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Epidemiology of rheumatic diseases

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Abstract

Rheumatic diseases are among the oldest diseases recognized. The classification of rheumatic diseases is sometimes difficult due to unknown aetiology and heterogeneity in their clinical presentation. Osteoarthritis (OA) and rheumatoid arthritis (RA) are the two most common rheumatic diseases, accounting for a large percentage of disability worldwide. The economic and social burden of these diseases is great. Their impact on both individuals and society results from a decreased quality of life, lost productivity and increased costs of health care. Without appropriate approaches to patient management and control of these diseases, this impact can be expected to increase as the population ages. One of the challenges in studying OA and RA, and rheumatic diseases in general, is deriving epidemiological data that can be used to understand better the factors that contribute to the initiation and progression of these diseases. Only with such an understanding can significant progress be made in the diagnosis, treatment and management of patients.

KEY WORDS: Osteoarthritis, Rheumatoid arthritis, Epidemiology, Disease burden, Health outcomes, NSAIDs.

Hippocrates first recognized rheumatic diseases in the fourth century B.C. Eighteen of his published aphorisms refer at least partially to joint diseases. In about the first century A.D., the term *rheuma* was first introduced to indicate a flow of pain through the joints of the body.

Guilliaume Baillou (1558–1616), a Parisian physician, was the first to conceptualize rheumatism as a musculoskeletal syndrome. He colourfully stated that '… one may designate the condition we are considering inexactly as rheumatism, better as a sort of precipitation like a seasickness of the vessels (which vomit), until better terms offer themselves' [1]. The term *rheumatology* was first introduced in a textbook edited by Joseph L. Hollander in 1949 [2]; the term *rheumatologist*, however, had been established 9 yr earlier by Bernard Comroe.

Although the appearance and distribution of lesions in ancient skeletons suggest that rheumatoid arthritis (RA) may have existed in North America at least 3000 yr ago [3] and was undoubtedly misdiagnosed as a variety of rheumatism during recorded history, the first clinical description of RA is credited to Augustin-Jacob Landré-Beauvais in his thesis in 1800.

The term *osteoarthritis* (OA) was first introduced by John K. Spender in 1886 in England, but as a preferable term to rheumatoid arthritis—not to designate the condition to which it is now applied. The more modern usage of the term OA, and its clinical differentiation from RA, were introduced by Archibald E. Garrod in 1907, who clearly identified the age-related onset of the disease, the stronger predomination in the female gender compared with RA, and the heritable tendency of the disease. However, he was unable to make consistent distinctions between some of the pathology of OA and RA.

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Classification of rheumatic diseases

The classification of rheumatic conditions is hampered by the absence of firm aetiological evidence for most of the diseases. Currently, classification is dependent on a combination of common clinical and laboratory findings, including observations of abnormalities of anatomical structures and organ systems involved; the presence of suspected aetiological mechanisms, genetic factors and, occasionally, infectious agents; and the general nature of clinical manifestations of the disease. Hence, we are often left with broad categories of conditions, particularly in the early stage of diagnosis. Moreover, there is considerable clinical and pathological overlap between many of the rheumatic conditions. Despite the weakness of our present concepts, classification schemes such as the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA [4] are widely used and of definite utility in daily rheumatology practice.

The term *rheumatic disease* does not have a clear boundary; more than 100 different conditions are labelled as rheumatic diseases, including RA, OA, autoimmune diseases such as systemic lupus erythematosus

Table 1. Epidemiology of major rheumatic diseases (adapted from [7])

Disease	Point prevalence/1000	Incidence/1000	Age ratio (65:25 yr)	Gender ratio (female:male)
Rheumatoid arthritis	8.0	0.5	6:1	2.5:1
Juvenile chronic arthritis[a]	0.7	0.1	N/A	2:1–7:1
Osteoarthritis (knee)[b]	100	N/A	0	2:1
Ankylosing spondylitis	2.0	0.07	0	1:3
Systemic lupus erythematosus	0.4	0.05	1.5:1	3:1 to 9:1
Systemic sclerosis	0.1	0.01	3:1	4:1
Gout	N/A	1.0	2:1	1:6

[a]Children <15 yr.
[b]Prevalence among persons aged 35–74 yr.

and scleroderma, osteoporosis, back pain, gout, fibromyalgia and tendonitis. Table 1 summarizes the prevalence of several of the major rheumatic disorders.

