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The Increasing Prevalence of Autoimmunity and Autoimmune Diseases: An Urgent Call to Action for Improved Understanding, Diagnosis, Treatment and Prevention

Frederick W. Miller, M.D., Ph.D. [Scientist Emeritus]

Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Bldg. 101, Maildrop A2-03, 111 T.W. Alexander Drive, Research Triangle Park, NC 27709

Abstract

Autoimmunity is characterized by self-reactive immune components and autoimmune disease by autoimmunity plus pathology. Both autoimmunity and autoimmune diseases are dramatically increasing in many parts of the world, likely as a result of changes in our exposures to environmental factors. Current evidence implicates the momentous alterations in our foods, xenobiotics, air pollution, infections, personal lifestyles, stress, and climate change as causes for these increases. Autoimmune diseases have a major impact on the individuals and families they affect, as well as on our society and health care costs, and current projections suggest they may soon take their place among the predominant medical disorders. This necessitates that we increase the scope and scale of our efforts, and coordinate our resources and studies, to understand autoimmune disease risk factors and pathogeneses and improve our diagnostic, therapeutic, and preventive approaches, as the costs of inaction will be profound and far greater without such investments.

Keywords

Autoimmunity; Autoimmune diseases; Risk factors; Global efforts; Prevention

Introduction

Autoimmunity can be considered as the presence of self-reactive adaptive immune components, and autoimmune diseases can be thought of as autoimmunity plus clinically

Phone: 984-287-3593, FAX: 301-451-5585, millerf@mail.nih.gov.

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apparent pathology [1,2]. Although proposals have been made regarding approaches to define autoimmunity and specific autoimmune diseases, there are still no commonly agreed upon general criteria for these [3,4]. This lack of consensus in autoimmune disease definitions, and even agreement on which specific illnesses constitute the autoimmune diseases, impede research and clinical care, and the development of international stakeholder-defined consensus on these issues would greatly enhance further progress in the field.

The precise mechanisms for the development of autoimmunity and autoimmune diseases remain unclear, however, a growing consensus has developed that they evolve from still-to-be-defined gene-environment interactions [5,6]. As a result of technological advances made possible by the human genome project and related investigations, many genetic risk factors for autoimmune diseases have been identified [7], but there has been relatively little progress in deciphering the even more profound impact of environmental influences [8,9]. This is not surprising given the difficult tasks of assessing the doses, durations, and effects of the myriad combined environmental exposures we experience over a lifetime [10] and the complex impacts they have on the maturation and function of the immune system [11].

Studies have found increased frequencies of autoimmunity and autoimmune diseases over recent decades [12,13]. Yet, there are many challenges in accurately assessing changes in the incidence and prevalence of autoimmunity and autoimmune diseases over time. First, as noted above, there is a lack of universal consensus on definitions of cases and disease criteria [3]. Secondly, many autoimmune disorders individually are rare and heterogeneous conditions that are likely underdiagnosed, with evidence of varying ethnic, racial, and geographic distributions, making current estimates of their actual numbers problematic [14–16]. Third, there are inadequate centralized and standardized national and international databases on which to base these estimates, and there are referral biases to tertiary care centers from which much of our current information arises. Methodologies for autoantibody and other immune assays are constantly evolving, and each varies in accuracy, sensitivity, and specificity [17]. Finally, with increased understanding, classification and diagnostic criteria for some autoimmune diseases have evolved over time [18].

Evidence for increasing autoimmunity

While autoantibodies alone are not diagnostic for disease, they do define the presence of autoimmunity. Some cases can develop transiently after infections, immunizations, drug use, or injuries [6,19,20]. However, in many situations, autoantibodies are persistent, pathogenic, and some of the best predictors of the development of autoimmune disease [21–24]. Investigators have been concerned that autoantibody frequencies have been rising for some time, yet most studies have not been population-based and did not always use validated assays. Recent investigations have studied autoimmunity using population representative samples and carefully assessed and consistent assays to overcome some of these limitations.

