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Osteoarthritis—the impact of a serious disease

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Osteoarthritis (OA) is common in the elderly, but also affects younger people. The disease symptoms are debilitating and, as well as causing physical impairment, can affect the psychosocial wellbeing of the patient. Furthermore, the impact of this disease is substantially increased by the common occurrence of comorbid conditions, such as hypertension and renal impairment. Non-steroidal anti-inflammatory drugs are commonly used to treat the symptoms of OA, but their related gastrointestinal side-effects increase the impact of this disease. Gastrointestinal tolerability should therefore be considered in the design of new therapies that reduce the symptoms and activity of OA. Furthermore, because this disease is associated with comorbid conditions, patient safety must also be considered when designing new therapies.

KEY WORDS: Selective COX-2 inhibitors, NSAIDs, Osteoarthritis, Comedication, Comorbidity.

Osteoarthritis (OA) is the most common form of arthritis [1–4], and the World Health Organization estimates that globally 25% of adults aged over 65 yr suffer from pain and disability associated with this disease [5]. Almost every age group is affected by OA, but prevalence increases dramatically after age 50 yr in men and 40 yr in women [6, 7]. In England and Wales in 1997, between 1.3 and 1.7 million people were affected by OA, and in France during the early 1990s, 6 million new cases were reported each year [3, 4]. These figures are likely to worsen with an increasingly aged population; the United Nations predicts that the proportion of the Western European population aged over 65 yr will increase from 20% in 1995 to 25% in 2010 [8].

OA is a debilitating condition characterized by pain, joint inflammation and joint stiffness, and results in a substantial degree of physical disability. Indeed, in the Framingham study ($n = 1769$), patients with OA required human assistance in carrying out four (stair climbing, walking a mile, housekeeping and carrying bundles) of seven functional activities [9]. In this respect, OA was ranked equally with heart disease, congestive heart failure and chronic obstructive pulmonary disease as a cause of physical disability [9].

OA is caused primarily by the degradation of the collagen and proteoglycans in cartilage, leading to fibrillation, erosion and cracking in the superficial cartilage layer. Over time this process spreads to the deeper layers of cartilage, and eventually large, clinically observable erosions are formed [10, 11]. The pathophysiology of OA involves many mediators, including leukotrienes (LTs), prostaglandins (PGs) and proinflammatory cytokines. The levels of PGs and LTs in joint tissues and synovial fluid are increased in OA [12–14], resulting not only in inflammation and pain, but also increasing production of the proinflammatory cytokines interleukin-1β (IL-1β) and tumour necrosis factor α (TNF-α) [15]. In turn, IL-1β and TNF-α stimulate increased production of matrix metalloproteinases [16], which are thought to play a key role in cartilage degradation.

The direct cause of OA is unknown, but it is thought that it results from intrinsic alterations of the articular tissue, or as a response to cumulative mechanical stress [17]. The proximal and distal interphalangeal joints of the hand are most commonly affected. The involvement of these joints is, however, often asymptomatic, and is usually only detected radiographically [10, 11]. The second and third most commonly involved joints are those of the knee and hip respectively, and OA in these joints, as well as being radiographically detectable, is almost always symptomatic. Early on in the disease, patients experience stiffness and localized pain in the affected joints, which are relieved by rest. In more severe forms of the disease, however, pain may also be felt at rest [10, 11]. Eventually, weight-bearing joints may 'lock' or 'give way' as a result of excessive internal damage to cartilage. The net results of these symptoms are pain, functional limitation and emotional suffering [10, 11].

Risk factors associated with osteoarthritis

Although OA is found in almost all age groups, the strongest predictive factor for the development of radiographically detectable damage is increasing age, with almost every individual over the age of 90 yr suffering from this disease [18, 19]. In fact, more than 13% of Americans aged 55–64 yr and more than 17% aged 65–74 yr have pain and functional limitation due to knee OA [6]. A similar age risk has also been shown in European studies. For example, a study in Rotterdam in 1997 showed that, of the 1040 participants aged 55–65 yr, only 135 (13%) were free of radiographically detectable OA [7]. It is thought that the influence of age may be a result of insufficient cartilage repair, hormonal changes and cumulative exposure to damaging environmental effects.

