Serum Urate in Chronic Gout — Will It Be the First Validated Soluble Biomarker in Rheumatology?

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ABSTRACT. ***Objective.*** To summarize evidence for and endorsement of serum urate (SU) as having fulfilled the OMERACT filter as a soluble biomarker in chronic gout at the 2010 Outcome Measures in Rheumatology Meeting (OMERACT 10).

Methods. Data were presented to support the use of SU as a soluble biomarker in chronic gout and specifically the ability to utilize it to predict future patient-reported outcomes.

Results. SU was accepted as having fulfilled the OMERACT filter by 78% of voters. However, consensus was not obtained regarding its use as a soluble biomarker in chronic gout. Although the majority of the criteria for a soluble biomarker were fulfilled, the key criterion of association of the biomarker with outcomes was not agreed upon. It was agreed that the appropriate choice of endpoint must be linked to its clinical importance to the individual with the disorder and its temporal relationship to the intervention. Appropriate outcomes in chronic gout may therefore include gout flares, reduction in tophi, and patient-reported outcomes.

Conclusion. SU is a critical outcome measure. It has the potential to fulfil criteria for a soluble biomarker. Further analyses of existing data from randomized controlled trials will be required to determine whether SU can predict future important outcomes, in particular disability. (J Rheumatol 2011;38:1462–6; doi:10.3899/jrheum.110273)

Key Indexing Terms:
SERUM URATE GOUT BIOMARKER

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The Outcome Measures in Rheumatology (OMERACT) consensus exercises identified serum urate (SU) as an important outcome measure in chronic gout studies with the highest median rating[1]. The underlying biochemical abnormality in gout is an increase in SU, and the clinical manifestations of gout are due to the inflammatory response to the presence of urate crystals. Thus, as an outcome measure, SU could be considered a surrogate biomarker for key clinical outcomes that are of importance to both gout patients and their physicians.

OMERACT has developed a schema for validation of soluble biomarkers for structural outcomes in rheumatoid arthritis (RA), psoriatic arthritis (PsA), and spondyloarthritis (SpA)[2]. While not specifically developed for chronic gout, the key essential criteria provide a useful framework for validating SU as a soluble biomarker in chronic gout. The criteria were adapted for use in chronic gout (Table 1). While evidence from the gout literature is sufficient to fulfil the majority of these criteria, a key criterion required of the biomarker is to independently predict future outcomes, and in this regard further work is required. Existing evidence for SU as a biomarker has been reviewed and the key areas requiring further analysis required are outlined below.

BIOMARKER CRITERIA

Feasibility

1. *The assay SU is internationally standardized and is readily accessible if used for clinical practice*. SU is widely available as a routine test in clinical chemistry laboratories. The reference method for SU is isotope dilution mass spectrometry and reference material is readily available.

2. *Stability of SU at room temperature, frozen, after storage*. SU is stable in serum stored at room temperature for up to 48 hours, in serum stored at 4°C for 8 days and in serum stored at –20°C for 4 months[3]. Storage for 10 years at –70°C and repeated freeze-thaw cycles have been shown to have no effect on SU concentrations[4].

Truth and Discrimination

1. *The assay for measurement of SU is reproducible*. Most routine assays for SU utilize the Trinder reaction with uricase. This assay is generally reliable with between-laboratory and between-method coefficients of variation < 5%. Quality assurance programs are required to ensure that laboratory precision is maintained and that between-laboratory differences are minimized.

2. *The sources of variability on levels of SU. Effect of age*. In males there is a consistent increase in SU between the ages of 10 and 19 years[5,6,7,8,9]. In girls, the data are more conflicting, with some studies showing a rise during puberty[6] while others show no change during the early teenage years[8]. In males > 18 years of age, the majority of studies show no convincing increase in SU as a function of age[10,11]. In comparison, there is a progressive increase in SU with age in women, especially noticeable in the perimenopausal period[12,13]. In general, women have a lower SU than men. A number of confounding variables [e.g., female hormone profile, body mass index (BMI), and alcohol intake] may contribute to the observed effects of age on SU concentration. Multivariate analyses have shown that age is an independent variable contributing to the increase in SU in some, but not all, studies[14,15].

Effect of sex. SU is approximately 1 mg/dl lower in adult females than adult males. Variables influencing SU such as age and BMI have been suggested to contribute more to variation in SU in women (20%) than men (9%)[16]. The major factor thought to account for the observed gender differences is the female hormone profile.

