlikely that sexual dysfunctions occurring in gout can exclusively result from increased UA levels, but actually depend on a more complex clinical phenotype in which comorbidities play a significant role [91].

Gout complications for sexual health

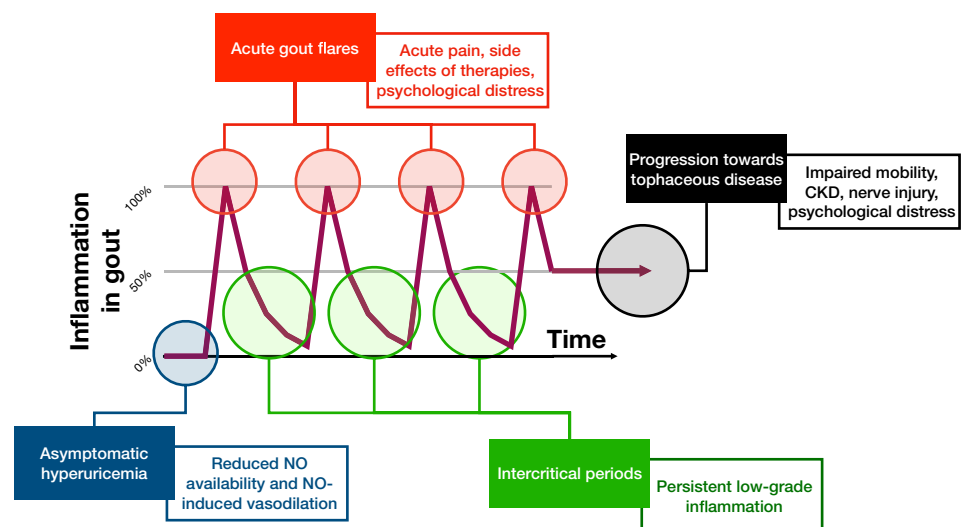
Hyperuricemia and gout have been associated with worse cardiovascular health [96], although whether they could be considered independent risk factors has largely been questioned. Several studies have proven worse cardiovascular health in patients with increased serum UA levels [97, 98], and it has even been suggested that the risk of having major cardiovascular events (myocardial infarction and stroke) and diabetes is increased among patients diagnosed with gout [99]; however, a meta-analysis study published in 2015 concluded that based on available evidence, it would

be impossible “to conclude that uric acid is an independent risk factor for cardiovascular diseases” [95]. This also raises the legitimate question of treatment: would ULT be helpful in preventing the onset or the progression of cardiovascular diseases, and would the same treatment yield the same results independently of deposits? It is however clear that untreated gout is associated with a worse clinical phenotype in regards to cardiovascular health, possibly because of several factors—endothelial dysfunction [100], dyslipidemia [101], and chronic/acute inflammation [102].

Gout is also associated with higher incidence of chronic kidney disease (CKD) [103], possibly because of renal toxicity of UA or because of deposition of MSU crystals in the tubules or medulla [104, 105]; however, frequent use of NSAIDs can also impair kidney function (Fig. 1). Sexual dysfunctions are a common complaint of CKD patients, both in men [13, 106, 107] and women [108, 109]. Several mechanisms have been hypothesized for sexual dysfunctions in CKD, including psychological distress and the side effects of the necessary treatments: in men, hypogonadism and endothelial dysfunction are also likely culprits [106, 110].

Disability secondary to MSU crystal deposition in gout is another complication with potential bearing for sexual health. Several studies have investigated the economic impact of persistent joint pain and impaired mobility on patients, reporting high economic burden of disease [111, 112], possibly accounting for tens of millions of dollars [113]. It is unsurprising that patients who face such limitations might also have worse sexual health: acute pain makes sexual activity impossible during gout flares, whereas chronic complications of gout can affect sexual performance by limiting freedom of movement due to joint deformity or fractures in tophaceous disease, or because of lacking personal hygiene, or side effects of gout medications [114]. Increased rates of infection occurring in gout patients as

