Gout and Association with Erectile Dysfunction

For greater than a century, and seemingly even exceeding a millennium, the clinical features of gout have been clearly recognized. These include rapidity of onset, crescendo escalation of joint pain and swelling, association with gluttony and excessive consumption of high purine foods and alcoholic beverages, and predilection for involvement of the first metatarsophalangeal joint (i.e., podagra) at onset of disease^{1,2}. Similarly, demographic aspects about gout are well known: the predominant involvement among men and the abrupt rise in disease incidence among women in the postmenopausal phase of life^{3,4,5}. In contrast, what is relatively new to the field of gout epidemiology is the increasing number of comorbid disorders that are associated with gout incidence and prevalence.

In fact, gout is not a condition that lives in isolation. Gout keeps company with many common and highly prevalent chronic medical disorders in contemporary society. For example, among data derived from the National Health and Nutrition Examination Survey 2007–2008, the large majority of Americans afflicted with gout have one or more concomitant comorbidities⁶. Over 70% of affected men and women have concomitant hypertension and/or compromised renal function; and over half are obese. Approximately one-quarter have diabetes mellitus; the same proportion has a history of nephrolithiasis. Moreover, in the subsequent 2009–2010 survey period, the prevalence of gout steadily rose in association with increasing number of involved comorbidities. As such, the overall prevalence of gout rose from 1.7% among those free of comorbidity, to 4.1% among those who were hypertensive, to 7.0% in those hypertensive with one additional cardiovascular risk factor, and then higher still, to 9.8%, among hypertensive adult Americans with 2 additional cardiovascular risk factors⁷. Such large population-based surveys also afford the opportunity to observe these comorbid associations among various demographic groups, including non-Hispanic whites, non-Hispanic African Americans, and Mexican Americans living in the United States⁸.

Further, recent reports have recognized yet additional comorbidities associated with gout, including obstructive sleep apnea and psoriasis^{9,10}. One by-product of the cumulative nature of these gout-comorbidity reports is to prompt consideration of the directionality of the association. Is gout only the consequence of this overt (or occult) comorbidity burden? Alternately, might gout (and related uric acid concentration) be the proximate cause in the biologic pathway to develop comorbidity?

In this context we learn of yet another disorder that is comorbid with gout in the current issue of *The Journal*. In the first of 2 related reports, the incidence of erectile dysfunction in Taiwan was compared in a nationwide cohort study among 19,368 men with gout compared to 77,472 age-matched controls¹¹. Four controls without gout were identified for each man with gout. Enrollment began between 2002 and 2008, with followup extending to the end of 2010. An immediate message is that men in Taiwan with gout are sicker, in that they have a greater comorbidity profile. Those with gout have a greater and statistically higher prevalence of diabetes, heart disease (both ischemic heart disease and congestive heart failure), hypertension, and renal failure than those without gout. Gout does not live alone. After age-adjustment, those with gout experienced a 20% increase in incidence of erectile dysfunction over the period of followup. Further, if gout coexisted with any other comorbid disorder, the relative risk to develop future erectile dysfunction rose 2-fold as compared to Taiwanese men free of comorbidity.

Notably, when the investigators examined this risk according to age categories, by stratification of the cohort in groupings of < 34 years, 35–44, 45–54, and 55–64 years of age, in each age stratum, the incidence of erectile dysfunction among those with gout exceeded the rate observed among those without gout. The heightened risk to develop erectile dysfunction was present both prior to and after adjustment for comorbidity. A dose-response association was

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demonstrated, in that an incrementally greater number of comorbidities was related to successively higher risk levels to develop erectile dysfunction.

An additional intriguing analysis conducted in this report examined the effects of urate lowering therapy on the outcome of interest. Because the Taiwanese dataset included detailed information on prescription drugs, the authors were able to integrate use of allopurinol and other urate lowering agents into their modeling. Notably, those with gout (in the absence of comorbidity) who utilized allopurinol (or similar agents) for 90 or more days had a modestly reduced risk to develop erectile dysfunction versus those on drug therapy for a shorter period. The hypothesis underlying the analysis is quite intriguing as to whether reduction in the serum urate level can mitigate (or even reverse) the vascular injury (or harm) that may be gout-mediated^{12,13}. Although the observed effect sizes were noteworthy, they were not statistically significant. The findings do suggest that the effect of urate lowering therapy to potentially diminish adverse vascular outcomes ought to be further examined.