Rheumatic diseases have a major impact on individuals and societies, and economic costs in all countries. However, one of the common challenges in studying rheumatic conditions is that of deriving epidemiological data to understand better the underlying disease process and the risk factors that contribute to onset and progression of the disease. Although rheumatic diseases affect people of all ages, the two most common and important diseases, OA and RA, have a high prevalence in the elderly. As the demographic structure of the population indicates an increasing tendency toward an older population, with the corollary of an increasing prevalence of these diseases, especially OA, the need for a better understanding of both OA and RA becomes critical for appropriate diagnosis and patient management.

Rheumatoid arthritis

RA is a chronic, multisystemic, autoimmune disorder of unknown cause. Although there are a variety of systemic manifestations, the major characteristic feature of RA is chronic, symmetrical and erosive synovitis, usually involving peripheral joints. The majority of patients have elevated titres of serum rheumatoid factors. Despite its destructive potential, the course of RA can be quite variable. Some patients may experience only a mild oligoarticular illness of brief duration with minimal joint damage, whereas others will have a relentless progressive polyarthritis with marked functional impairment and disability. Associated non-articular manifestations may include subcutaneous nodules, vasculitis, pericarditis, pulmonary nodules or intestinal fibrosis, mononeuritis multiplex, episcleritis or scleritis.

Definition

Epidemiological studies of RA are dependent on the criteria used to define the disease. This is challenging, because no aetiological agent has been identified and there are no unique clinical or laboratory features that can be used to define the disease clearly. Therefore, diagnosis is based on the presence or absence of combinations of clinical, laboratory and radiological abnormalities. Unfortunately, these assessments are prone to measurement error. In epidemiological research, the most widely used criteria to estimate the prevalence of RA have been those of the 1958 American Rheumatoid Association [5]. This set of criteria indicates that 1–2% of the global adult population is affected by definite or classic RA.

Table 2. The revised criteria of 1987 for RA [4]

Criterion	Comment
1. Morning stiffness	Duration >1 h lasting >6 weeks
2. Arthritis of at least 3 areas	Soft tissue swelling or exudation lasting >6 weeks
3. Arthritis of hand joints	Wrist, MCP, PIP joints lasting >6 weeks
4. Symmetrical arthritis	At least one area, lasting >6 weeks
5. Rheumatoid nodules	Observed by a physician
6. Serum rheumatoid factor	Assessed by a method positive <5% of control subjects
7. Radiographic changes	Seen on anteroposterior films of wrists and hands

MCP, metacarpophalangeal; PIP, proximal interphalangeal.

A modified definition of RA, referred to as the ACR 1987 revised criteria for the classification of RA, was published in 1988 (Table 2) [4]. These criteria distinguish RA from other rheumatic conditions, with a specificity of 89% and sensitivity between 91 and 94%. The conditions most often confused with RA are systemic lupus erythematosus, psoriatic arthritis and rheumatoid factor-negative spondylarthropathies. Although the 1987 revised criteria have not been used extensively in epidemiological studies, they generate estimates of prevalence similar to those interpreted using the 1958 criteria.

Prevalence

RA is evident throughout the world, and affects all races. Nearly all studies indicate a point prevalence of between 0.5 and 1% [6]. However, there is a lower prevalence in rural Sub-Saharan Africa and Caribbean blacks, and a higher prevalence in the Pima Indians of the USA [7].

