Review

Treatment failure in inflammatory arthritis: time to think about syndemics?

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Abstract

Social determinants of health play a crucial role in health and disease. In current times, it has become increasingly known that biological and non-biological factors are potentially linked and help to drive disease. For example, links between various comorbidities, both physical and mental illnesses, are known to be driven by social, environmental and economic determinants. This contributes to worse disease outcomes. This article discusses the concept of syndemics, which although well-described in some conditions, represents a novel concept in the context of rheumatic and musculoskeletal diseases. Written in the form of a viewpoint, the article focuses on a novel theoretical framework for studying inflammatory arthritis, based on a syndemic approach that takes into account the social context, biocultural disease interaction, and socio-economic characteristics of the setting. Syndemics involving inflammatory arthritis may be most likely in a social context involving limited access to health care, lack of physical activity and obesogenic diets, high rates of alcohol consumption, and high exposure to stressful life events.

Key words: syndemic, social determinants, health inequity, inflammation, DMARD, depression, comorbidity, disability

Rheumatology key messages

- Syndemics involve multimorbidities patterned by specific social context.
- A syndemic approach in inflammatory arthritis is appropriate for studying complex disease interactions and outcomes.
- Syndemic knowledge in inflammatory arthritis would enable effective intervention at both policy and clinical levels.

The concept of syndemics

As science advances, it is becoming increasingly known that mechanistic links exist between several comorbidities, including physical and mental illnesses, driven by social, environmental and economic determinants. The study of potential links and adverse interactions among comorbidities that are more likely in the context of specific social determinants such as, for example, low education, unemployment, low household income, racial/ethnic

discrimination, forced migration, and exposure to violence, have been referred to as syndemics [1–3]. The syndemic framework also allows for the study of large-scale social, environmental, economic and other factors that promote disease interaction and clustering [3, 4]. The hallmark of a syndemic is the presence of two or more disease states that ‘adversely interact with each other, negatively affecting the mutual course of each disease trajectory, enhance vulnerability, and which are more deleterious by experienced inequities’ and that these interactions occur more frequently or with greater morbidity in the setting of specific negative social determinants [2].

The first model of a syndemic was based on observations of how Substance Abuse, Violence, and AIDS cluster together and impact on one another among impoverished inner-city populations in the USA—this was termed the SAVA syndemic [5]. More recently, the VIDDA syndemic describes how Violence, Immigration, Depression, Diabetes, and Abuse cluster among Mexican immigrant women in Chicago, USA [6].

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Inflammatory arthritis in the era of syndemics

Inflammatory arthritis (IA) represents a group of arthritides that are characterized by autoimmune-driven inflammation of the joints, which represent the primary target. It is a leading cause of pain, fatigue, physical and mental disability and substantial loss of quality of life [7]. The incidence of early IA has been reported to range between 115 and 271 per 100 000 adults [8, 9]. Common IA subsets include RA, SpA and PsA. Although not previously studied in IA, it is possible that there exists a syndemic in IA that builds on the principles of influences between both biological and non-biological factors that may drive the disease.

Aetiopathogenesis of IA

Although a definitive cause of IA has not been identified, an environmental trigger in a genetically predisposed individual has been attributed as the most likely mechanism [10]. Traditional research in IA has for many years focused on genetic and biological factors and their role in disease. The current understanding is that multiple complex molecular networks are implicated in disease development and progression [11].

Treatment of IA

IA has been associated with poor clinical outcomes of disease, especially if not treated early [12]. Treat-to-target management principles [13] for intensive reduction of inflammation early on in RA, the commonest IA subtype, are now well recognized and a therapeutic window of opportunity early in the disease process, identified. These treatment principles are broadly applicable to most forms of IA. In RA, the use of an early and intensive treatment approach has been shown to be cost effective and widely advocated in countries like the UK; yet, significant geographical variations have been demonstrated in the care of people with RA [14].

Beyond the conventional synthetic DMARDs, the advent of biologics and more recently small molecules and targeted synthetic DMARDs on the market, has transformed the treatment landscape and prognosis of people affected. What was once an incurable illness, resulting in joint destruction and severe disability, these days represents a potentially treatable disease? These newer, albeit more expensive biologic treatments, are generally widely available in high-income countries, although in some stringent guidelines preclude their early use in view of their cost [15].