In this same issue of *The Journal*, we learn of a related investigation undertaken in an entirely different setting, which similarly examined whether gout is related to erectile dysfunction. The authors evaluated 201 men with a variety of arthropathies receiving care at a rheumatology ambulatory clinic over a 3-year period, from 2010–2013, at the Rutgers-Robert Wood Johnson Medical School in New Jersey¹⁴. Each participant completed the Sexual Health Inventory in Men instrument, a widely used tool in both the clinical setting and for clinical research purposes, from which a diagnosis of erectile dysfunction can be assigned and disease severity can be ascertained¹⁵. Among these men, 83 had gout while the remaining 118 were without gout and served as the comparator group ($n = 27$, rheumatoid arthritis; $n = 27$ osteoarthritis; $n = 16$, psoriatic arthritis; $n = 10$, ankylosing spondylitis; $n = 9$, scleroderma; $n = 6$, polymyalgia rheumatica; $n = 5$, low back pain; $n = 4$, lupus; $n = 2$, granulomatosis with polyangiitis, and $n = 6$, other).

Importantly, whereas three-quarters ($n = 63$) of those with gout reported experiencing erectile dysfunction, only half ($n = 60$) of those without gout reported these same symptoms. Moreover, severe erectile dysfunction was observed among one-quarter of those with gout compared to 14% of those without gout. In this cross-sectional study, these associations persisted after adjustment for age and comorbidities. In this study, however, gout severity, as assessed by presence of tophaceous deposits, was not related to the presence or severity of erectile dysfunction.

Interestingly, in the univariate analyses, the odds ratio (OR) of heart disease exceeded that of gout (OR 3.9 vs 3.0, respectively) for its association with erectile dysfunction. However, no comorbid disorder, including heart disease, retained statistical significance in the fully adjusted model. Further, the frequency of many of the comorbidities,

including heart disease, hypertension, diabetes, and hypercholesterolemia was higher among those with gout than among the aggregation of the various other arthropathies and rheumatologic disorders, albeit with differences that were not statistically significant. Thus, while these clinic-based data similarly support a relationship between gout and erectile dysfunction, they do not as compellingly demonstrate an association that is independent of heart disease and other comorbidities.

Prior to embracing the findings from this pair of reports, one need consider any potential systematic flaws or bias that may have contributed to the reported association. In this regard, there is no reason to suspect that an ascertainment bias for future erectile dysfunction would prevail among those with antecedent gout. In the Taiwanese dataset, the investigators were able to determine that 80% of the diagnoses of erectile dysfunction were made by urologists, a diagnostic formulation unlikely to have been influenced by prior or concomitant gout. Further, one of the important methodologic strengths of the Taiwanese dataset is its derivation from a single-payer, health insurance program, which insured virtually all of the nation's population. It is therefore comprehensive in scope. Although the reported analyses were conducted on a subset of the population, the participants were randomly selected. Further, diagnoses of gout in the New Jersey study were identified upon chart review and were assigned with high face validity, after demonstration of urate crystals by arthrocentesis, examination evidence of a tophus, or satisfaction of the classification criteria for gout¹⁶. In contrast, the Taiwanese administrative database lacked this richness in clinical detail.

While the epidemiologic evidence derived from this issue's 2 reports supports an association between gout and erectile dysfunction, and in the Taiwanese report, emphasizes a temporal relationship between antecedent gout and the subsequent development of erectile dysfunction, how might the 2 entities be mechanistically linked? Is there a potential biologic plausibility underlying this epidemiologic association? Otherwise stated, might gout, in and of itself, pose a direct risk to vascular disease? Is hyperuricemia in the direct causal pathway to arterial vascular disease?

The answer may lie in the physiologic effects exerted by elevated uric acid (the most important risk factor for the development of gout) on the vasculature¹². These include the induction of vascular smooth muscle cell proliferation, oxidative stress, and activation of the renin-angiotensin axis in vascular beds. The resultant effects appear deleterious to local arterial and arteriolar structures and produce microvascular damage. Further, experimental data, albeit on a small scale thus far, demonstrate that among 30 adolescents with both hypertension and hyperuricemia, treatment with allopurinol resulted in a lowering of systolic and diastolic blood pressure¹⁷. Thus, lowering of serum urate levels among adults with moderate-to-severe gout may hypothetically

diminish their adverse cardiovascular morbidity and mortality profile.

While it is known that gout is associated with hypertension, coronary artery disease, cerebrovascular disease, carotid artery disease, renovascular disease, and peripheral arterial disease, the penile vasculature with resultant compromise to the network of smooth muscle cells and endothelial cells within the corpora cavernosa may also be a downstream target of uric acid-mediated vascular injury¹⁶. The present pair of studies reported in this issue of *The Journal* lends credence to this notion.

ALLAN C. GELBER, MD, MPH, PhD
Professor of Medicine,
Johns Hopkins University School of Medicine,
Baltimore, Maryland, USA.

Address correspondence to Dr. A.C. Gelber, Johns Hopkins University School of Medicine, 5200 Eastern Ave., Mason F. Lord Bldg., Center Tower, Suite 4100, Baltimore, Maryland 21224, USA; E-mail: agelber@jhmi.edu

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