Overall, the prevalence of RA is clearly higher in females. Although the ratio varies widely among studies, it has been estimated to be ~2.5:1 [8].

An age-associated increase in the prevalence of RA has been observed in both males and females. A US National Health Examination Survey (1960–2) reported a prevalence of only 0.3% in adults under the age of 35, but >10% in people older than 65 [9]. Prevalence studies,

however, have not provided any solid insights into the aetiology or pathogenesis of RA.

Incidence

Considering the difficulties in establishing an early diagnosis of RA, it is not surprising that only a few studies have addressed incidence. The studies that have addressed this issue report a gender-dependent annual incidence that ranges from 0.14 to 0.2/1000 for males and from 0.36 to 0.5/1000 for females, with overall annual incidences ranging from 0.24 to 0.29/1000 [10–13]. One of these studies [13] was unique in the respect that the authors derived their incidence rates from a population registry that had access to all cases presenting to general practitioners and hospitals in Norfolk, UK.

Risk factors

Sex hormones, menstrual and reproductive factors. Despite the inability to provide country-specific incidence data, the above-mentioned studies have generated some provocative observations regarding sex hormones as predisposing factors.

The obvious predominance of RA in the female gender has initiated an interest in examining the association of menstrual, hormonal and reproductive factors with the development of RA. For example, several studies have indicated that nulliparity is a risk factor for RA [14]. It is also well established that pregnancy is associated with remission of RA, and exacerbations are common during the postpartum period [15, 16]. Following the first reports by Wingrave and Kay in 1978 [17], there have been multiple studies examining the possible protective effect of oral contraceptives against the development of RA. These studies represent the entire repertoire of investigational methods in epidemiology, and though none of these studies is conclusive, there seems to be a consensus that oral contraceptives protect or postpone the development of severe RA [18].

Genetic factors. Several lines of evidence suggest that genetic factors other than gender play a role in development of RA.

Family studies indicate a genetic predisposition for RA. Severe RA is found at approximately four times the expected rate in first-degree relatives of individuals with disease associated with the presence of rheumatoid factor, and ~10% of patients with RA have an affected first-degree relative [7]. Furthermore, monozygotic twins are at least four times more likely to be concordant for RA than dizygotic twins, who have a similar risk of developing RA as non-twin siblings, while only 15–20% of monozygotic twins are concordant for RA [19]. However, this also implies that factors other than genetics play an important aetiopathogenic role.

One of the major genetic factors in the aetiology of RA is the class II major histocompatibility complex (MHC) gene product HLA-DR4 [20]. As many as 70% of patients with classic or definite RA express HLA-DR4, compared with 28% of control individuals. An association with HLA-DR4 has been noted in many populations, including North American and European whites, Chippewa Indians, Japanese and native populations in India, Mexico, South America and southern China. However, in a number of groups, including Israeli Jews, Asian Indians and Yakima Indians of North America, there is no association between the development of RA and HLA-DR4. In the former two groups, there is an association between RA and HLA-DR1; and in the latter two groups, there is an association with HLA-Dw16. These observations form the basis for the suggestion that shared epitopes determine susceptibility to RA [21].

Other factors. In addition to age- and sex-related predisposing factors, a number of other factors, including socio-economic status [22], education [23] and stress [24], have been suggested to play predisposing roles.

Mortality in RA

Evidence that the mortality rate is increased in patients with RA has accumulated since the 1950s [25]. The increased mortality in this population has been attributed mainly to infections, renal disease, respiratory disease and RA itself.

According to a study from The Netherlands, life expectancy in patients with RA is reduced by ~7 yr in men and ~3 yr in women [26]. Two more recent studies, from Japan and the USA, additionally suggest that stress, age, male gender, poor functional status and low education are predictors of mortality due to RA [27, 28].

