THE PROBLEM OF AGEING AND OSTEOARTHRITIS

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ABSTRACT

Increase in the number of elderly population is a worldwide phenomenon, which has its own pros and cons including various medical and social problems. Amongst the medical problems osteoarthritis is a leading one. The various aspects and dimensions of this problem have been proposed to be discussed threadbare in this review article. The drugs that are to be used in near future including the newer modalities of treatment like gene therapy will also be included with in the scope of this article.

KEYWORDS

Old age- altered demographic profile - osteoarthritis- aggrecanase inhibition – gene therapy – Orthokine.

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INTRODUCTION: Ageing is a multidimensional process; old age is the closing period of the life of an individual. The elderly population has increased progressively worldwide. India is the second largest populous country in the world (Census 2001). The proportion of older people in India has risen from 5.63% in 1961 and is expected to be 12.4% in 2026.[1] Elderly population in India accounts for 8% of total population in 2010 (World Health Statistics report 2012). The problem of old age was never a problem in India. Old age homes were alien in concept and abuse of elders was considered a western problem. As life expectancy has increased, hundreds of old age homes sprung up in India. Older individuals usually have various health problems. To ensure optimum quality of life and also to alleviate the financial and psychological burdens arising from ageing for the individuals and their families and the society as a whole, good health is important. Ageing is progressive impairment of functions resulting in loss of adaptive response to stress and an increasing risk of age-related diseases. Ageing occurs at different levels: Social, chronological, behavioural, physiological, morphological, cellular and molecular.

The physiological decline refers to the physical changes as individual experiences because of the decline in normal functioning of the body resulting in poor mobility, vision, hearing of the body resulting in poor mobility, vision, hearing along with decline in memory, inability to eat and digest food properly, inability to control certain physiological functions, and various chronic conditions. Nutritional wellbeing is an integral component of the health, independence and quality of life of older individuals.[2,3] Change in socioeconomic status adversely affects the individual's way of life after retirement. The economic loss is due to a change from salary to pension or unemployment leading to economic dependency on children or relative. A feeling of low self–worth may be felt due to the loss of earning power and social recognition. This state of mind is harmful. With the prospect of this situation worsening in the coming decades, ways and means of managing the stress effectively needs to be examined.[4]

Old age is a vital last phase of human life. Old age implies consideration not only of biological but also of psychological and social attributes of an individual.[5] Ageing is accompanied by changes, which may impair bodily functions viz. food acquisition, digestion and metabolism and finally causing multifactorial disorders.[6,7]

The review of demographic ageing of population in India highlights the fact that one out of every seven elderly in the world is an Indian. Due to longevity of life, a great extent of people has the risk of developing chronic and debilitating diseases.[8] Studies on health and nutritional status of elderly had reported high intake of saturated fats, irregular meals, addiction towards alcohol and smoking started in young age seen to be a major culprit of high morbidity prevalence in old age.[9]

With respect to disease profile, data on major and minor illness, CVD and bone related problems, whereas lethargy, lack of appetite and pain in joints were most prevalent minor problems among all the age group elderly subjects.

Osteoarthritis is a major problem in the elderly associated with morbidity. This article will deal mainly with this problem of the elderly and particularly of the osteoarthritis occurring in the knees. It also will review newer modalities of therapy with their efficacy and their experimental stages.

Definition of osteoarthritis according to ACR (American College of Rheumatology) is - A heterogeneous group of conditions that leads to joint symptoms and science which are associated with defective integrity of the articular cartilage and related changes at the underlying bone in the joint margins.

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Osteoarthritis is a major problem in the elderly associated with morbidity. This review article is restricted to primary osteoarthritis of knee. It reviews the available modalities of therapy with their efficacy and an account of some new experimental therapies.

Osteoarthritis (OA) is currently defined by the American College of Rheumatology (ACR) as a "heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins.[10]

Approximately, 25 percent of persons 55 years of age or older have had knee pain on most days in a month in the past year,[11,12] and about half of them have radiographic osteoarthritis in the knee, a group considered to have symptomatic osteoarthritis. Physical disability arising from knee OA can be severe and loss of functional capacity reduces quality of life.[13,14] The disease can exist without radiographic evidence of osteoarthritis of the knee, an imaging procedure insensitive to early disease.

