Review

Does seasonality of the microbiota contribute to the seasonality of acute gout flares?

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ABSTRACT

Gout, the most common inflammatory arthritis worldwide, is an auto-inflammatory metabolic disease that leads to monosodium urate crystal deposition. Hyperuricaemia is a significant risk factor for the development of gout; however, hyperuricaemia alone is not sufficient to induce gout.

Gout flares have circadian rhythms. Gout flares vary during the day and have strong seasonality, with flares being more common in the spring. The reasons for the predominance of flares in the spring are unclear since serum urate (SU) levels show seasonal variation; however, SU levels are highest in the summer.

Immune function varies significantly throughout the year, with enhanced immune responses increasing during the winter. In addition, chronic disruption of circadian rhythms is associated with metabolic syndrome and diseases driven by metabolism. The most telling example relates to Xanthine oxidase (XOD/XDH). The analysis of XOD/XDH established its circadian regulation and demonstrated that inhibition of the activity of XOD is characterised by distinct, cross-regulating diurnal/seasonal patterns of activity.

The gastrointestinal microbiota of gout patients is highly distinct from healthy individuals. In a small series of gout patients, Bacteroides caccae and Bacteroides xylanisolvens were found to be enriched. Bacteroidales levels were highest during the spring and summer, and loading values were highest in the spring.

Our review discusses gout's circadian rhythm and seasonality, possible influences of the microbiome on gout due to our new knowledge that Bacteroidales levels were highest during spring when gout is most common, and potential opportunities for treatment based on our current understanding of this interaction.

Introduction

Gout, the most common inflammatory arthritis worldwide, is an auto-inflammatory metabolic disease that leads to monosodium urate (MSU) crystal deposition. Hyperuricaemia is a significant risk factor for the development of gout. However, hyperuricaemia alone is not sufficient to induce gout. In one study, only 9% of patients with hyperuricaemia had a gout flare over a 15-year period, and even at SU concentrations above 10 mg/dL, only 50% developed clinically evident gout (1). Hyperuricaemia represents elevated circulating serum urate (SU) levels of 6.8 mg/dl. Throughout the paper, we use the term uric acid (UA) for the end-product of purine metabolism and the term SU since UA is predominantly found in the ionised form in the circulation (2). Gout has been variably classified as a metabolic disorder and, more recently, an auto-inflammatory disease (3). Gout treatment aims at mitigating the precipitation of MSU crystals and alleviating inflammation.

The incidence of gout is increasing, at least partly because of the obesity epidemic. Approximately 3.9 percent of Americans have gout, or about 9.2 million people (5.9 million men and 3.3 million women) (3). Gout prevalence increases with age and is more common in adult men. Still, it can occur in adults at any age (4). Gout increases in women post-menopause and is associated with a higher comorbidity burden than men (5). Comorbidities are more common in gout patients than in the general population. Gout patients have an average of four associated comorbidities. Cardiovascular disease (CVD), hypertension (HTN), chronic kidney disease (CKD), obesity, metabolic syndrome (MetS), and diabetes mellitus (DM) are highly prevalent in individuals with gout (6). Hyperuricaemia is a predictor of obe-

sity, MetS, DM, CKD, HTN, and CVD (7). UA may play a role in causing these conditions. There is a significant role for both crystalline (MSU crystals) and soluble urate in driving metabolic inflammation (8). However, most randomised studies evaluating the relationship of SU to cardiovascular endpoints have been negative, and clinical trials have also been mixed (7).

Gout is considered a paradigm in acute *sterile* inflammation when SU is in the range of supersaturation (9). However, this static view of the disease fails to take advantage of the fact that the onset of an acute flare expresses the breaking of the delicate balance of the dynamics of the metabolic activity and immune response. This, in turn, leads to exacerbation of the symptoms and points to the inability of the "system" to properly manage its regulatory components. Furthermore, studies revealed that the risk for acute gout flares during the night and early morning hours *(i.e.* during the transition from the inactive to the active phase) is 2.4 times higher than in the daytime (10). Recent evidence indicates that circadian disruption, in the form of shiftwork, significantly increases circulating levels of SU (11-12) exacerbating gout. These observations indicate that life-style circadian disruptions also impact UA metabolism and excretion. The implications are twofold a) further emphasising the strong dependence of SU levels of physiological diurnal rhythms; and b) the broader, systemic factors likely driving SU levels. Although several factors could be potentially implicated (body temperature, dehydration during sleep, lying position, cortisol levels, etc.), the fundamental challenge remains gout flares have circadian rhythms. A deeper and better understanding of these "time-of-day" dependencies will significantly improve our understanding of the disease and have implications for anti-gout prophylactic and treatment approaches.

