

A Changing Landscape of Gout: Comorbidity Matters



Gout is the most common inflammatory arthritis, with an increasing prevalence in many parts of the world^{1,2}. Fewer studies have estimated the incidence of gout and its global trends. The Second and Third National Studies of Morbidity in General Practice in the United Kingdom estimated the respective gout incidence of 1.0 and 1.4 per 1000 person-years in the periods 1971–1975 and 1981–1982³ while database-based research estimated an incidence of 1.19–1.80 per 1000 person-years in the period 1990–1999⁴ and from 1.36–1.77 per 1000 person-years in the period 1997–2012¹. Data from the Rochester Epidemiology project estimated an age- and sex-adjusted incidence of gout of 45 per 100,000 people in the period 1977–1978 and 62 per 100,000 people in 1995–1996⁵. In this issue of *The Journal*, Elfishawi, *et al* also used data from the Rochester Epidemiology project to compare the incidence of gout between periods 1989–1992 and 2009–2010⁶. The incidence more than doubled, from 66.6 to 136.7 per 100,000 people. This study used the same cohort in Olmsted County, Minnesota, USA, and the same system of medical recording (for case identification) as the previous study by Arromdee, *et al*⁵. They collectively provide serial measurements of gout incidence covering over 3 decades and document a tripling of gout incidence. Overall, data from the United Kingdom and the United States portrayed a similar pattern of accelerating gout occurrence.

How to explain this worrisome phenomenon? In general, a significant change in disease incidence implies a change of risk factors or population composition. Elfishawi, *et al* provide their interesting observations: a multifold increase in many associated comorbidities of gout and hyperuricemia⁶. For example, there was a 4-fold increase for diabetes, 3-fold for renal diseases and hyperlipidemia, 50% for obesity, and 30% for hypertension. A closer look at the data found that the vast majority of incident gout patients in 2009–2010 in Minnesota had at least 1 such comorbidity that is known to associate with hyperuricemia and subsequently, gout, while fewer patients diagnosed with gout in 1989–1992 had any of these comorbidities. However, data from the National Health and Nutrition Examination Survey described a more modest increase in the prevalence of hyperuricemia: from 19.1% in

1988–1994 to 21.5% in 2007–2008⁷. Therefore, although hyperuricemia is the most important risk factor for gout, it alone cannot explain the substantial increase in gout incidence. Other mechanistic factors are required to explain the association between an increase in gout incidence and the increasing prevalence of associated comorbidities among these patients.

However, this study and previous evidence undoubtedly indicate a changing landscape of gout and that our strategy to manage gout must consider the high prevalence of comorbidities rather than treating them as arthritis alone. First, the initial assessment of incident gout patients should include a comorbidity checklist. Currently, the European League Against Rheumatism recommendations⁸, the British Society for Rheumatology⁹, and the American College of Rheumatology guidelines¹⁰ all recommend comorbidities that may contribute to or associate with hyperuricemia as part of an initial assessment of patients with gout. The comorbidity checklist, including obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, urolithiasis, and chronic kidney diseases, is roughly consistent with the comorbidities that occurred more commonly in newly diagnosed patients with gout, as reported by Elfishawi, *et al*⁶. Despite recent evidence indicating that gout is associated with a greater array of comorbidities¹¹, it seems reasonable to consider the most common comorbidities that are also risk factors for major adverse cardiac events such as coronary heart diseases. Second, clinicians must consider the effects of short-term or long-term gout treatment on the associated comorbidities. For example, repeated use of nonsteroidal antiinflammatory drugs to control arthritis may be dangerous for patients at high risk for cardiovascular or renal diseases, while selected patients with heart failure may benefit from allopurinol¹². Medications such as aspirin or thiazide diuretics may interfere with hyperuricemia control. These complex drug-disease interactions require careful consideration to maximize clinical benefits while minimizing risks. Third, comorbidities can be used as an indicator of prognosis to assist patient categorization and to identify high-risk patients. However, although gout is a well-accepted risk factor for

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cardiovascular¹³ and renal diseases¹⁴ and is associated with a higher risk for mortality¹⁵, the effects of interaction between gout and comorbidities on the overall prognosis are still unclear. Nevertheless, gout patients with associated comorbidities should be considered high-risk individuals, and they need a thorough assessment and observation.

The study by Elfishawi, *et al* has raised questions that remain to be answered: First, is the increasing incidence of gout a unique problem in developed countries such as the United States, or is it an epi-phenomenon across the globe? The Global Burden of Disease 2010 study found no increase in global gout prevalence between 1990 and 2010¹⁶, which seems to contradict the results of Elfishawi, *et al*⁶. More studies are needed to harmonize these differences. Second, does the increased prevalence of comorbidities in incident gout patients imply a pathogenic link between these conditions? A recent metaanalysis summarizing studies investigating the association between urate levels and comorbidities concluded that a causal role of urate levels linked to comorbidities such as diabetes, hypertension, metabolic syndrome, and renal diseases has not been demonstrated by Mendelian randomization study (which eliminates confounding using genetic tools) with sufficient evidence, despite a strong support from epidemiological studies¹⁷. Third, should gout patients with comorbidities be managed differently from those with “primary” gout? How should they be categorized?

Elfishawi, *et al* demonstrated an increased incidence of gout in the past 2 decades in Olmsted County, but whether this finding can be generalized externally remains to be observed. The alarmingly high prevalence of associated comorbidities in newly diagnosed patients with gout reminds us that most gout patients are complicated, with many conditions that may have dire consequences. We still are not sure about the causative relationships between gout and associated comorbidities, but it is prudent to consider a comorbidity checklist for all newly diagnosed patients, and probably also for all patients with existing gout. Last, a research agenda to fully understand the global trends of gout incidence in other areas/countries and the occurrence of associated comorbidities and their effect on the clinical management of gout is warranted for better care of patients with gout.

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