Treatment failure in IA

Although remission is nowadays an achievable goal in many patients with IA [16–18], a proportion of patients will not achieve what is perceived as an optimal treatment target: remission or at least low disease activity. This is partly due to the fact that, innate variation in biological and genetic factors explains only part of the variation in disease outcomes or health in general. This poses distinct

challenges to clinicians and health-care professionals, who often seek for explanations other than genes or a disease activity level, as a cause of poor treatment response in those affected. The so-called DAS blindness, in which the consultation focuses purely on components pertinent to the DAS-28 [19], is catching headlines, along with the increasing desire to apply patient-centred care and the traditional approach of focusing solely on the level of inflammation, when treating patients. Patients for whom treatment fails to control their disease are at risk of ongoing, unsuppressed inflammation that consequently leads to joint destruction, poor function, long-term disability and low quality of life. Treatment failure is not just about not achieving an optimal disease activity score, but all the other consequences that people experience, such as ongoing pain, fatigue, low mood, and inability to work or have a normal life [20].

IA and comorbidities

IA frequently co-exists with other conditions (comorbidities). A wealth of evidence [21–25] demonstrates the increasing comorbidity burden over time and the impact on outcomes in people who live with IA. In the case of RA, one-third of patients have at least one comorbidity on first presentation, increasing up to ~80% in established disease [21, 22], with similar rates reported in PsA [26]. Rising life expectancy along with coexisting conditions in patients makes management more complex and costly, with increased use of clinical services and higher medication costs. The development of multimorbidity (two or more co-existing long-term conditions) results in lower achievement of treat-to-target goals [27], with many pathophysiological/mechanistic processes implicated.

Patients have pointed out the largely fragmented care they commonly receive that can lead to failure to assess multimorbidity regularly and treat the person holistically (National Voices/Departmental patients). Multimorbidity is complex, affected by a number of factors; inattentiveness to multimorbidity and disease interactions may reduce the effectiveness of disease-specific treatment. Furthermore, multimorbidity results in functional decline [22], worse quality of life (QoL) [28] poorer survival [29] and higher health-care utilization [30]. The unmet need of addressing comorbidities in the treatment of difficult-to-treat RA has been highlighted at the European level [31, 32], and also endorsed by the EULAR through the work of a task force dedicated to the development of management recommendations for difficult-to-treat RA (https://www.eular.org/clinical_affairs_initiatives.cfm).

Physical comorbidity: focus on obesity

Important physical comorbidities in IA include obesity, a major contributor to global disease burden [33]. In the context of musculoskeletal diseases, the study of obesity is pertinent in view of its serious adverse effects on health, including the association with disability through complex interactions with social and environmental factors [34]. In RA, obesity has been implicated as a risk factor for the development of the disease [35–38], and also as a common comorbidity, increasingly seen on first

presentation of RA [21]. Evidence suggests common mechanistic pathways shared between the inflammatory states mediated by obesity and those mediated by inflammatory rheumatic diseases, for example, through abnormal expression of adipokines such as TNF- α and IL-6 [39–42]. The immunomodulatory and pro-inflammatory properties of adipose tissue are suggestive of obesity being a low-grade, chronic inflammatory condition [43]. In RA co-existing with obesity, the immune- and obesity-mediated inflammatory states may work synergistically, affecting disease activity and consequently other clinical and structural outcomes of disease. A recent meta-analysis supports the view that obesity and overweight reduce the chances of achieving minimal disease activity in patients diagnosed with RA and PsA who receive treatment with conventional or biologic DMARDs [44]. From a clinical point of view, it should be noted that obesity might hamper proper grading of disease activity, resulting in an overestimation of the level of disease activity. The latter could be through, for example, an erroneously increased count of actual swollen joints due to excess adipose tissue overlying the joints.

Mental illness comorbidity: focus on depression

The presence of mental illness comorbidity such as depression in IA, and specifically in RA, is now widely recognized as an important problem [22]. Accumulating evidence suggests the possibility of shared pathophysiological mechanisms between RA and depression, also supported by clinical trials in immunomodulatory therapy [45]. The understanding that immune-mediated inflammatory diseases and depression can co-exist is therefore not new [45] and is supported by strong evidence showing raised levels of cytokines, including IL1, IL6, TNF α and CRP, in the peripheral blood of patients with depression compared with healthy controls [46–48]. These evolving insights shed light into potential therapeutic interventions for depression in the IA setting; yet, if the trigger of depression lies in non-biological as opposed to biological ongoing underlying factors e.g. social isolation, loneliness or poverty, medical treatment may well fail.

Social determinants of health

Social factors, referred to as ‘social determinants of health’ (SDH) by the World Health Organization (WHO) refer to conditions in which people are born, grow, work, live and age, and the wider set of circumstances and systems (e.g. economic, social and political policies/systems) that influence their daily life [49]. SDH are known to have a major impact on health outcomes in general, especially for the most vulnerable populations.

There is growing recognition of the powerful role of SDH and how these shape health across a wide range of health indicators, settings, and populations [50, 51]. Yet, in IA, unlike the well-established role of biological factors on disease outcomes such as level of inflammation, less is known about the impact of SDH on IA outcomes and their interplay with other disease parameters such as comorbidity.