There may also be a genetic component to OA. In a study of 130 identical and 120 non-identical female twins, the magnitude of this component was estimated to be 39–65% [20]. Various studies have attempted to identify candidate genes [21, 22], but so far none have been identified that could explain more than a minority of OA cases.

Mechanical stress resulting from a high body mass index is also known to be a risk factor for the development of knee OA. It has been calculated that a reduction of 2 kg/m^2 would decrease the risk of developing knee OA by 20–30% [23]. This observation is supported by studies indicating that mechanical stress due to extreme sporting activity [24] or heavy physical workload [25] can result in OA.

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Comorbidities in patients with osteoarthritis

The impact of OA may be worsened by the presence of other diseases or conditions. A large proportion of patients with OA suffer from comorbidities, including hypertension, cardiovascular disease, peripheral vascular disease, congestive heart failure, renal function impairment, diabetes and respiratory disease (Fig. 1) [26, 27]. In a study of 1000 patients undergoing surgery for OA of the hip, those with two or more comorbidities had a greater degree of functional impairment than those with none ($P < 0.05$) [26]. However, half of the patients in this study had at least one comorbidity, and only 10% of patients had no comorbid disease or history of comorbid disease. In this latter group of patients, 78% were overweight or obese. The reasons for the high incidence of comorbidities in this study's participants are not known, and whether patients with OA are more likely to develop comorbidities or *vice versa* remains to be established.

Other studies have shown that patients with OA often have risk factors for cardiovascular disease, including respiratory disease, hypertension, high cholesterol levels, low high-density lipoprotein levels, renal impairment and diabetes (Fig. 2) [28, 29]. Hypertension is common in patients with OA [6]; of the 24.3 million American adults with OA aged ≥35 yr, 41% receive pharmacotherapy for hypertension [30]. Therapeutic intervention for hypertension is particularly important in this population because an increase in blood pressure of only 5 mmHg has been shown to result in a 7% (29 000 cases) annual increase in the risk of ischaemic heart disease and stroke (Table 1) [30]. It is possible that this situation exists in European populations, but studies confirming this could not be found in the literature.

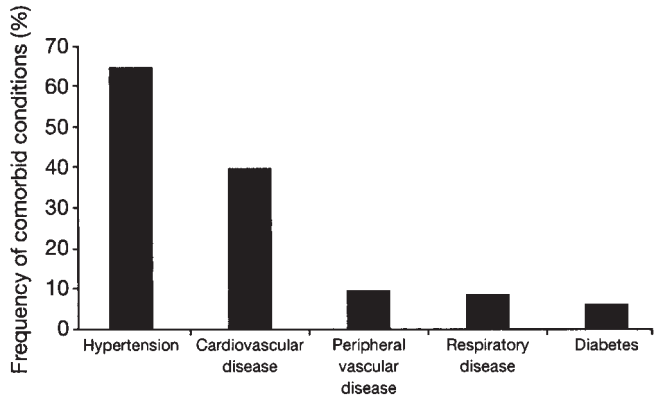

FIG. 1. Comorbid diagnoses in patients with end-stage hip osteoarthritis. Adapted from [26].

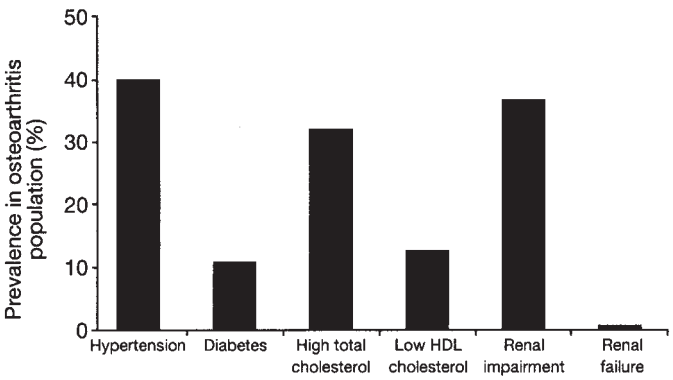

FIG. 2. Prevalence of cardiovascular risk factors in American osteoarthritis patients. Data sourced from [28].