The National Health and Nutrition Examination Survey (NHANES) is a Centers for Disease Control and Prevention (CDC) program of studies begun in the 1960s designed to define the health and nutritional status of adults and children in the United States (https://

www.cdc.gov/nchs/nhanes/index.htm). The NHANES databases and serum repositories provide unique opportunities to assess the prevalence of autoimmunity in nationally representative samples of the US population across multiple time periods. One NHANES study showed that autoimmunity is common in the US [25]. For example, thyroid autoantibodies alone were present in 18% of US adults, including 10% of younger adults and 25% of older persons. Remarkably, 32% of adults 60 or more years of age had at least one of the four autoantibodies studied: rheumatoid factor (most often associated with rheumatoid arthritis), anti-thyroglobulin or anti-thyroperoxidase autoantibodies (associated with autoimmune thyroid disease), or anti-tissue transglutaminase autoantibodies (associated with gluten-sensitive enteropathies).

Antinuclear antibodies (ANA) are a diverse group of autoantibodies directed against nuclear and other cellular components and a frequent clinical screening assay for autoimmune diseases. NHANES data have shown that ANA prevalence was 11.0% in 1988–1991, 11.4% in 1999–2004, and 16.1% in 2011–2012 (P trend < 0.0001, Figure 1) [12]. This represents 22.3, 26.6, and 41.5 million affected individuals, respectively. The most impressive increase was in adolescents, where ANA prevalence rose steeply, with odds ratios of 2.07 and 2.77 in the second and third time periods compared to the first (P trend = 0.0004). Yet ANA prevalence also significantly increased in both sexes (especially males), older adults, and non-Hispanic whites [12].

Evidence for increasing autoimmune diseases

Consistent with the ANA findings above, which argue against the notion that increased physician recognition of autoimmune diseases alone may be causing their apparent rises, local, national, and international epidemiologic studies have discovered similar increases in the frequencies of most autoimmune diseases. Estimates of the yearly increases in the overall worldwide incidence and prevalence of autoimmune diseases are 19.1% and 12.5%, respectively [26]. Despite the limitations noted above in obtaining accurate estimates, prevalence data collated from multiple investigations of various autoimmune diseases in many global locations have confirmed an overall rising trend (Figure 2). Perhaps the best studied of these is type 1 diabetes [27], where investigations found a consistent 3–4% annual increase in incidence over the last three decades [28]. Not only are core currently recognized autoimmune diseases increasing, but the range of autoimmune and chronic inflammatory diseases continues to expand in number and scope, as additional disorders are found to have laboratory or clinical features implicating involvement of the immune system and autoimmune signatures [10].

Understanding the causes

Familial clusterings and recent molecular genomic advances clearly show the importance of genetic factors in the development of autoimmune diseases [7]. Nonetheless, most genes are neither good nor bad, but only their environments make them so. Moreover, our genetic architecture, which has evolved over millennia to allow us to thrive in prior environments, may in many ways be ill-suited to our rapidly changing modern environmental challenges. The contemporary consensus is that in autoimmune disorders,

multiple genetic and environmental risk factors interact in complex ways over long time spans to induce disease evolution from the genetic risk factor stage, to subclinical immune activation and autoimmunity, to early clinical signs and symptoms, and to finally result in a phenotype meeting classification or diagnostic criteria [5,29–31].

There are numerous complementary yet intersecting reasons for considering that environmental influences play a crucial role in the development of autoimmunity and autoimmune diseases [32]. These include: low to moderate concordance in monozygotic twins [33]; biologic plausibility from experimental in vitro and animal studies [34]; strong temporal associations with specific exposures and disease onset [35]; clear examples of dechallenge (improvement after suspect agent removal) and re-challenge (recurrence after suspect agent re-exposure), especially for drugs [36,37]; seasonal and geographic clusterings with disease onset [14,38,39]; seasonal associations with birthdates [40–43]; changes in incidence over time [26]; migration studies showing disease increases in groups moving from a low-incidence to a high-incidence region [44]; the major genetic risk factors are environmental response genes [7]; and strong observational epidemiological associations between exposures and certain diseases [9,32].

Taken together, the confluence of growing evidence points to many environmental factors that are possibly related to the development of autoimmunity and autoimmune diseases [45–48]. Of most concern are the major changes in our diets and the effects on microbiomes [49–52], xenobiotic contacts [53,54], infections [55,56], personal lifestyles and attendant increased obesity rates [57] and sleep deprivation [58], stress [59], air pollution [60], and the impacts of climate change [61], as possible contributing factors to these increases.