Effect of ethnicity. There is clear evidence that SU varies among different ethnic populations. Some of the highest mean SU concentrations are in New Zealand Maori[17]. Other Pacific Island peoples also have high SU concentrations, including Pukapukans and Rarotongans[17]. In America, studies examining the difference in SU concentrations between Black Americans, Hispanics, and Whites have shown variable results[11,18].

Effect of circadian rhythms. The majority of studies that report diurnal variation in SU show the peak SU in the morning (0500–0800 hours) and trough SU in the evening (1700–1900 hours)[19,20]. A number of studies also report no diurnal variation[21,22]. Overall the diurnal variation in SU is generally small [< 0.50 mg/dl (0.03 mmol/l)] and unlikely to be of clinical significance.

Effect of BMI. The relationship between increased BMI and gout is well recognized[23]. A number of studies also confirm the positive association between BMI and SU concentration in univariate and multivariate regression analyses.

Table 1. Essential criteria from the OMERACT soluble biomarker criteria adapted for use in chronic gout; from J Rheumatol 2009;36:1785–91[2].

Truth and discrimination	The assay for measurement of serum urate (SU) is reproducible according to reliability analysis
	The effects of sources of variability on SU concentrations in appropriate controls are known for the following core variables — age, sex, ethnicity, circadian rhythms, body mass index, renal/hepatic function, fasting/non-fasting
	SU demonstrates independent association with clinical and patient-centered endpoints. The key clinical/patient-centered endpoints in chronic gout are number of gout flares, tophus regression, dissolution of crystals, radiographic damage, and patient function and quality of life
Feasibility	The assay for measurement of SU is internationally standardized (availability of reference standards), and is readily accessible if used for clinical practice
	Stability of SU at room temperature, in frozen specimens, after repeat freeze/thaw cycles, and after longterm storage has been documented

Effect of renal function. A number of studies have shown that serum creatinine correlates with SU independently of age, diuretic use, and BMI, and that serum creatinine is one of the most important determinants of SU concentration[24,25,26]. Creatinine clearance adjusts for some of the variability in creatinine due to age, weight, and gender, and is a better indicator of renal function. Creatinine clearance correlates inversely with SU[27].

Effect of hepatic function. A number of important liver enzymes are involved in purine metabolism and production of urate. These include xanthine oxidase, adenosine monophosphate deaminase, and glucose-6-phosphatase. Despite roles for these enzymes in urate metabolism, there is no evidence to suggest that variations in their activities, abnormal hepatic function, or raised liver function tests are associated with changes in SU.

Effect of fasting/non-fasting. Diet has an important influence on SU. Intake of purine-rich foods, such as meat and seafood, as well as sugar-sweetened soft drinks has been associated with an increase in SU[28,29]. Alcohol, in particular beer, is also associated with an increase in SU[30]. In comparison, increasing intake of dairy products and coffee has been associated with lower SU[28,31]. Fasting has also been shown to result in a substantial increase in SU, by virtue of the associated generation of organic acid products that reduce renal urate clearance[32].

Effects of other variables to be explored in chronic gout. While the importance of the above variables was accepted at the recent OMERACT 10 meeting, it was recognized that other variables unique to chronic gout may be of interest. For example, the effect of common medications, such as antihypertensives and aspirin, may need to be documented. However, this was not felt to be necessary for formal validation of SU as a biomarker.

3. *SU demonstrates independent association with clinical and patient-centered endpoints*. The soluble biomarker criteria for RA, PsA, and SpA focus on the structural endpoint of radiographic change. However, the relationship between the SU and clinical and patient-reported outcomes (PRO) are perhaps more relevant in chronic gout. Potential outcomes include gout flares, tophus regression, and important PRO such as impaired physical function and health-related quality of life (HRQOL; e.g., Health Assessment Questionnaire, HAQ; Gout Assessment Questionnaire, GAQ; and/or Medical Outcome Study Short-Form 36, SF-36). It is recognized that an independent association with outcome of interest should be demonstrated to occur in patients at different disease stages and populations. Similarly, the independent predictive ability of a change in SU should predict a later change in the relevant outcome.