Osteoarthritis

In contrast to RA, which has multisystemic components, OA, also known as degenerative joint disease, is a disease affecting joint cartilage and the underlying (subchondral) bone. It is characterized by progressive loss of articular cartilage, appositional new bone formation in the subchondral trabeculae, and formation of new cartilage and bone at the joint margins (osteophytes). Pain, stiffness, functional limitations and diminished quality of life are the primary features associated with OA. Although its cause is not known, biomechanical and biochemical changes in cartilage and subchondral bone are believed to be important in its pathogenesis.

Definition

Like RA, there are inherent difficulties in defining and classifying OA. The three principal techniques used for diagnosis and classification—symptoms, physical examination and radiographic assessment—all have their limitations. There is no discrete onset, laboratory abnormality or pathognomonic features, and there is heterogeneity in the disease spectrum. OA has been classified by the joints involved (hip, knee, hand, spine, other), and by whether it is primary (idiopathic) or secondary (caused by metabolic, anatomical, traumatic or inflammatory conditions). Primary generalized OA includes involvement of the distal and proximal interphalangeal joints of the hand, the first carpo-metacarpal joint, knees, hips and the metatarsophalangeal joints. Limited forms of primary OA also occur.

Systems proposed for the classification of OA are based on radiographic criteria, clinical criteria or a combination of both. This lack of standardized diagnostic criteria is one of the primary impediments to large-scale epidemiological studies, and may also impact on design and outcome measurement of clinical trials. In epidemiological studies, OA is most commonly defined by radiological criteria. However, 60% of patients with radiographically defined changes in the knee have no symptoms. Nevertheless, radiographic criteria proposed in 1957 by Kellgren and Lawrence [29] remain the principal method for defining OA and were adopted by the World Health Organization in 1961. For the purpose of epidemiological studies, there are methodological problems with the Kellgren and Lawrence criteria [30], including reliability of assessing joint space narrowing, the cardinal radiographic feature used to define OA. Other factors that influence the reliability of radiographic assessment, leading to misclassification, include site of measurement, measuring methods and training of readers. Recent modifications to improve diagnostic methodology include rating different compartments of the knee [31] and degrees of joint space narrowing [32]. Finally, as stated before, X-ray classification alone does not define a clinically important group, since there is not necessarily a relationship between X-ray features and presence of symptoms. Not everyone who has radiographic disease has pain, as is shown in Fig. 1 by the poor correlation between the prevalence of pain and presence of radiographic OA [29]. It still has not been determined whether there are any reliable predisposing factors that might result in progression to symptomatic OA in a subset of patients with radiographic OA.

The ACR has developed classification criteria for OA of the knee [33], hand [34] and hip [35]. These criteria, because of their dependence on an expert physical examination and/or use of expensive and questionably justifiable radiation, are of greater use in reporting disease-specific data than for either epidemiological purposes or use in everyday clinical or community practice. Additionally, the ACR criteria require that joint pain be present on most days for a minimum of 1 month. The use of these criteria has not been extensive, and studies comparing various criteria suggest that the ACR criteria lack sensitivity and produce low prevalence rates [36].

In summary, there are no standardized or widely used criteria for OA in epidemiological studies. However, most studies use criteria that include clinically important features such as pain and functional limitation rather than radiographic features alone.

Prevalence

Current information on prevalence comes from population-based cohorts [37–41]. However, estimates of the 'true' prevalence of OA have been imprecise because of difficulties in diagnosis. Radiographic evidence of OA can be found at some site in most people older than the age of 65, and >80% of those over the age of 75 are affected [29].

Age is the most powerful predictor for OA at all joint sites. Data from the National Health and Nutrition Examination Survey (NHANES) demonstrate that the prevalence of OA of the knee increases from 0.1% in people aged 25–34 to 10–20% among those aged 65–74 and to >30% in those aged ≥75, and that women are twice as likely as men to have OA of the knee [42]. In the Framingham Study, the prevalence of OA of the knee was 30% among the population aged 65–74 [37].