Social and economic impact of osteoarthritis

The social and economic impact of OA is substantial (Table 2) [31, 32]. As the most common form of arthritis, OA is one of the most prevalent causes of physical disability in the non-institutionalized elderly population [9]. The disease results in a significant degree of physical trauma, but its impact is not limited to physical symptoms, and can be manifested as depression or anxiety. A 1998 study of OA patients examined the effect of knee pain on depression and anxiety, as well as on physical function [33]. Patients with knee pain ($n = 300$) were assessed for quadriceps strength, physical disability, joint osteophyte development and space narrowing (by radiograph), and anxiety and depression, relative to individuals lacking knee pain ($n = 300$). The study found that knee pain was independently associated with quadriceps strength (odds ratio 18.1), radiographic change (odds ratio 4.1) and depression (odds ratio 2.4). Furthermore, disability was independently associated with quadriceps strength (odds ratio 8.2) and depression (odds ratio 6.2), but not with radiographic score [33]. A recent US study measured the health-related quality of life of patients with OA using a generic quality of wellbeing (QWB) scale. The QWB of these patients was 0.64, which was lower than that of the community-matched cohort (0.71) and similar to scores from patients with depression (0.64) or advanced cancer (0.63) [34].

The economic impact of OA includes direct costs relating to drugs, medical care, hospitals and research, and indirect costs, such as lost work productivity due to chronic and short-term disability (Table 2) [31, 32]. While treatment of OA may relieve symptoms and therefore reduce the social impact and perhaps some of the

TABLE 1. Ischaemic and stroke events attributable to an increase in systolic blood pressure in patients with osteoarthritis

Osteoarthritis patients	Events status quo	Events attributable to systolic blood pressure increase of 5 mmHg
Treated hypertensive		
Men	108 248	7006
Women	112 291	8129
Untreated hypertensive/normotensive		
Men	117 279	8579
Women	65 607	5582
Total	403 425	29 296

Data sourced from [30]. Data are estimated annual occurrences of ischaemic heart disease and stroke events before and after an increase of 5 mmHg among American osteoarthritis patients.

TABLE 2. The social and economic impacts of osteoarthritis

Social impact	Economic impact
Disability and pain (chronic/short-term)	Direct costs
Decreased ability to perform activities of daily living	Non-pharmacological/pharmacological treatment
Increased depression/anxiety	Caregiver time
Decreased overall quality of life	Hospital resource use
	Research
	Management of side-effects caused by pharmacological treatments for osteoarthritis
	Indirect costs
	Lost time from work
	Decreased productivity
	Premature mortality
	Disability compensation/ pension/benefits

indirect costs of this disease, the costs associated with OA therapy itself and the management of possible adverse drug reactions may be substantial [31, 35]. A number of studies have compared the cost-effectiveness of pharmacological therapies for OA, such as conventional non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase (COX)-2 inhibitors [35, 36]. However, differences in the methods used to assess costs and the lack of data on resource consumption in some studies make firm conclusions about the most cost-effective therapies difficult [36]. Furthermore, one Australian study showed that OA patients incur significant treatment-related, personal expenses. In fact, older women with OA spent 25% more on community services than younger women with the disease [37]. Furthermore, higher disease-related expenditure was correlated with greater pain levels, poorer social and mental functioning, and increased duration of disease [37].

Therapeutic options for osteoarthritis

It is clear from the data discussed here that any intervention for OA must take into account the comorbidities commonly suffered by patients with this disease. There are currently a number of pharmacological and non-pharmacological therapeutic management options available, the overall goals being to control symptoms and minimize disability [38, 39].