For example, there are ever-increasing numbers and amounts of xenobiotic chemical pollutants in commercial use [53], most of which have not been studied for their long-term immune effects, and some of which are associated with the development of autoimmunity [62]. It is also of concern that the list of therapeutic drugs implicated in the development of lupus continues to grow [37,63] and that cases of autoimmune diseases following biologic agent treatments are also rapidly escalating [64]. While the specific impacts of climate change on autoimmune diseases have not been well-studied, their many adverse effects on human health -- including increased food-borne, water-borne, vector-borne, and zoonotic infectious diseases, cardiopulmonary, renal, and pregnancy complications, malnutrition, ultraviolet radiation exposure, air and water pollution, toxin exposures, allergies, physical and mental stress, and compromised access to health care services -- are well known [65]. Given the growing evidence of the role of many of these factors in the development of autoimmune diseases, it is reasonable to suspect that climate change is an additional element contributing to their increased prevalence [9,32,45,47,56,59,61].

Implications

These findings have many profound implications. Regarding public health costs and the economy, the total direct and indirect costs of autoimmune diseases are difficult to assess for the reasons mentioned above and due to our fragmented health care systems. Nevertheless, autoimmune diseases clearly cause much personal suffering, high morbidity and mortality,

and are a significant driver of health care utilization and costs [66,67]. Direct costs in the US have been estimated at over $100 billion per year, but this is likely a gross underestimate [67]. A study of Korean national databases has estimated direct medical costs of the more common autoimmune diseases as high and rapidly increasing [68] (Figure 3). These estimates do not capture indirect costs, including lost productivity and incomes, and the negative impacts on patients' health, dependent care, families, and society in general.

A recent review of NIH's autoimmune disease research activities by the National Academies of Sciences, Engineering, and Medicine has found a number of gaps and limitations in the approaches that the different NIH institutes pursue, and among their recommendations was the creation of an Office of Autoimmune Disease/Autoimmunity Research within the Office of the NIH Director to enhance research collaboration and coordination in this area [69]. The committee also recommended the establishment of long-term systems to collect and ensure optimum usability of population-based surveillance and epidemiological data [69]. One tactic to increase understanding of the scope, epidemiology, and possible environmental risks would be to establish a central reportable system for autoimmune diseases similar to the NCI Surveillance, Epidemiology, and End Results (SEER) Program, which provides information on cancer statistics in the US population (https://seer.cancer.gov/). These recommendations could certainly aid in achieving some of the many unmet needs in autoimmune disease research in the US, but an even more global approach is needed for the worldwide coordination and enhancement of studies and clinical care in this area.

An urgent call to action

The rapid rise of autoimmune diseases around the world outlined here has had significant impacts on the public health, and which will continue to increase without intervention and change. Overcoming the growing negative personal and societal effects, as well as the rising costs, of this group of increasingly frequent disorders will require systematic planning and action on a global level. Increased research and clinical efforts, resources, and coordination, to intervene on a scale not previously seen, are needed to halt or reverse these trends. Some approaches that could be helpful are outlined below (see Box). Central to these is the integration of the international community of stakeholders – including caregivers, researchers, public health officials, regulatory and funding agencies, pharmaceutical companies, and patient support groups – to pool their expertise and resources and develop an agenda that coordinates global activities to expand current efforts, increase efficiencies, and minimize duplication of efforts.

Conclusions

Autoimmune diseases have had a devastating personal and caregiver impact on our society, with significant health care utilization resulting in high public and private costs, yet current projections suggest they will become even more prominent disorders in the future. This demands that we increase our attention and resources to coordinate and enhance our efforts in understanding their pathogeneses and risk factors, and to improve our diagnostic, therapeutic, and preventative approaches. The costs of inaction will be profound, and only

by dedicating additional resources now can we decrease the future frequency, morbidity, mortality, and costs of these conditions.