The prevalence of pathological features of OA has been assessed in systematic autopsy studies that showed almost universal cartilage damage in patients over age 65 [43].

What is clear from all of these studies is that the prevalence of radiographic OA rises steeply with age, at all joint sites. Both hand and knee disease appear to be more frequent in women than in men; the female:male ratio ranges from 1.5:1 to >4:1. Racial differences also contribute to the prevalence of OA and the pattern of joint involvement [44], and these differences can impact outcomes and costs. In a US study, Americans of Asian origin had the lowest rate of hip arthroplasty [45], a surgical intervention that adds significantly to the cost of treatment.

Risk factors

Risk factors for OA (Table 3) can be conceptualized as acting through two major pathogenetic mechanisms: (i) factors influencing or marking a generalized predisposition to the condition; and (ii) factors resulting in abnormal biomechanical loading at specific joint sites.

Sex hormones and menstrual factors. OA of the knee is more common in women than in men, with a female:male ratio that ranges between 1.5:1 and 4:1. This has led to the

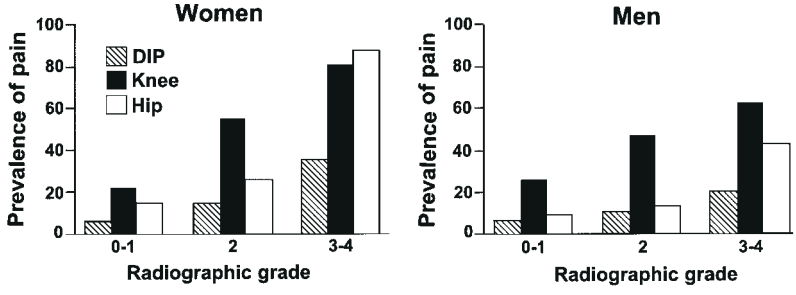

FIG. 1. Prevalence of pain in individuals with radiographically diagnosed osteoarthritis. (Reprinted with permission from [29].)

Table 3. Risk factors for osteoarthritis

Known	Probable	Contentious
Age	Joint overuse	Running and/or other intense physical activity
Female gender (after age 50)	Instability	
Obesity (knee OA)		Oestrogen
Prior inflammatory joint disease		Early hysterectomy
Diathesis		
Occupation		

hypothesis that, as in RA, female sex hormones might be associated with the onset and/or severity of OA of the knee, and several lines of evidence in animal models are supportive of this hypothesis [46–49]. However, human epidemiological studies remain equivocal, and although there are biological reasons to suspect that female sex hormones increase the risk of OA, there are currently no data that clearly support a role for these hormones in the onset or progression of OA [50–53].

Obesity. Obesity has been shown to have a positive association with OA of the knee in cohort, case–control and cross-sectional studies, but less of an association with OA of the hip or hand [54–58]. Felson *et al.* demonstrated that in the Framingham cohort, obesity predicts subsequent OA of the knee up to 30 yr later, with a 4- to 7-fold increase in risk of OA of the knee between the lowest and highest quintile of the body mass index (BMI) [54]. Furthermore, in a prospective study, it was demonstrated that a weight loss of 5 kg was associated with a 50% risk reduction of developing symptomatic OA of the knee [59]. A more recent German study has corroborated the positive independent association between an increased BMI and bilateral OA of the knee [60].

Smoking. Several studies have examined the association between OA and smoking. While one report has suggested that there is no association [61], other studies have suggested a protective effect—even after controlling for a variety of possible confounding variables [52, 62–65]. A protective effect of smoking is biologically plausible, and several mechanisms of action have been suggested: (i) smoking may affect cartilage directly (tar and/or nicotine may stabilize progressive OA changes); (ii) smoking may cause osteopenia and protect joints by making bone more deformable to impact load; and (iii) smoking is anti-oestrogenic and therefore, based on the hypothesis discussed above, may potentially contribute to a reduction in disease onset or progression.