Even more striking is the observation that acute gout flares vary not only during the day, but also, have a strong seasonal dependence, with spring flares being more common (13-16). The reasons for the predominance of flares in the spring are unclear since SU levels show seasonal variation, but SU levels are highest in the summer (17). This is a pattern that seems to broadly characterise rheumatic diseases in general (18).

Immune function varies significantly throughout the year in most vertebrates, with enhanced immune responses and disease severity increasing during the shorter winter days. Thus, several aspects of the immune system are modified to adapt to winter-related stresses associated with lower ambient temperatures (19). Inability to adapt to seasonal variations would compromise the host's immune competence. As such, evidence has shown that human serum concentrations of interleukin (IL)-6, soluble IL-6 receptor, and C-reactive protein (CRP) are higher during the summer-winter months (20-21), whereas pro-inflammatory human mRNA and protein expression in peripheral blood mononuclear are enhanced during winter (22). These inflammatory components are considered risk biomarkers, and inflammatory diseases (18) exhibit seasonality with higher prevalence and symptom aggravation during winter and spring on top of exhibit diurnal activity fluctuations whereby symptom intensity is augmented in the late night and early morning (23). In rheumatoid arthritis (RA) patients, the peak cytokine levels for serum IL-6, and tumour necrosis factor (TNF) increase by a factor of 10, and the rhythms are phase shifted to a later time in the morning (24). Since one of the defining factors of a "season" is photoperiod which is known to drive circadian rhythms. Seasonal variations are intimately related to changes in circadian rhythms (25-26).

Importantly, not only is the immune response under circadian/seasonal control, but also the metabolism. The intricate relationship between circadian rhythms and metabolism has been studied in the context of enzymes and hormones involved in digesting the nutrients and their interaction with peripheral clocks (27-28). The rest/active cycles and fast/feed cycles that mammals experience diurnally lead to an alternating nutrient supply throughout the day. The metabolic organs of the host must manage these diurnal fluctuations in nutrients to maintain physiological homeostasis (29). The circadian regulation of metabolism is thought to provide the host organism with the flexibility in regulating metabolic activities in response to changing environmental conditions. Naturally, the circadian dependence of metabolism extends to seasonal dependence (30). Considering the intricate relationship between circadian rhythms and metabolism, it is not surprising that chronic disruption of circadian rhythms is associated with the development of metabolic syndrome and a variety of diseases driven by metabolism (31-35). In that respect, rodent (36) and human (37) data demonstrate clear diurnal oscillations of SU levels. Both exhibit higher SU levels during the active period or near the transition from inactive to active. Of note is the likely sex-dependence of SU levels (38). The most telling example relates to *Xanthine oxidase* (XOD/XDH), aka *xanthine dehydrogenase*, a rate-limiting enzyme in purine metabolism, critical for UA production is, eventually, under the regulation of the peripheral clock machinery (39). The analysis of XOD/XDH not only established its circadian regulation, through PPARα but also demonstrated that pharmacologic inhibition of the activity of XOD, using febuxostat (a drug sold under various brand names for the treatment of chronic gout and hyperuricaemia) exhibited a strong time-of-day dependence indicating that taking the drug at the beginning of the rest period, as opposed to the beginning of the active period, resulted in more aggressive SU reduction.

Since both metabolic and immune mediators are characterised by distinct, cross-regulating diurnal/seasonal patterns of activity; it is critical to better describe these interacting dynamics, which shift the balance of power and tips the scale, initiating an inflammatory reaction and a flare. The failure to account for this dynamic balance leads to our inability to properly characterise, and eventually take advantage of, the diurnal/seasonal patterns of the disease.

