Editorial

Should we be morbid about comorbidities in the rheumatic diseases?

Understanding the impact of comorbidity on rheumatic disease

The importance of comorbidities in the treatment of rheumatic diseases, and the timeliness of this subject, is exemplified by the overwhelming response to the call for papers in this themed issue on comorbidities in Rheumatology.

Rheumatology has seen an explosive growth in our ability to diagnose and manage many of the rheumatic diseases over the past two decades, with the development of a number of remarkable therapeutic breakthroughs, in terms of both timing of treatment and development of new molecules. Because of adverse effects of many current treatments and longer survival rates of patients, the influence of comorbidity on treating rheumatic disease has become more prominent and clinically relevant. In addition, increasing the use of surveillance registries and well-designed cohort studies has allowed more longitudinal data to be captured and has helped with recognition of comorbid conditions. Although there has been a reduction in the frequency and severity of some comorbid conditions, we do see an increase in the frequency and severity of others that occur in a variety of rheumatic conditions across a wide age range.

The excellent response to our call for papers has made it possible to assemble an exciting issue of original articles and reviews authored by leading researchers on important subjects such as malignancy, cardiovascular diseases, infections, lower airway disease and comorbidities in paediatric diseases.

This issue has a number of articles that discuss the prevalence and impact of comorbidities in RA, OA, SLE, gout, SS, progressive SSc and PsA. Other papers focus on disease impact on physical and mental health status.

The most commonly recognized and frequent type of comorbidity is cardiovascular disease and associated risk factors such as metabolic syndrome. Not surprisingly, about half the original articles relate to this area. The wide impact of comorbidities across this spectrum of diseases is illustrated by the contributions in each of these entities. The original contributions raise interesting concepts.

An example is the burden of comorbidities in patients with gout. While the association between gout and cardiovascular disease has long been recognized, the epidemiological studies submitted by Robinson et al. [1] and Kuo et al. [2] provide some estimate of the size of the cardiovascular comorbidity burden. The articles by Taylor-Gjevre et al. [3] and Stamp et al. [4] highlighting associations between gout, obstructive sleep apnoea and metabolic syndrome, are thought-provoking and challenge our assessment of gout patients in clinical practice. The precise reason for these associations is not entirely clear. The article by Thornley et al. [5] discusses whether serum urate may be causally linked based on results from a screening study for cardiovascular diseases in primary care.

Another example is the link between cardiovascular disease and metabolic syndrome, both of which are known to be associated with chronic inflammation. While it is well established that cardiovascular events are a major cause of mortality in patients with ANCA-associated vasculitis, there is limited evidence that explains the mechanisms responsible for this association. The article by Wilde et al. [6] highlights the increased prevalence of metabolic syndrome in ANCA-associated vasculitis vs controls. The frequency of metabolic syndrome has almost doubled, which may contribute to excessive loss due to cardiovascular mortality observed in these patients. Also, since metabolic syndrome is associated with a pro-inflammatory state, this could increase the risk of relapse in ANCA-associated vasculitis.

For the past several decades, the effect of anti-rheumatic therapies on cardiovascular comorbidities has been intensely studied. Mathieu et al. [7] reported that TNF inhibitor blockade over 1 year does not decrease arterial stiffness in AS patients, but whether this is related to a change in cardiovascular events is unknown.

More precisely, a key question is whether control of inflammation is directly linked to a reduction in the risk of cardiovascular incidents. This raises issues, in observational studies, of confounding by indication, whereby the patients with the most severe inflammatory disease are exposed to a higher intensity of treatment. It therefore becomes difficult to know whether cardiovascular comorbidity is associated with disease or whether it is due to effects of its treatment. Avina-Zubieta et al. [8] present an elegant study that attempts to address this question with regard to corticosteroid (CS) use in RA. They describe the immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in RA patients and conclude that their use is associated with an increased risk of cardiovascular events.
As inflammatory rheumatic diseases are often treated intensively with immunomodulatory medications, the risk of long-term complications, especially an increased risk of malignancies, has been an area of concern, and extensive follow-up studies of patients treated with these new therapies have been conducted, in both long-term clinical trials and registries. Although several international biologics registries have been established and long-term extension studies have been conducted, the impact of non-biologic disease-modifying therapy for RA on the development of cancer is much less studied. Mercer et al. [9] provide a key insight into this group of patients based on the results from the British Society for Rheumatology Biologics Register (BSRBR) Control Center Consortium and show an overall increase in cancer, particularly lung cancer, Hodgkin and non-Hodgkin lymphoma in patients not treated with biologic therapies.

Lung involvement in rheumatic diseases is thought to be relatively rare, but a feared and potentially life-threatening complication. This is especially the case for SSc, where it is not uncommon and a frequent cause of morbidity and death. Moore et al. [10] illustrate the impact on the extent of disease with high-resolution CT of the lungs where baseline abnormality is a clear predictor of decline and mortality in SSc-related interstitial lung disease. This highlights the importance of early recognition of pulmonary involvement and may provide a window of opportunity where early intervention with appropriate medication can result in more effective treatment and prolonged survival.

Overall, it is clear that many rheumatic diseases, including the ones discussed in this issue of *Rheumatology*, are often complicated by comorbidities that influence our therapeutic decision-making on a daily basis. The development of some comorbidities leads to the cessation of ongoing therapies, while in other instances the addition of other therapies is required.

Comorbidities occur in association with all rheumatic diseases and with many of our therapies, and, as these papers illustrate, occur across the entire spectrum of internal medicine.

This issue of *Rheumatology* widens our present knowledge on the role of comorbidities and their implications for treatment; it is a challenging but important task for rheumatologists to incorporate the monitoring and management of these comorbidities in the daily management of our patients.

Enjoy reading it!

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**References**