Although there is a need to establish further if and how the putative effect of smoking occurs, it is inconceivable from a public health perspective that one could ever recommend smoking in light of its overwhelming negative health effects.

Trauma and repetitive stress. Trauma and repetitive stress may cause knee OA, but these risk factors have had little epidemiological study.

Slemenda *et al*. demonstrated that loss of the anterior cruciate ligament or damage to the meniscus leads to knee OA [66]. Repetitive use of specific joints in certain occupations (e.g. jackhammer operators, cotton mill or shipyard workers, coal miners) may be associated with substantial joint degeneration [67]. However, the relationship between physical activity and OA remains equivocal. While some studies have determined that athletic activity does not appear to be a risk factor for OA [68–70], other studies suggest that the issue is more complex, with age as well as intensity and duration of physical activity possibly acting as confounding variables [71–74]. With high levels of physical activity also comes the risk of injury, and it is likely that it is a combination of these factors that contributes to the risk for developing OA [75].

Bone density. An inverse relationship between osteoporosis (low bone mineral density) and OA has been suggested but has not been adequately studied epidemiologically [76]. One hypothesized mechanism is that bone with lower density has a better capacity to absorb loading [77]. The association is supported by the findings that there is a higher than expected prevalence of OA in subjects with osteopetrosis, a condition with overly dense bone [78], but, as with most reported risk factors, more research is needed.

Diet. Several studies have suggested that, at least in animal models, the risk and severity of OA may be modified by diet. Fats and calcium may increase the risk of OA [79–81], while riboflavin (vitamin B2) and selenium may decrease the risk [82–84]. Human studies have been limited, but one study did determine that folate and cobalamin may have a protective effect on OA of the hands [85], and data from the Framingham cohort suggest a risk reduction with dietary intake of antioxidants (vitamin C, vitamin E, β-carotene) [86]. More research is needed to substantiate these early results.

Disease management

Treatment of RA is targeted toward both symptoms and disease modification. The approaches to therapy are illustrated in Fig. 2, where standard therapies to alleviate symptoms and slow disease progression are built on a base of education and non-pharmacological intervention, and therapies such as corticosteroids, analgesics and surgery may be used adjunctively or in the case of severe or recalcitrant disease. Within the past year, several new approaches to the treatment of RA have been established, including monoclonal antibody therapy, tumour necrosis factor receptor constructs, pyrimidine synthesis inhibition and immunoabsorption. Although these new therapies seem promising, they are expensive, and their usefulness in widespread clinical practice has yet to be proven. Analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) continue to be used for symptomatic relief. Of the new cyclooxygenase-2 (COX-2) inhibitors, which show promise for use in RA, only celecoxib has as yet been approved for this indication.

For OA, treatment is more problematic. The absence of defined aetiology and a lack of disease-modifying

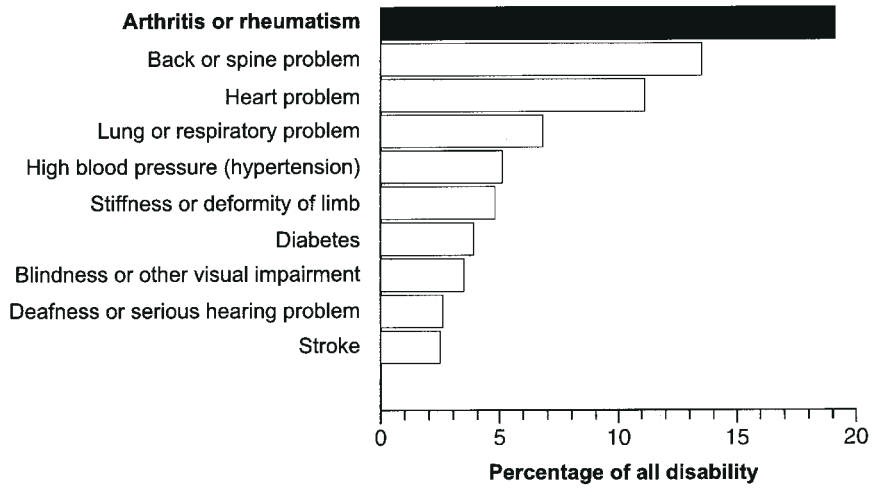

FIG. 2. The 10 primary causes of disability in the USA among persons ≥15 yr of age. Data are for the years 1991–2 (reproduced from [98]).