In recent studies, overwhelming evidence begins to emerge highlighting the critical role the gut microbiome plays in regulating not only metabolism but also diurnal and seasonal rhythms

in a bidirectional manner (40). Since the evidence overwhelmingly suggests that the gut microbiome plays an essential role in regulating metabolism it is expected that the microbiome would also be critical in regulating metabolic diseases, such as gout. Recent studies characterising the temporal variation of the microbiome's composition determined that seasons impacted not only the relative taxa abundance but also overall composition (41). Since circulating metabolites are significantly impacted by the nature of the microbiome, the potential importance of the microbiome-joint axis is gaining increasing attention (42) (Fig. 1).

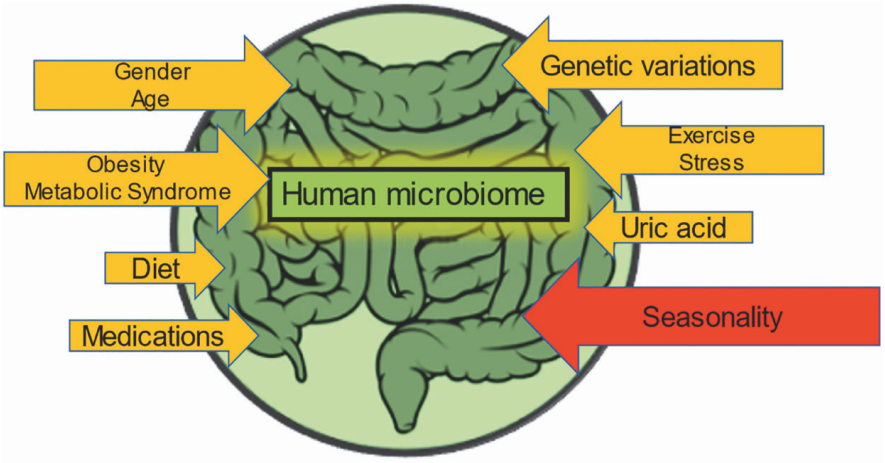

Fig. 1. Factors affecting the microbiome.

Gout is seasonal. Is the seasonality of gout in part the result of the seasonality of the microbiota?

The microbiome composition

Human health and well-being are closely linked to the diverse set of microorganisms in the intestine known as the gut microbiota (43). The gut microbiome has been linked to human metabolism, intestinal homeostasis, and immune development (44). Alterations in the gut microbiota, known as dysbiosis, can disrupt these essential health-promoting properties and lead to gastrointestinal, cardiovascular, autoimmune, and metabolic diseases (45). Hence, the gut microbiome operates much like an organ that functions to promote health and prevent disease.

Throughout life, various factors modify the microbiota early in a full-term baby, born vaginally and fed with breast milk, as the basis for developing intestinal microbiota. Later, age, antibiotics, diet, and comorbidities, including being overweight and the MetS, effect the microbiota. The most significant microbiota changes occur when the child eats solid food (46). The inflammasome pathway plays a beneficial role in intestinal homeostasis and is influenced by products of the gut microbiota (47). Recently, short-chain fatty acids have been found to detect metabolites derived from the microbiota. Acetate is the most abundant short-chain fatty acid produced in the gut by microbiota. Long-chain saturated fatty acids activate the NLRP3 inflammasome (48). The short-chain fatty acid G protein coupled receptor GPR43 is necessary for effective activation of the inflammasome *in vivo* and in macrophages. Acetate and GPR43 contribute significantly to inflammasome assembly in response to MSU crystals, suggesting that these molecules contribute to the development of gout (49). Acetate rapidly increases up to 20-fold after consuming alcohol. Increased acetate, which signals through the GPR43 could contribute to the association of acute gout flares with alcohol consumption (49).

The gut microbiota comprises bacteria, archaea, fungi, and viruses, including a diverse bacteriophage community (50). Bacteria dominate the microbiota in abundance and diversity, with commensal members from seven phyla including *Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia,* and *Cyanobacteria*, the majority of which are uncultivated and novel phylotypes (51). Members of the microbiota can be permanent "residents", transmitted through close contact between individuals or transient "travelers" from ingested food, water, and various components of the environment (52). The gut microbiota is ubiquitous, some of which have profound impacts on our health and our microbiomes (53).