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Box:

Possible approaches to address the rapid rise in autoimmune diseases

- Convene international, multidisciplinary, stakeholder consensus conferences to: identify research opportunities and priorities; develop a standardized definition of autoimmune diseases and maintain a comprehensive listing of these; coordinate efforts to improve the integration and prioritization of basic, animal model, and clinical research; define approaches to measure direct and indirect costs to facilitate prioritizations; and assist in the coordination and oversight of other efforts
- Establish comprehensive standardized registries and repositories for all autoimmune diseases around the world
- Provide resources for well-designed studies of autoimmune diseases with similar features to define common and unique pathogeneses and risk/protective factors for various phenotypes
- Assess multiple gene-environment interactions for autoimmune diseases, including those grouped together based on shared mechanisms or risk factors, to allow for preventative strategies
- Coordinate efforts to identify a matrix of clinical features, risk factors, and laboratory biomarkers to allow for earlier and more accurate diagnoses that could minimize damage from chronic inflammation
- Conduct more efficient “basket/umbrella” investigations and other clinical trials involving multiple autoimmune diseases with similar therapeutic targets (e.g., interferon-targeted therapies for disorders with increased interferon signatures), as are now being performed in cancer studies
- Define best practices for medical care, therapies, and access to them
- Develop studies and practical guidance on prevention by evaluating a combination of promising biomarkers, lifestyle modifications, avoidance of environmental risk factors, and, particularly for those with major genetic risks, preventative therapies

Highlights

- Autoimmunity is defined by self-reactive components of the adaptive immune system, which cause clinically apparent pathology in the case of autoimmune diseases.
- Multiple lines of evidence suggest that autoimmunity and autoimmune diseases are on the rise.
- Probable causes for such increases include the major recent changes in our foods, contacts with xenobiotics, air pollution, infections, lifestyles, psychosocial stress, and climate change.
- These increases in autoimmune diseases have induced significant upsurges in individual and societal suffering as well as in private and public health care costs.
- Increased global-scale multidisciplinary research and coordination, with systematic improvements in our ability to understand, diagnose, treat, and prevent autoimmune diseases, are urgently needed and are likely to be cost-effective.

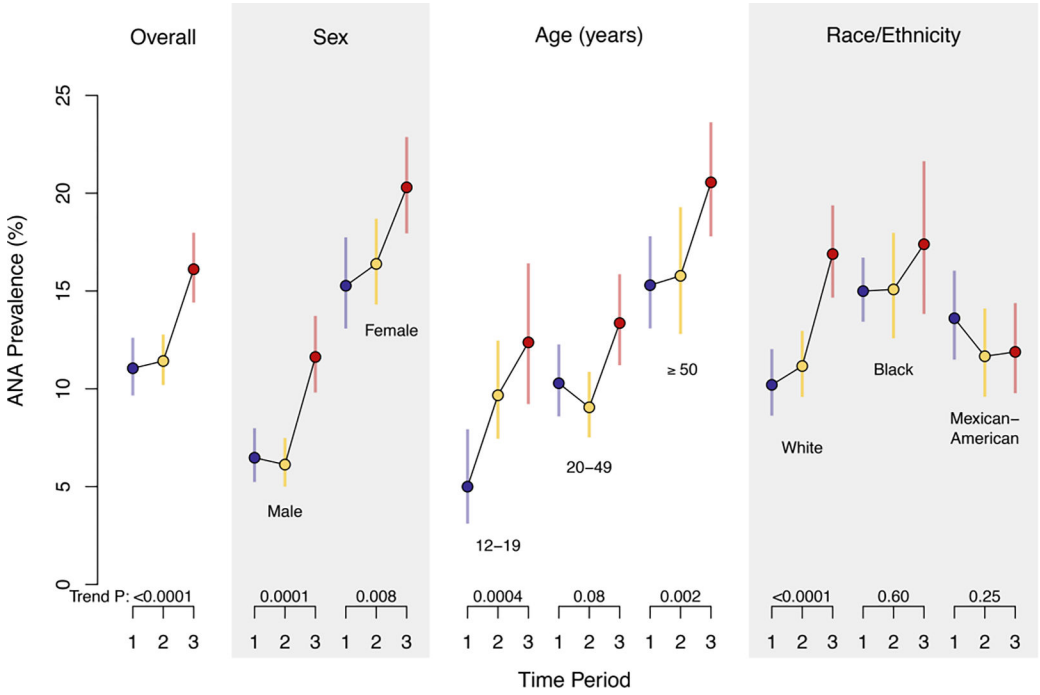

Figure 1.

The estimated prevalence of antinuclear antibodies (ANA) in demographic groups in the US population over time. Colored circles represent the weighted estimate of ANA prevalence, and the colored lines show the 95% confidence interval for period 1 (1988–1991, blue), period 2 (1999–2004, yellow), and period 3 (2011–2012, red). *P* values for ANA time trend are displayed below each category and were derived from a logistic regression model that was adjusted for sex, age, and race/ethnicity (reprinted with permission [12]).