REVIEW OF LITERATURE: The invention and use of writing, the birth of the first great civilisations: We have moved from prehistory to antiquity. The first medical treatises were soon to appear. The archaic conceptions involving gods and demons in the sickness and healing process were gradually replaced by a more rational approach based on observation but also on empiricism. To find out what the concepts of the ancients for osteoarthritis and its treatment were, let's review the works of classical authors, examine the Egyptian mummies and finish this stage of our journey in China.

- The strange silence of Greek physicians
- Egypt at the time of the Pharaohs: Osteoarthritis of the hip for the scribes, vertebral osteoarthritis for the peasants!
- And our ancestors the Gauls?
- Rome, osteoarthritis and herbal medicine: Dioscorides attributed therapeutic virtues to ivy.
- And acupuncture, since the earliest times.

While texts on diseases of the bones and joints written by the founding fathers of Western medicine (Hippocrates, Celsus, Galen) thoroughly describe how to reduce the number of fractures and dislocations and how to treat war wounds (stabbings), no chapter is devoted specifically to rheumatic diseases. Taking the example of Hippocrates and his 412 famous Aphorisms, only six of them, of which here is a rough translation, refer to rheumatism:

- In the elderly, dyspnoea, catarrh and coughing, dysuria, joint pain, kidney inflammation, vertigo, etc.
- Swelling and joint pain, ulcers, those of a gouty nature and muscle strain are usually improved by cold water, which reduces swelling and eliminates the pain, as a moderate degree of numbness eliminates pain.
- In gouty disorders, inflammation disappears within 40 days.
- Typically, gouty disorders are exacerbated in the spring and autumn.
- In chronic diseases of the hip joint, where the bone comes out of its socket and then returns, indicates mucositis in this region.

Hippocrates (470 - 410 av. J.-C.)

- In people with a chronic disease of the hip joint, if the bone comes out of its socket, the limb atrophies and is lost unless the site is cauterised.

The only rheumatic disease clearly identified in these lines is gout. It is difficult; however, to recognise hip osteoarthritis in the last two of these aphorisms which are otherwise very unsavoury: Hippocrates seems rather to refer to an evolved form of infectious arthritis. Osteoarthritis appears only implicitly among the joint pain affecting older people, but we know that such pain can be of various origins.

Could the short life expectancy of the Ancients account for a logical disinterest in age-related diseases? Would mechanical factors leading to osteoarthritis have made this disease a disease of slaves, doing the toughest jobs, but regarded as mere instruments unworthy of interest? In reality, we are with Hippocrates at the very beginning of the rational approach to medicine. Everything remains to be invented, beginning with the identification and accurate description of the disease (or nosography). However, osteoarthritis has existed since ancient times. Demonstrated by the techniques of spinal manipulation (very unwise!) recommended by Hippocrates and more accurate data that has survived from ancient Egypt. Egypt at the time of the Pharaohs: Osteoarthritis of the hip for the scribes, vertebral osteoarthritis for the peasants! Some perfectly preserved skeletons dating from the Pharaonic era indeed provide valuable information on the existence of several rheumatic diseases! We thus know that ankylosing spondylitis, an inflammatory disease mainly affecting the joints of the lumbar region, has existed at least since the third millennium BC.

Osteoarthritis is not lagging far behind and osteoarthritic joint damage, common in Pharaonic Egypt, even gives some indication of the occupational activities of the sufferers. The "office" work of that time did not confer any protection against osteoarthritis. Scribes and viziers sat cross-legged which predisposed them to osteoarthritis of the hip. Moreover, we find the predisposing factor at the present time in regions of the world where sitting cross-legged is one of the favourite resting positions. Egyptian peasants, constantly bending down and straightening up were more likely predestined to develop early bone spurs (osteophytes) characteristic of osteoarthritis of the spine. At the present time, these osteophytes appear in most people only from around the age of 50 years onwards and affect virtually all people of 90 years and over. Egyptian documents reveal that the joint pain was treated with ointments containing fat, oil,

honey or bone marrow, to which could be added the most diverse ingredients: Flour, baking soda, onion, cumin, incense and so on. According to some sources the Egyptian peasants still use it today in the form of ointments with animal fat from snakes and lizards in an attempt to relieve rheumatic pain.