The human microbiome is a microbiota collection that resides on or within the skin, lung, saliva, conjunctiva, urinary tract, and gastrointestinal tract – these surfaces house collections of the microbiome with a unique signature (53-54). The gut microbiota, and its associated microbiome, play an integral role in human metabolism, immune capability, and tolerance (55). Composed mainly of bacteria and viruses, fungi, and archaea, the gut microbiota is thought to consist of over 100 trillion cells (56). Many factors contribute to variation in humans, such as diet, host genetics and metabolism, familial relationships, culture, and demographics (57-58). According to global surveys of fecal microbiota from healthy populations, variation between individuals in the richness of gut microbiota is primarily explained by age, ethnicity (59), geography, medication exposure, blood parameters, diet, health, anthropometric, and lifestyle (60-61).

An extensive global dataset analysis of fecal samples, including the Belgian Flemish Gut Flora Project and the Dutch LifeLines-DEEP study in healthy volunteers, collectively represented almost 4,000 people (n= 3948), found 664 genera. There is a 14-genera core gut microbiota common to 95% of people. These genera account for 72% of the total gut microbiome. The main difference between individuals is the relative quantity of microbes from these core groups, including *Ruminococcicea, Bacteroides, Prevotella, Faecalibacterium,* and *Roseburia*. (60). Factors associated with gut microbiota composition include health status, drugs, gender, age, and stool transit time (61-62). In addition, diet and its fibre content, genus abundances, antibiotic intake (amoxicil-

lin, for example), and SU levels were suggested as contributing factors. Although the human microbiome can mediate the human host's interaction with environmental factors, research in gout has not had a fundamental impact on clinical practice (63-64).

Serum urate is seasonal

Epidemiologic surveys of SU levels have been interpreted to indicate that multiple factors, including race, social strata, intelligence, and stress, influence the prevalence of hyperuricaemia in otherwise healthy persons. Unfortunately, many of these surveys are cross-sectional and do not consider the possibility of daily or seasonal variations in SU levels (17). Substantial variations may occur when SU levels and 24-h urinary uric acid excretions are measured in the same person during 24-hours. Transient and monthly variations are not uncommon (65).

SU levels peak in the summer months (June-August) (66). Seasonal elevations in SU levels were higher in summer than in winter (17). Another study showed higher SU levels when comparing the summer to the autumn (67). Dehydration during the summer months has been postulated to precipitate crystal formation (68).

Diet, gut human microbiome and serum urate levels

The SU levels in each individual represent a complex interplay between non-modifiable factors, such as genetics, and modifiable factors, such as diet and body weight (69). The connection between gout and hyperuricaemia with gluttony, overindulgence in food and alcohol, and obesity dates to ancient times. Although most UA is derived from the metabolism of endogenous purine, eating foods rich in purines contributes to the total pool of UA. The introduction of the Western lifestyle to non-Western people has been associated with increases in SU levels, the incidence of gout, or both hyperuricaemia and gout. Higher consumption of meat, seafood, and fat, combined with inactivity current dietary trends, have contributed to a rising prevalence of obesity and hyperuricaemia. Obesity is associated with both increased production and decreased renal excretion of urate. Consumption of alcohol was found to be a significant dietary risk factor for gout (49, 70). Even moderate regular consumption of beer was associated with a high risk of development of gout (multivariate relative risk of 1.49 per 12-oz beer serving per day). In contrast, moderate wine consumption of 1–2 glasses per day was not associated with significant change in the risk of incident gout (70). Diet can play a role in the risk of recurrent gout flares. Alcohol and obesity increase the risk of flares, whereas polyunsaturated fatty acid (PUFA) -rich fish consumption was significantly associated with a lower risk of recurrent gout flares (49, 71). Vegetarians have the lowest SU levels followed by vegans and non-vegetarians. In addition, vegetarians experienced a lower risk of gout. This effect was evident also after adjustment for hyperuricaemia, suggesting anti-inflammatory benefits of plant-derived compounds, unsaturated fat, and fibre (72). Tart cherries have the highest anthocyanin concentration amongst berries. We have found components of tart cherry juice concentrate to inhibit NFκB activation and inflammation in gout. (73).