Non-pharmacological intervention may take the form of social support through routine telephone contact to discuss disease-related issues such as joint pain, treatment compliance and side-effects. Aerobic exercise can maintain or improve joint function, and, as part of a weight management programme, can reduce body mass index and therefore the mechanical stress on joints. An occupational therapist can suggest techniques for joint protection and provide devices that can help the patient perform activities of daily living. Furthermore, a physiotherapist may employ modalities (such as heat), suggest specific exercises to improve joint motion and muscular strength, and provide devices to aid walking.

Various pharmacotherapies are available for the treatment of OA. Treatments aim to relieve pain, decrease joint stiffness and swelling, maintain joint function, prevent loss of cartilage, and preserve the patient's quality of life [39, 40]. In many cases, pain is the symptom that leads individuals to seek treatment. Although current therapies provide pain relief, they do not reduce cartilage loss or disease progression. First-line pharmacological therapy may be simple non-opioid analgesics, such as acetaminophen. However, in many patients these drugs do not adequately control pain, and they do not have anti-inflammatory properties [40, 41]. Opioid analgesics, such as codeine, may therefore be useful for the short-term treatment of acute pain [42].

NSAIDs, such as ibuprofen, are also often used to control the pain and inflammation of mild to moderate OA. However, the long-term use of these drugs may be limited by gastrointestinal (GI) or renal toxicity, and the former may prove fatal [41]. In the Rochester Epidemiology Project, 441 patients with OA were compared with 450 patients with rheumatoid arthritis and 891 control individuals [27]. The risks of patients with OA developing peptic ulcers and renal disease were 2.59 and 2.10 respectively, relative to community controls, and these increases were statistically significant (P value not given). The study concluded that these increases were likely to be due to the use of NSAIDs. The GI toxicity of non-selective NSAIDs is thought to be because these drugs inhibit COX-1, resulting in a reduction in the levels of the gastroprotective PGs (PGE_2 and PGI_2) produced by this enzyme [43]. The anti-inflammatory and analgesic effects of non-selective NSAIDs are due, at least in part, to their inhibition of COX-2.

NSAID usage and comedications

As a class, NSAIDs are globally the most commonly used drugs [44, 45]. Consequently, NSAID-induced gastropathy is one of the most common drug-related serious adverse events [46]. It has been estimated that the incidence of GI bleeding or perforation due to NSAID use is 0.69%, compared with 0.002% in patients not taking these agents. NSAID-induced gastropathy also results in a significant number of hospital admissions. For example, in the USA, it is thought that over 100 000 people are hospitalized following NSAID use each year [45, 47]. Furthermore, death resulting from NSAID-related GI complications is one of the most common causes of death in the USA, exceeded only by leukaemia, diabetes and human immunodeficiency virus (HIV) [47, 48]. In fact, it has been estimated that one in every 1200 patients taking NSAIDs for longer than 2 months will die from GI complications [46].

In a systematic review of 18 studies involving NSAIDs conducted between 1990 and 1999, the major risk factors for NSAID-related GI toxicity were a history of peptic ulcers and advanced age (Fig. 3) [49]. The pooled relative risk of GI toxicity after exposure to NSAIDs was 3.8. This risk was maintained during treatment, but returned to baseline when treatment ceased [49].

Several strategies have been suggested to reduce the incidence of NSAID-related GI toxicity, including using non-NSAID analgesics, prescribing lower doses of NSAIDs, using better-tolerated NSAIDs or selective COX-2 inhibitors, avoiding the concomitant use of corticosteroids and anticoagulants, and administering a co-therapy. This last option is illustrated by a study comparing GI toxicity in individuals using non-selective NSAIDs (mostly naproxen, ibuprofen or diclofenac), diclofenac plus misoprostol (PGE_2 analogue), or selective COX-2 inhibitors (rofecoxib or celecoxib), with community controls [50]. There was an increased use of gastroprotective drugs—including proton pump inhibitors, histamine-H_2 receptor antagonists, misoprostol and sucralfate (polysaccharide antipeptic)—in all groups but the community