Fig. 1 Time course of the “sex-gout”: in the progression from asymptomatic hyperuricemia to chronic tophaceous disease, the different phases of gout feature different complications relevant to sexual health, also owing to the changes in inflammatory status. *NO* Nitric Oxide, *CKD* Chronic Kidney Disease



consequences of treatment and/or inadequate hygiene [115, 116] can also worsen sexual health, leading to erectile and ejaculatory disorders in men [117, 118] and sexual dysfunction in women such as low vaginal lubrication, dyspareunia, and, possibly, reactive hypoactive sexual desire disorder [119, 120]. Spinal gouty arthritis, a rare, often misdiagnosed form of the disease affecting the spine [121], leads to nerve compression in more than half of patients [122]: nerve impingement from gout generally manifests as weakness or numbness, but reports from other forms of spinal injury suggest that both male [123–125] and female sexual function [25, 123, 126] can be affected. Overall, there is solid evidence highlighting the possible organic factors leading to worse sexual health in gout patients; however, as occurring in many chronic diseases [127], disability and chronic conditions are also an important source of psychological distress [128], with severe effects on health-related quality of life [129], including, unsurprisingly, sexual function (Fig. 1). While treatment of gout and gouty arthritis is likely to have beneficial effects on sexual health, to the present date, no studies have directly investigated the effects of allopurinol or febuxostat on male sexual or reproductive function.

It is also worth mentioning that two case reports of acute gouty arthritis occurring following intake of sildenafil [130, 131], a phosphodiesterase type 5 inhibitor (PDE5i), used in the treatment of erectile dysfunction. While these case reports have been extraordinarily rare, and more studies are therefore needed in these regards, this evidence should drive clinicians toward careful use of PDE5i in patients with gout, or possibly even asymptomatic hyperuricemia.

Psychological burden

The psychological burden of gout has been largely proven [132–136]: however, despite being a relevant issue for the patient's quality of life (QoL), this issue is generally underestimated by clinicians. Several factors might exacerbate the psychological distress: recurrence of flares, feelings of inadequacy or stigmatization [132], or even difficulty of getting the needed treatments, as occurring during the COVID-19 pandemic [137]. In these regards, the psychological burden of COVID-19 and related containment measures, such as lockdowns and social isolation, have also been proven to exert negative effects on sexual health [138–140]. Several studies have indeed reported higher rates of depression, anxiety, and fatigue among gout patients [129, 141, 142], with worse symptoms occurring during acute gout flares but persistently decreased QoL even during remission. Depression, anxiety, and fatigue are independently associated with increase prevalence of male and female sexual dysfunctions [143]. This is not surprising, given the association of gout and hyperuricemia with other conditions, such as obesity, metabolic syndrome, type 2 diabetes mellitus, hypertension,

and cardiovascular disease, which contribute to a worse clinical phenotype [78, 79]. The psychological burden associated with gout and its comorbidities can influence sexual response [144–152], potentially leading to sexual dysfunctions in men and women alike.

Chronic low-grade inflammation

As previously described, gout is a chronic metabolic condition featuring a persisting state of low-grade inflammation, mostly driven by interleukin IL-1 β , and to a lesser extent by IL-6 and IL-8 [31, 32, 153], released upon activation of the NLRP3 inflammasome by the interaction between MSU crystals and macrophages [151]. The NLRP3 has been considered as a candidate target for treatment in gout [154], as shutting down the inflammatory response could potentially act on the whole clinical phenotype of the disease. The chemokines involved in gout, however, are also responsible for other conditions: overproduction of IL-1 β leads to a plethora of autoimmune conditions [155], IL-6 has been associated with acute myocardial infarction and atherosclerosis [156], and IL-8 has pro-inflammatory properties [157] and is a strong predictor of overweight/obesity [158]. Increased production of IL-1 β , IL-6, and IL-8 is involved in the hypercoagulability state featured in inflammatory response [159]; furthermore, pro-inflammatory cytokine levels are seemingly associated with lower serum sex steroid concentrations [160–163], and testosterone modulates immune response by promoting production of anti-inflammatory cytokines, such as IL-10, and inhibiting pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β [163]. Low testosterone levels might also be involved in the pathogenesis of gout, as well as other chronic diseases [164], possibly because of the changes in immune response. Several reports suggest that the inflammatory state can potentially contribute to worse sexual health, resulting in male and female sexual dysfunctions [165–168]. More recently, early response pro-inflammatory cytokines have also been considered as a pathogenetic mechanism for increased vascular permeability in COVID-19 patients [169] and a potential risk for erectile dysfunction secondary to SARS-CoV-2 infection [170–172]. Based on these premises, it is clear that the persistent low-grade inflammation occurring in gout patients can potentially have negative effects on endothelial function, leading to erectile dysfunction in affected men (Fig. 2).