The gut microbiota plays a role in increasing the SU by high-fat diets and reducing SU by drugs. Reducing intestinal absorption of dietary purines may reduce SU levels. Several genera were observed to decrease purine absorption and UA decomposition, such as *Lactobacillus*. Thus, a reduction can be achieved by ingesting bacteria such as *lactobacilli* strains to decrease purine absorption (74). Moreover, genera that increased in the hyperuricaemia model rats may be responsible for high UA levels.

Proteus strains can convert purine into UA through the secretion of xanthine dehydrogenase (75). Several altered genera in the rat hyperuricaemia model are consistent with alterations of gut microbiome observed in gout patients (76). The intestinal microbiota of gout is similar to those of type-2 DM rather than liver cirrhosis patients. In contrast, depletion of *Faecalibacterium prausnitzii* and reduced butyrate biosynthesis are shared in each of these components of the MetS (75).

Urate lowering therapy may influence the microbiome and vice versa

Pharmacomicrobiomics evaluates the effect of the microbiome on drug disposition, action, and toxicity. Studies have demonstrated that human gut microorganisms and their enzymatic products can affect drug bioavailability, clinical efficacy, and toxicity through direct and indirect mechanisms (77). Thus, the microbiome can alter drug bioavailability, bioactivity, and toxicity, thus changing an individual's response to a drug. Microbiome derived metabolism of drugs can result in the production of metabolites or consumption of the active drug. As a result, the biodisposition of medications may be altered. Specifically, the gut microbiome is capable of metabolising allopurinol, a key therapy in gout (78-79). Constraint-based reconstruction and analysis (COBRA) models have been leveraged to simulate, analyse and predict metabolic phenotypes resulting from the host microbiome. Combining COBRA with physiologically based pharmacokinetic modeling, Krauss and colleagues predicted that daily administrations of 200 mg allopurinol would result in a 69.3% reduction of uric acid concentration (80). Impressively, the prediction matches what has been demonstrated in clinical practice.

Just as the gut microbiome can alter allopurinol bioavailability, allopurinol influences the gut microbiome composition. In the rat hyperuricaemia model, allopurinol and benzbromarone were used to lower SU (81). These drugs decrease SU and thus lead to gut microbiota modification. Gut microbiota modifications in rats treated with allopurinol and benzbromarone revealed increased *Bifidobacterium and Collinsella and decreased Adlercreutzia* and *Anaerostipes*. The authors suggested that alterations of the gut microbiota could be indicative of the effectiveness of drug therapy. The genus *Bifidobacterium*, a probiotic therapy, has decreased SU levels in a hyperuricaemia mouse model (82). In addition, oral *Bifidobacterium* reduced the inflammatory response to MSU crystals in an experimental murine model of gout. Bifidobacterium caused inhibition of CXCL1 and IL-1β production in

the joints (83). The genus *Anaerostipes* is a butyrate-producing bacterium (84). Gut microbiota can convert nucleotide into UA and excrete UA to the outside of the bacterial cell through ion-coupled transporters (85). Thus, reductions of nucleotide metabolism and ion-coupled transporters caused by allopurinol may reduce UA in the gastrointestinal tract. Collectively, these data support the postulation that changes to the gut microbiome composition induced by allopurinol may be a secondary mechanism by which it confers a benefit in gout.

Gout and the human microbiome

Circadian rhythms and the microbiome

The (gut) microbiome has been largely acknowledged as a key regulator of the metabolic, immune, and nervous systems. Although the microbes composing it are not directly exposed to light systemic signals induce circadian rhythms in, both, abundance and function of gut bacteria (40). Extensive studies have demonstrated that the abundance of about 15% of the microorganisms in (fecal) microbiota oscillate during the day, with specific sub-populations' relative abundance peaking either during the active or the rest phase. The compositional oscillations translate into the oscillatory activity of genes encoding for specific pathways. As a result, genes associated with energy metabolism, DNA repair and cell growth are abundant during the active phase, whereas genes associated with detoxification, motility and sensing peak during the rest phase. Such daily fluctuations are likely associated with bacteria anticipatory activities, and the activation of specific pathways is indicative of the microbiome expecting changes in gastrointestinal function (86). Such changes in relative abundance and pathway activity translate into distinct patterns of metabolite production as a result of the microbiota metabolism. Detailed metabolomic analyses have revealed distinct oscillations of groups of metabolites (87). Furthermore, animals with mutations in core clock genes exhibited alterations in their microbiome, compared to wild type (88), whereas germ free mice, *i.e.* animals without gut microbes, exhibit altered circadian rhythms (89). Such results point towards a strong association between circadian rhythms and the gut microbiome, extending the strength of the bidirectional regulation between circadian rhythms and metabolism/metabolic disorders mediated by the microbiome.