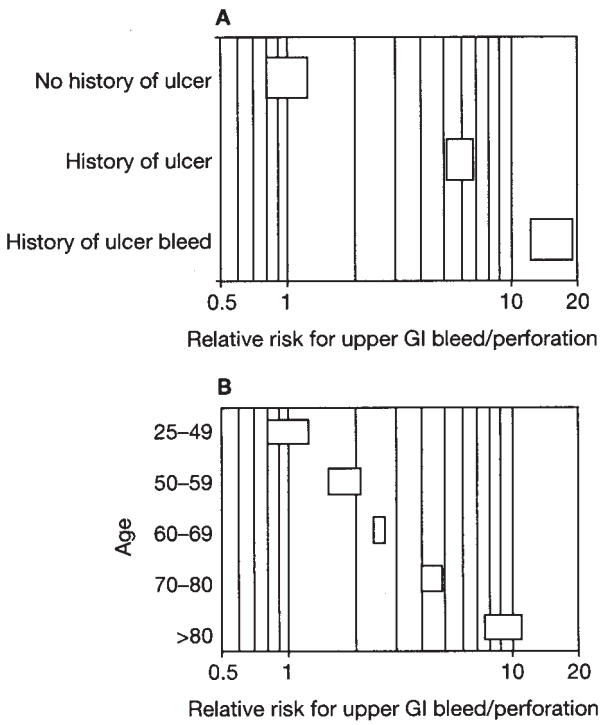

FIG. 3. The effect of (A) ulcer history and (B) patient age on risk of NSAID-induced upper gastrointestinal bleeds. Data sourced from [49].

controls. Despite the use of these gastroprotective drugs, there was an increased incidence of upper GI toxicity. The highest incidence was with the use of non-selective NSAIDs (12.6 events per 1000 person-years) and the lowest with the use of celecoxib (3.6 events per 1000 person-years), compared with the community controls (2.2 events per 1000 person-years).

In an attempt to improve tolerability, drugs that selectively inhibit COX-2 (such as celecoxib, rofecoxib and valdecoxib), and therefore lack much of the GI toxicity of non-selective NSAIDs, have been developed [43, 51–53]. However, controversy exists over the improved GI safety of selective COX-2 inhibitors—there is debate as to the incidence rate of GI damage seen with these drugs relative to non-selective NSAIDs [54, 55]. Furthermore, there is evidence to suggest that selective COX-2 inhibitors, like NSAIDs, are associated with renal impairment, and may be associated with cardiovascular side-effects [56–60]. Hence, there is a clear unmet medical need for new therapies that are efficacious in treating the pain and inflammation of OA but do not have the GI side-effects of non-selective NSAIDs. The toxicity of selective COX inhibitors and NSAIDs will be discussed in greater depth in the following article in the Supplement.

Conclusions

Worldwide, OA is the most common form of arthritis, and in Western Europe the incidence of this disease seems likely to increase. The pathophysiology of OA is not completely understood, but is known to involve mediators such as LTs, PGs, IL-1β and TNF-α, which ultimately induce the destruction of cartilage. The net result of these changes is pain, functional limitation and emotional stress. OA can affect people at almost any age, but is common in the elderly. The impact of OA is exacerbated by the common occurrence of comorbidities, such as hypertension, in this age group. As a result, the socio-economic effect of OA on the individual and on society is substantial. There is a clear, unmet medical need for therapies that are efficacious in treating OA while avoiding the renal, cardiovascular and GI side-effects seen with current therapies. This is of particular importance with reference to comorbidities such as hypertension, cardiovascular disease, peripheral vascular disease, congestive heart failure, renal function impairment, diabetes and respiratory disease, which are common in OA patients. Furthermore, therapies that reduce the disease activity of OA and thereby maintain function—rather than simply targeting symptoms—are required. The development of treatments that fulfil these needs will undoubtedly reduce the impact of this serious disease.

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Rheumatology	Key messages
	• Osteoarthritis is a common disease in the elderly and has a significant socio-economic impact. • The impact of osteoarthritis is increased by comorbidities. • Therapies for osteoarthritis must bear comorbidities in mind.

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