Additionally, metabolic syndrome, a well-described risk factor for gout, features a similar low-grade inflammation state [173], which can potentially worsen sexual function by promoting endothelial dysfunction. Inflammation mediated by IL-1 β and other pro-inflammatory cytokines can also affect sexual desire and arousal in men and women alike,

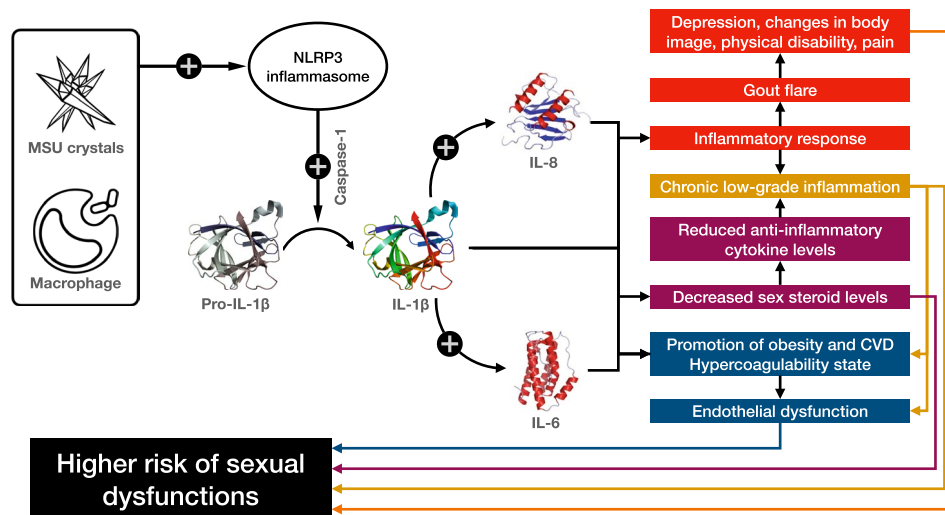


Fig. 2 The pathogenetic mechanisms linking gout and sexual dysfunctions. The activation of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome occurring upon interaction between macrophages and monosodium urate (MSU) crystals results in increased levels of caspase-1, which transforms pro-interleukin-1 β

(pro-IL-1 β) to the bioactive IL-1 β , the main driver of inflammation in gout. The subsequent inflammatory cascade, which also involves IL-6 and IL-8, affects sexual function by several direct and indirect pathways. CVD: cardiovascular diseases

although evidence in these regards is far from conclusive [168].

Conclusions

Hyperuricemia with crystal deposition is a highly prevalent condition with potential bearings for sexual health. While hyperuricemia is possibly by itself a cardiovascular risk factor with negative bearing on sexual health, several other mechanisms can promote the onset or worsening of sexual dysfunction. Despite the multiple pathogenetic mechanisms through which gout can influence male and female sexual function, this condition is rarely investigated by the sexual medicine expert; at the same time, sexual health is frequently ignored by the endocrinologist and the rheumatologist facing gout, as well. We therefore highlight the need to promote awareness of the two conditions, or rather, of the “sex-gout” to all healthcare providers involved in sexual medicine and gout management. Improving clinicians’ awareness of the relevance of gout for the development of sexual dysfunction could potentially have long-term benefits; additionally, by stressing the importance of treatment compliance to preserve good sexual health, the additional benefit of preventing progression to more severe forms of gout would be achieved. Owing to the pathophysiology of sexual dysfunctions in gout, it is likely that treatment with urate-lowering medications might provide beneficial effects on sexual function in affected patients. However, more studies are warranted to provide the much-needed evidence in these regards, also to

shed a light on those pathogenetic mechanisms which, while logical, are not yet proven in the clinical setting.

Author contributions EAJ conceived the present study. AS and EAJ performed literature review. AS and YR drafted the first version of the manuscript. All authors revised subsequent versions of the manuscript critically for important intellectual content and approved the final version.

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Code availability No code to share.

Declarations

Conflict of interest The funder had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. EAJ has been speaker and/or paid consultant for Bayer, Ibsa, Lundbeck, Menarini, Otsuka, Pfizer, Shionogi, and Viatrix. YR has been speaker and/or consultant for Lundbeck, Pfizer, Boston, Ibsa, and Besins. AS has no conflict of interests to declare.

Ethical approval No approval needed.

Consent to participate No patients were involved in the present research.

Consent for publication All authors give consent for publication.

Disclosures Emmanuele A. Jannini is an Editor for the Journal of Endocrinological Investigation. Andrea Sansone has been invited in November 2021 to join the Editorial Board.

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