The choice of the most appropriate endpoints that should be predicted by a surrogate may be informed by their clinical relevance to the patient, temporal relationship to the intervention or measurement of the surrogate, and difficulty in actually measuring the endpoint or its rarity. Frequency of gout flare is a key manifestation of chronic gout. While it may initially worsen after successful control of SU, and may be difficult to measure accurately, it may be an appropriate endpoint for which change in SU could usefully substitute. Therapeutic studies have shown that while there may be an increase in gout flares in the short term, in the longer term gout flares reduce or cease with sustained reduction of SU to subsaturating levels. For example, in a study of 762 patients treated with febuxostat or allopurinol, the incidence of flares increased with withdrawal of gout prophylaxis after the 8th week, with a gradual reduction in the number of flares thereafter. Post-hoc analysis revealed that between weeks 49 to 52, the proportion of patients with gout flares was lower among those with mean post-baseline SU < 6 mg/dl (< 0.36 mmol/l) compared to those with mean post-baseline SU ≥ 6 mg/dl (≥ 0.36 mmol/l — 6% vs 14%; p = 0.005)[33]. In an open-label extension study, as SU was maintained < 6 mg/dl (< 0.36 mmol/l) the number of gout flares decreased such that only 4% of patients reported a gout flare after 18 months[34]. Conversely, withdrawal of urate-lowering therapy has been associated with an increase in SU and recurrence of gout[35].

Further analysis of existing longterm clinical data is required to determine whether PRO with regard to HRQOL and function can be predicted by SU. Both physical function and HRQOL are impaired in patients with gout[36,37,38]. From the few published studies that have addressed the relationship between SU and HRQOL and/or function, no association between SU and HRQOL for patients with chronic gout has been shown. Pegloticase has been shown to improve PRO, but a direct analysis between change in SUA and a change in PRO was not reported[39]. Data from a phase II febuxostat study show no difference in SF-36 at 6 months and 12 months, despite all patients achieving SU level < 7.8 mg/dl (< 0.46 mmol/l)[40]. However, this SU remains significantly above the recognized target SU of 6 mg/dl (0.36 mmol/l). In addition, PRO may not be noted until the SU stabilizes and the total urate pool decreases, which can take many months or years.

However, there are some unpublished data that support an association between SU control and PRO. At OMERACT 10, an analysis from 2 replicate Phase 3 randomized controlled trials of pegloticase was presented that considered the association between change in urate levels from baseline to final followup (6 months) and change in PRO scores [pain, patient global, HAQ-Disability Index, SF-36 Physical Component Score (PCS) and Mental Component Score (MCS), as well as across all 8 domains]. This analysis indicates that changes in plasma urate (PU) are significantly associated with changes in PRO in the context of powerful urate-lowering therapy, even over a short timeframe of 6 months. Both change in PU and final value of PU were significantly associated with changes in all PRO, including SF-36 PCS and 8 domains, with the exception of the MCS. The magnitude of the beta coefficients in regression models for change and final value in PU were similar (ranging from 0.16 to 0.36).

DISCUSSION AND VOTING

During OMERACT 10, there was clear consensus that measurement of SU met the OMERACT filter for truth, discrimination, and feasibility as an intrinsic outcome of importance, with 78% of voters in agreement with this notion (Table 2).

However, there was much less consensus regarding the status of SU as a soluble biomarker, with about one-third of participants agreeing, disagreeing, or being uncertain regarding this concept (Table 2). Plenary discussion noted particularly that it was unclear for which outcome SU was being proposed as a surrogate. The appropriate choice of endpoint mainly revolves around its clinical importance to the individual with the disorder, and its temporal relationship to the intervention. Thus, endpoints such as structural joint damage, death, or disability are typically appropriate endpoints for which surrogate biomarkers aim to predict. In the case of chronic gout, while there are data that support the idea that changes in SU are associated with changes in PRO (pain, patient global, disability, HRQOL) over the same time period, there are no available data that clearly show any of the important endpoints listed are associated with changes in SU at more proximal timepoints.

CONCLUSION

SU is a critical outcome measure in chronic gout. It has the potential to fulfil the criteria for a soluble biomarker. Existing evidence for SU as a soluble biomarker has been compiled and will be reported more comprehensively as a literature review. Further analysis of existing data from clinical studies is required to determine whether SU can predict future important outcomes, in particular disability. It is possible that such an analysis could be considered by OMERACT via Web-based voting before OMERACT 11 (so-called OMERACT 10b) to further address this issue. Further research that examines the influence of excellent SU control upon structural damage is also required.

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Table 2. Results of plenary voting related to serum urate measurement.

Question	Yes (%)	No (%)	Don't Know (%)	Total
Do you agree that serum urate meets the OMERACT filter for truth discrimination and feasibility?	56 (78)	8 (11)	8 (11)	72
Do you agree that serum urate meets the OMERACT biomarker criteria?	27 (34)	25 (32)	27 (34)	79

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