The extent to which social dimensions may play a key role in the development and progression of RA, and their

complex interactions with biological factors (e.g. the inflammatory disease processes, presence of comorbid conditions) needs to be systematically examined. In RA, evidence supports differential responses to treatment, for example based on different ethnic backgrounds and other social determinants. For example, despite the significant progress in the therapies available for RA and their use, clinical outcomes appear to vary across certain groups, such as African Americans and Hispanics relative to their White counterparts and among those of lower socio-economic status [52–54]. Furthermore, RA is more prevalent, the disease burden is greater and the risk of mortality larger among individuals of low socio-economic status [52–55]. Finally, time to commence DMARD treatment takes longer in minority populations, as well as in those seeking public hospital care compared with private care [56].

SDH, social gradients and comorbidities

There is strong evidence of a social gradient for comorbidity risk, including mental health [57]. Conventional health-care frameworks often fail to address the effects of social factors on key aspects of disease. Recent studies in OA suggest comorbidity mechanisms differ by socio-economic strata, highlighting the need for different approaches to prevent comorbidity [58]; less is known in IA. Reports on RA as early as the 1990s suggest that patients from deprived areas have poorer function, which is associated with greater medical/paramedical and social needs and call for ‘strategies and resources for healthcare to be adjusted according to this variation’ [59].

Social isolation and pathophysiological links

Perceived social isolation (PSI) has been the focus of sociological research in recent years, in particular in view of the advent of increasing social isolation and life expectancy, resulting in rising populations of elderly people [60]. PSI has been associated with neuroendocrine among other physiological effects [61] and pathophysiological links to a variety of illnesses via complex processes [62]. Links between social isolation and poor health, including inflammation, depression and cardiovascular disease (three common afflictions in IA), have now been well established [63, 64]. With a shifting treatment paradigm in IA (e.g. treating intensively with combination therapies and biologics) that potentially gives everyone with IA better chances of remission, understanding why in a significant group of people treatment continuously fails (resulting in devastating consequences of disease) and the potential role of social parameters is crucial.

Health inequity in IA

It is now widely accepted that SDH are responsible for significant levels of health inequity [65]. While some health inequities are the result of natural biological differences or free choice, others are beyond the control of individuals or groups that could be avoided. Globally, over 400 million people are reported to lack access to essential health care [66]. Where it is accessible, it is too

often fragmented or of poor quality, with low health system responsiveness and satisfaction with health services reported in many countries [67].

In IA, despite the great advances in the diagnosis and management of disease, and in particular the spectrum of therapeutic agents available, for some people disease remission remains unachievable. This paradox seems to primarily derive from failure to address individual and social factors that may be driving the disease. This imbalance represents an important cause of health inequity, demonstrated already in IA, including RA [68–71] and SpA [72], based on data from our group. Distribution of health is determined by a wide variety of individual, community, and national factors, and there is a growing body of evidence that suggests inequalities not just in the distribution of health (i.e. health outcomes) but also in access to health care. Health inequalities are estimated to cost the National Health System (NHS) in the UK around £5.5 billion per year and require urgent attention (www.local.gov.uk/marmot-review-report-fair-society-healthy-lives).

Are there IA syndemics?

A syndemic framework for studying IA is particularly relevant, especially because conventional frameworks in medicine focusing on multimorbidity, for example, often overlook the effects of other factors such as SDH. Such an approach using a so-called syndemic lens may be helpful in identifying the associations between genetic, biological and social factors and why comorbidities may cluster together in specific settings. With regard to social determinants, and as an example, the diverse, multi-ethnic South London population in urban and deprived areas may subject patients to disadvantaged care. For example, poverty, unemployment and language barriers in the context of multimorbidity are potentially among the key issues that prevent fast and easy access to intensive treatment in IA, resulting in poor outcomes. This may vary between regions, where social determinants, including factors influencing access to care, are different, thus influencing which types of comorbidities are most likely to occur in different social context.

A recent study exploring the prevalence of musculoskeletal disorders in Latin American indigenous communities demonstrated for the first time the close relationship between rheumatic diseases, comorbidities and socio-economic conditions [73]. Among the American indigenous communities, diabetes comorbidity ranged from 0.7% to 10%, heart disease ranged from 1% to 18%, obesity ranged from 7% to 18%, and depression ranged from 5% to 12%. For all of the comorbidities, there was wide variation between the communities. In their network analysis, lack of access to affordable health care was important, but had differential effects by site. Regardless of site, being employed was a protective factor against comorbidities. In communities with high alcohol use, there was a stronger rate of cardiovascular disease and arthritis comorbidity.