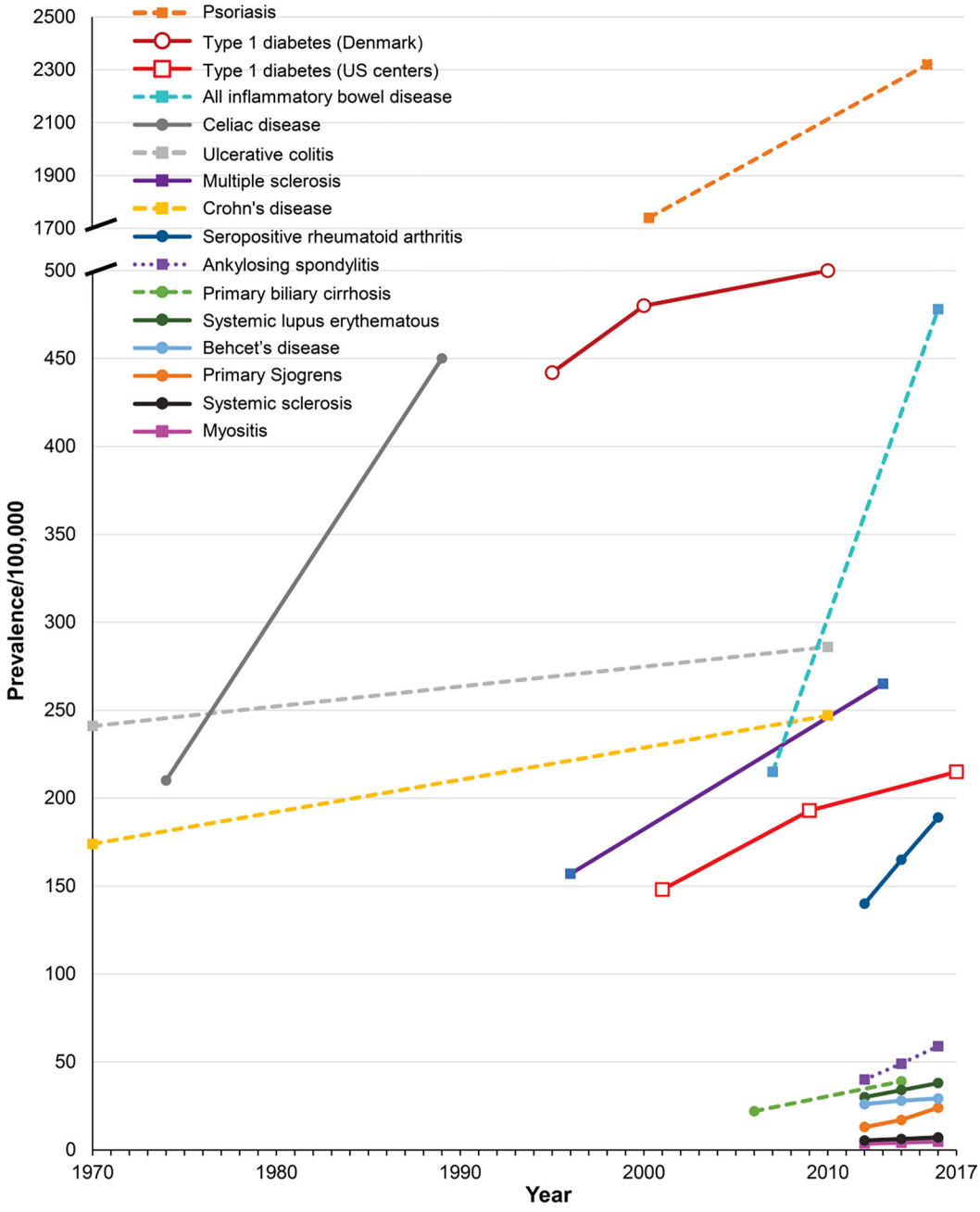

Figure 2.

Examples of the increasing prevalence of autoimmune diseases around the world over recent decades. The estimates for the time periods are connected by lines to visualize trends. Data sources are for: psoriasis in Canada [70]; type 1 diabetes in Denmark [71] and in the US [72]; celiac disease in the US [73]; multiple sclerosis in Canada [74]; primary biliary cirrhosis in the US [75]; all inflammatory bowel disease in the US [76]; Crohn's disease and ulcerative colitis in the US [77]; and seropositive rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, Behçet's disease, primary Sjogren's syndrome, systemic clerosis, and myositis in Korea [68].