drugs put a constraint on therapeutic options, which are primarily targeted toward alleviation of symptoms. Lifestyle modification (including weight reduction), patient education and non-pharmacological therapy are considered important approaches in the treatment of OA—especially in Europe, where physical therapy is considered a main component of treatment, even in advanced disease. In contrast, rehabilitation and physical therapy are not key features of treatment in the USA, particularly in early-stage disease, even though these are recommended in the ACR guidelines [87, 88].

Treatment in the USA relies heavily on pharmacological intervention. Recommendations from several sources, in both the USA and the UK, suggest that analgesics such as acetaminophen or paracetamol be used as first-line pharmacological therapy [87–89]. However, the anecdotal evidence previously suggesting that patients have a preference for NSAIDs over analgesics has recently been confirmed by two US surveys showing that a significantly higher percentage of patients prefer NSAIDs to acetaminophen [90, 91]. This patient preference for NSAIDs is not unreasonable since NSAIDs reduce inflammation in addition to pain, and variable degrees of inflammation have been recognized as a component of OA [92]. Other pharmacological interventions include corticosteroids, the new COX-2 inhibitors, and synovial fluid supplementation with hyaluranon, as well as experimental drugs such as diacerhein, a cytokine inhibitor with multiple actions and a putative disease-modifying effect [93].

Finally, surgery is a treatment that is often used in severe or refractory OA and is a tremendous cost factor for most health care systems. Of the surgical techniques currently used, arthroplasty is one of the more common interventions, but other standard and experimental techniques, such as autologous chondrocyte transplantation, are also being used and have shown promise for use in long-term treatment [94].

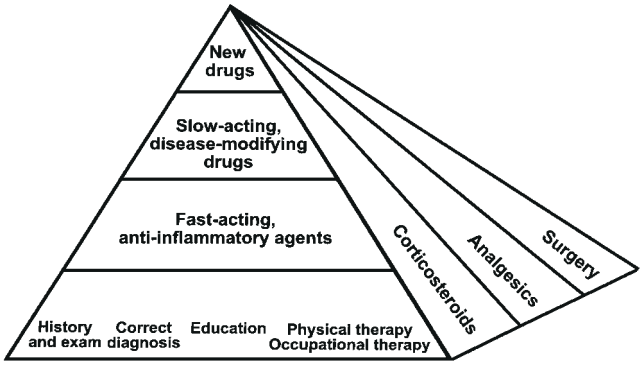

FIG. 3. Treatment pyramid for RA.

Burden of rheumatic diseases

Studies have suggested that musculoskeletal conditions are among the most prevalent chronic conditions, accounting for a high proportion of those with disability in the work force as well as in the elderly [95–97]. In the USA, arthritis and rheumatism have been demonstrated to be the leading causes of disability in persons >15 yr of age (Fig. 3) [98]. It has been estimated that >43 million Americans are affected by arthritis; and as the population ages, this number is expected to increase to >60 million by the year 2020 [99].

The burden of rheumatic diseases is related to treatment and outcomes, which were described in a paradigm by Fries *et al.* [100] as death, discomfort, disability, drug toxicity and dollars, to which dissatisfaction (mainly with currently available treatment modalities) may also be added.