As a contrast, in the USA, arthritis comorbidities vary considerable by region, but tend to be considerably higher

than the comorbidity rates observed for indigenous communities [74]. Comorbidity rates of arthritis with obesity range from 25% to 41% across the states, with the greatest comorbidity in the Southeast and Appalachian regions of the USA. These regions are characterized by state governments with limited support for health care and education, higher rates of unemployment, and low leisure-time physical activity. This pattern is echoed for arthritis and diabetes, with the lowest comorbidity of 27% in California and rates twice that in Missouri, Arkansas, South Carolina and Maine. However, patterns for arthritis and coronary heart disease follow a different pattern (range 26–73%), with the greatest comorbidity in Iowa, New York and Rhode Island. These regions tend to have relatively better health care access, suggesting that other factors may contribute to these rates.

These findings justify the need for the design of multidisease and multidimensional interventions more globally [75, 76]. The regional specificity of these recommendations is crucial, because syndemic approaches are rooted in the idea that the specific social, economic, political and cultural factors influence the frequency and severity with which multimorbidity occurs. The approach needed to address musculoskeletal diseases and associated multimorbidities among indigenous communities in Latin America would differ from those solutions proposed for regions of London where similar multimorbidities exist. This is because the pattern of social determinants and the solutions for mitigating them will differ in different social contexts.

We believe comorbidity with depression should form a core part of this theoretical framework in IA under some context, in view of its association with most long-term conditions, but in particular those characterized by inflammation and pain, as is the case with IA (Fig. 1A and B) [77]. Depression is in fact a component of many syndemics [2, 78]. According to the WHO World Health Survey, comorbidity with depression incrementally worsens health beyond each of angina, arthritis, asthma and diabetes alone or in any combination of these four long-term diseases without depression. Targeting depression alone (e.g. with pharmacological therapy) may not be enough. This is because its pharmacological treatment may not ensure swift recovery when symptoms stem from problems in the patient's social circumstances. Ultimately, these examples highlight the fact that despite the pharmacological agents and psychological therapies being potentially the same for IA multimorbidity all over the world, the social determinants differ, driving different types and severity of multimorbidity and varying outcomes.

Conclusions

Syndemics are multimorbidities patterned by specific social context. The use of such a framework in studying treatment failure in IA would provide insights into inter-linked factors and how these could and need to be targeted to prevent the problem of treatment failure in IA. To respond to a syndemic, one needs to prevent or control

Fig. 1 Example of syndemic aetiology (1A) and a syndemic-informed care model (1B) in inflammatory arthritis

(A) Environmental trigger(s) in genetically susceptible individuals is a crucial first step in the onset of inflammatory arthritis. The condition can be worsened by lack of appropriate health care, due to health inequities, and further worsened by comorbidities impacting inflammation and immunomodulation, e.g. depression, obesity, and metabolic disorders. Conserved transcriptional response to adversity (CTRA, <https://www.pnas.org/content/110/41/16574>) represents an important step in the process, driven by social factors. Based on the syndemic model, inflammatory arthritis multi-morbidities are more likely to occur under specific patterns of negative social determinants, whereas settings with more social protective factors and lower exposure to negative determinants will have less frequent and less severe multi-morbidity. **(B)** DMARDs, if used early, can influence the severity and progression of inflammatory arthritis. Targeting comorbidities, especially modifiable ones (e.g. obesity) can also help improve the severity of inflammatory arthritis as well as other comorbidities like depression. Psychological interventions can help reduce exposure to psychological trauma and stress in people with lower socio-economic status and negative social determinants of health. Inflammation, the culprit of inflammatory arthritis, can thus be targeted through pharmaceutical, psychological and socio-economic interventions. Based on a syndemic framework, multimorbidity care and associated social interventions would be more important in settings characterized by a higher burden of negative social determinants of health.

not only each individual affliction, but also the forces that tie those conditions together and the underlying social determinants. Importantly, it would provide a deeper understanding of how patients with IA and their families within their social context may potentially be vulnerable to syndemics, and what local protective risk factors would

be most important to promote. Syndemic knowledge would make it possible to intervene effectively at both the policy and clinical levels by addressing both the roots of illness (e.g. local patterns of inequality) and the treatment of symptoms. This would naturally enhance the more holistic treatment of people affected by IA,

comorbidities and other patient and disease parameters localized to the context in which they may occur.

We strongly advocate a syndemic approach to the study of IA and other long-term musculoskeletal conditions, with a multidisciplinary team research focus to systematically examine the social context, biocultural disease interaction, and socio-economic characteristics of the setting. A syndemic framework approach may be helpful in studying treatment failure in IA in settings characterized by the poorest regional outcomes. Such a paradigm shift in rheumatological research enables deepening of our understanding of social inequalities. The implementations of its findings, with the support of and demand by patients, will achieve integrated person-centred health service as put forward by the WHO 2016 framework [67]. This would promote the implementation of contextually and culturally sensitive interventions, tailored to the community and individual needs, and ultimately advance health equity around the world.

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