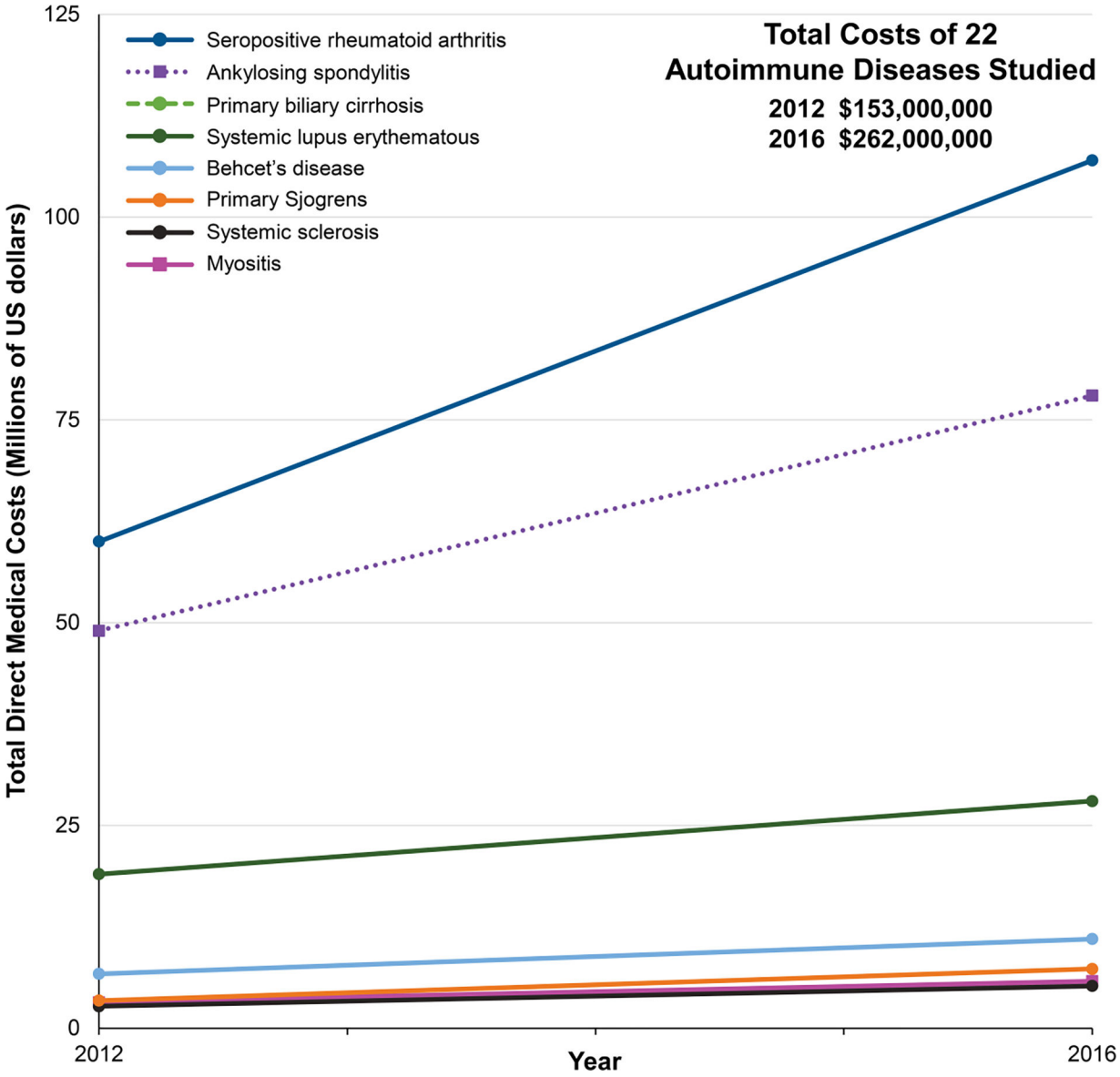

Figure 3.
Examples of increasing total direct medical costs of selected autoimmune diseases in Korea [68].