From a societal perspective, the burden of disease is generally measured in terms of dollars. For countries for which data are available—the USA, Canada, the UK, France and Australia—the cost of rheumatic diseases

has been estimated to account for 1–2.5% of the gross national product of these countries [101], with a cost of over $149 billion in the USA alone in 1992 [102]. Costs are usually broken down into direct costs (medical costs usually associated with resource utilization) and indirect costs, generally resulting from lost productivity (related to discomfort and disability in the above paradigm). For example, the economic impact of RA in the UK was estimated to be £1.256 billion in 1992/3, with 48% of the costs attributed to medical expenses and >52% of the costs (£0.65 billion) due to lost productivity [103]. A similar distribution was calculated for the US costs of rheumatic diseases mentioned above. However, a Swedish study suggested that the cost of treatment of RA could be compensated for by a corresponding reduction in lost productivity [104], although limitations of this study included a retrospective design and a lack of adequate controls.

Both direct and indirect costs have been shown to be significantly greater in patients with RA or OA than in non-arthritic controls [105, 106].

The per-case cost of treatment of RA is >1.5 times greater than with OA, but because of the higher prevalence of OA, the overall economic impact of OA is greater [107].

While for RA much of the costs of resource utilization may be disease-related, for OA a large proportion of the overall medical costs may be related to drug toxicity, since NSAIDs are one of the mainstays of OA therapy. These drugs have a high rate of adverse events, such as the widely prevalent nuisance side-effects that may require additional physician visits, diagnostic procedures and co-medication. Additionally, there are rarer, but more costly, side-effects, such as perforations and bleeds that require hospitalization [108]. Recently, it has been suggested that the cardiac side-effects of NSAIDs have been underestimated, and resource utilization and costs related to these adverse events may exceed those of the gastrointestinal side-effects [109]. Thus, the iatrogenic costs related to NSAID treatment, whether for OA or RA, have been shown to increase the overall disease burden significantly [103, 110–113]. A reasonable corollary is that more tolerable and safer NSAIDs will help reduce the cost of treatment.

While economic analyses have provided the primary measure of disease burden, the last few years have witnessed an increasing emphasis on the psychosocial burden of disease that cannot be quantitated directly in the way that medical costs can. These 'intangible costs' of disease are closely related to quality-of-life issues. Attempts have recently been made to validate these issues, develop generic and disease-specific evaluation indices that incorporate measurement tools, and quantitate the extent of this aspect of the disease burden [102, 114]. Several health assessment questionnaires and quality-of-life surveys have now been incorporated into standard assessment tools that measure disease outcome [115]. However, a recent review suggested that most of the studies incorporating generic health-related quality-of-life instruments do not adequately address the issue or pass the recommendations set forth by the Outcome Measures for Rheumatology Trials (OMERACT) group [116]. Additionally, many pharmacoeconomic analyses are now discussed not only in terms of actual dollar cost for the treatment of OA or RA, but also in terms of quality of life (QOL) or quality-adjusted life-year, a semi-quantitative measurement unit. Validation of these tools and widespread acceptance and incorporation of this aspect of the burden of disease are needed in post-marketing analyses, pharmacoeconomic models and clinical trials.

Conclusions

Rheumatic diseases are a huge burden on the health care systems of countries worldwide and account for significant disability, lost productivity and reduction in QOL. However, the heterogeneity of the two most common rheumatic diseases, RA and OA, and the lack of any clear clinical correlation with pathology make an exact estimate of incidence and prevalence difficult, although risk factors have been identified. The lack of standardized clinical criteria, especially in OA, may also affect our ability to evaluate outcomes in clinical trials adequately, which are often of short duration in selected populations and have surrogate or biological endpoints for determination of both efficacy and safety, rather than patient-oriented endpoints. The use of QOL assessments or other patient-sensitive efficacy and safety endpoints needs to be incorporated into clinical trials, pharmacoeconomic analyses and post-marketing surveillance. Together with an accurate evaluation of resource utilization and cost reduction potential, these types of outcome studies can provide important data that will enhance our ability to make decisions related to the management of these diseases.

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