Seasonality of the gut microbiome

Dysbiosis is a disruption to the microbiota homeostasis caused by an imbalance in the microflora, changes in their functional composition and metabolic activities, or a shift in their local distribution. The gastrointestinal microbiota of gout patients is highly distinct from healthy individuals in both organismal and functional structures (39). In a small series of gout patients, *Bacteroides caccae* and *B. xylanisolvens* were found to be enriched, while Faecalibacterium *prausnitzii* and *Bifidobacterium pseudocatenulatum* are depleted (39). Alteration of microbiome 'dysbiosis' can induce gout in people with certain genetic backgrounds and environmental factors. Dysbiosis in gout may be due to loss of beneficial organisms- *Faecalibacterium prausnitzii* and *Bifidobacterium pseudocatenulatum*, excessive growth of potentially harmful miicroorganisms- *Bacteroides caccae* and *B. xylanisolvens* Bacteroidales levels were highest during spring/summer, and loading values were highest in the spring (76). Is this part of the cause of gout being more common in the spring?

The seasonality of gout is a clue to the pathogenesis of the disease

Seasonality is a time-dependent, fundamental shift in environmental conditions expected to vary significantly across geographical scales. However, seasonal variation of acute gout flares is similar worldwide, in geographical areas that differ widely and over many years. It is of interest that the serum concentration of HDL-C, LDL-C, and triglycerides show striking seasonal variations, as well (16, 90-92). The most favourable lipid/lipoprotein plasma profile, *i.e.* lowest total cholesterol and LDL-C and highest HDL-C, occurred in the summer. In contrast, the least favourable profile occurred in the winter with the highest total cholesterol and low HDL-C levels. The plasma triglycerides levels were highest in the autumn (93). The pattern of seasonal variations in HDL-C levels, LDL-C, and triglycerides in the southern hemisphere was similar to that described in the northern hemisphere, except that the months were antipodean. Thus, Wahlquist *et al.* (94) showed that in Australia, the most favourable lipid/lipoprotein plasma profile occurred in the antipodean summer (November/December) while the least profile occurred in the winter (July/August). The plasma triglyceride levels were highest in the autumn (March) and lowest in the spring (November). It has been shown that the seasonal rhythm of HDL was not induced by either dietary intake or physical activity and might be determined by endogenous factors that are directly related to seasonal changes in the environment (95).

Seasonal variations in hormonal levels have also been shown. Striking seasonal variations have been demonstrated in plasma (96) and saliva (97) cortisol levels. The lowest cortisol levels were found in healthy individuals during the spring and summer, while the highest levels were found during autumn/winter. The fall of cortisol levels during spring may facilitate acute gout flares.

Several acute-phase reactants were shown to display seasonal variations, as well (98). CRP showed a highly significant seasonal variation in levels, with higher values during winter and spring than in summer (20-21). Plasminogen activator inhibitor-1 (PAI-1), alpha-1 glycoprotein, and ceruloplasmin displayed cyclic seasonal variations in their levels. PAI-1 and ceruloplasmin attained their maximal concentration in March (99). The importance of PAI-1 in the pathogenesis of arthritis has been demonstrated in mice with PAI-1 deficiency (100). The induction of experimental antigen-induced arthritis (AIA) was found to be inhibited in PAI-1-deficient mice. These results suggest that deficiency of PAI-1 results in increased synovial fibrinolysis, which leads to reduced fibrin accumulation in arthritic joints and reduced severity of AIA. Studies are required to determine whether PAI-1 plays a role in gout.

We studied the effects of weather on the

incidence of acute gout flares (101). We found no correlation between gout incidence and mean monthly temperature or mean monthly humidity levels that could have explained the seasonal variation. We find it interesting that acute flares are less common in the winter since (102) lower temperatures augment the precipitation of MSU crystals. Indeed, we have demonstrated that using ice to cool joints with acute gout flare accelerates recovery from the flare (103).

Striking seasonal variations were found in the immune system. In spring, the absolute number of neutrophils in the blood was at its peak, while the number of lymphocytes was the lowest (104). Since neutrophils play a critical role in the inflammatory response in acute gout, the seasonal elevation of neutrophil number in the spring may be an important predisposing factor for the seasonality of gout flares.

Acute gout flares are more common in the spring, while SU levels are highest in the summer. The relatively weak link between hyperuricaemia and gout indicates that the inflammatory process of gout is precipitated not only by high SU levels but also by other factors that possibly exhibit seasonal variation. The lipid profile shows a seasonal variation. It is conceivable that gout patients have a greater propensity to promote MSU crystal formation at specific UA-cholesterol- triglyceride levels.

Not enough is known about the possible contribution of seasonal changes in the patients' diet (including alcohol consumption) in eliciting gout flares. Still, it should be borne in mind that only one-third of the SU level is contributed by diet. The low cortisol level, high absolute neutrophil count, and high levels of PAI-1 during the spring may give us clues as to why gout flares are more common in the spring.

Conclusions and implications

There has been a recent interest in the microbiome, its influence in maintaining health, coordinating physiological functions, and contributing to disease. Gout is an inflammatory disease associated with disrupted purine metabolism leading to an elevated UA pool. Recent studies have associated the disease with the gut microbiota both directly and indirectly. The gut is not only responsible for producing about 30% of UA, but also secreted metabolites that greatly impact the metabolic and immune state of the patient (105-106). Both attributes greatly impacted the microbiota composition. At the same time, drug pharmacokinetics and pharmacodynamics (PKPD) are also impacted by the microbiome and *vice versa* (107-108). At the same time, the microbiome, as well as drug PKPD, are under the regulation of the body's internal rhythms (109-110).

Understanding the links between the microbiome and gout may provide prophylactic and therapeutic tools to improve human health. Altering the diet may be helpful. Low-carbohydrate, high-fat ketogenic diets alter Bifidobacterium-modulated host phenotypes, increase β-hydroxybutyrate in the microbiome and thus possibly contribute to alleviating gout (111-112). Fecal microbiota transplantation has become a viable way to alter the human gut, as well and preliminary studies have shown some efficacy in beneficial outcomes in metabolic syndrome (113). In addition, pharmacomicrobiomics can facilitate the advent of microbiome-based precision medicine approaches in gout, including predicting response to treatment and modulating the microbiome to improve response to therapy or reduce drug toxicity.

Circadian rhythms and seasonality manifest as the emergence of a complex equilibrium that may play a part in gout (Fig. 2). Given the strong interactions between the microbiome and circadian/seasonal rhythms, it becomes imperative to fully delineate the relations between them to understand the onset and paths for resolution of gout as we maximise the impact of non-pharmaceutical interventions such as diet modification as well as potential pharmaceutical interventions.

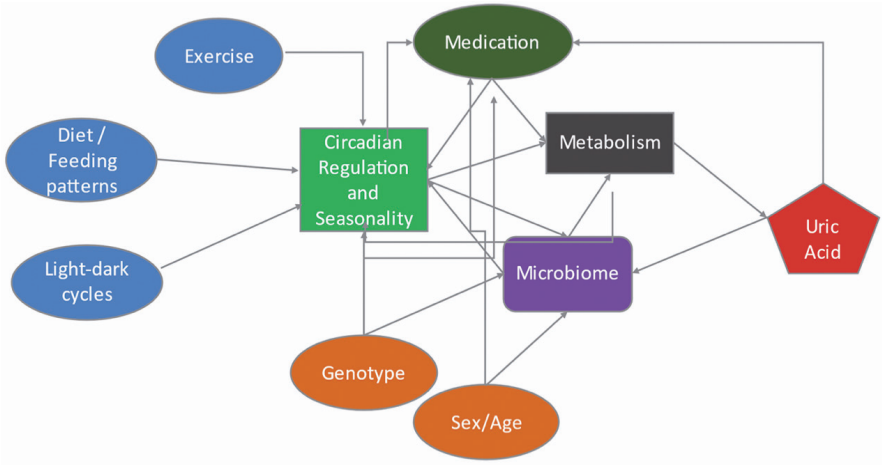

Fig. 2. Host-microbiome interactions in gout patients.

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