The little known story of the Celts or Gauls (the two terms being synonymous before Julius Caesar reserved the second term for the Celts of what are now France and Belgium) extends over more than a millennium over the whole of Europe. In the sixth and fifth centuries BC, the first Celtic "Princes" appeared in Central Europe. A princely tomb was discovered intact in Hochdorf, near Stuttgart (Germany). The Prince of Hochdorf delivered valuable information to archaeologists because he was surrounded by everything you need to travel conveniently in the other world (weapons, jewellery, dishes). A man measuring 1.87 metres. However, he suffered from osteoarthritis of the joints and his teeth were half worn down. He was also suffering from periodontal disease.

Dioscorides was a Greek physician, but he worked in Rome in the 1st century AD at the time of Nero. Author of the book De Materia Medica, translated and plagiarised many times over, and ancestor of phytotherapy or herbal medicine (his descriptions of plants; however, contain many errors), he recommends using ivy against what seems to be osteoarthritis of the hips. A remedy from which we could probably expect a good placebo 1 effect, as with the Egyptian potions.

Patients who volunteer to participate in studies measuring the effectiveness of current drugs are often randomly divided into two groups. In one of these groups, patients receive the active drug being studied. In the other group, patients receive a completely inactive "placebo" but whose appearance is strictly identical to that of the active drug.

During the study, neither the physician nor the patient knows which of the two products was used. It is known that up to 30% of people "treated" with a placebo administered with sufficient conviction by the doctor can feel an improvement in subjective symptoms such as pain. This suggests that Dioscorides obtained some "improvements" in his patients, even if he ignored that to be considered truly active, a drug must be significantly more effective than the corresponding placebo.

Let's leave the countries bordering the Mediterranean and push on to the East. The oldest book devoted to Chinese medicine is "Neiching", also known as the "The Yellow Emperor's Classic of Internal Medicine." The book is written in the form of a dialogue between the Emperor "Huang Ti" and the doctor "Chi Po." The Yellow Emperor, supposed to have lived around 2700; BC, is in fact a legendary figure. In fact, the "Neiching" seems to be a compilation written by several authors between 2500 and 1000; & nbsp BC. This is, in particular, the first reference book on acupuncture. The techniques described have remained virtually unchanged until today, where acupuncture is sometimes used in the symptomatic treatment of pain caused by osteoarthritis.

The aetiology of OA is multifactorial, with inflammatory, metabolic, and mechanical causes. A number of environmental risk factors, such as obesity, occupation, and trauma may initiate various pathological pathways. Though OA indicates the degeneration of articular cartilage together with changes in subchondral bone; an intra-articular inflammatory component should not be overlooked as it forms the basis of therapeutic strategies.

Although there is no known cure of OA, treatment is directed to reduce pain, maintain and/or improve point mobility, and limit functional impairment.[15] in 1995, the American College of Rheumatology (ACR) published recommendations for the medical management of OA of the hip and knee.[16] Several therapeutic strategies have been developed for better medical treatments for OA.[17]

However, development of disease-modifying osteoarthritis drugs (DMOADs) encounters obstacles like regulatory issues, length of clinical trials, the lack of validation and consensus on new biological markers. Moreover, the duration of treatment is likely to be lifelong.

DIAGNOSIS: OA knee is classified on the basis of ACR criteria as given in Table 1.[18]

Clinical and laboratory	*Clinical and radiographic*	*Clinical +*
Knee pain	Knee pain	Knee pain
+ at least 5 of 9:	+ at least 1 of 3:	+ at least 3 of 6:
- Age > 50 years	- Age > 50 years	- Age > 50 years
- Stiffness < 30 minutes	- Stiffness < 30 minutes	- Stiffness < 30 minutes
- Crepitus	- Crepitus	- Crepitus
- Bony tenderness	+ Osteophytes	- bony tenderness
- Bony enlargement	- Bony enlargement	
- No palpable warmth	- No palpable warmth	
- ESR < 40 mm/hour		
- RF <1:40		
- SF OA		
92% sensitive	91% sensitive	95% sensitive
75% specific	86 specific	69% specific

Table: Criteria for classification of idiopathic osteoarthritis (OA) of the knee (1986)*

ESR = erythrocyte sedimentation rate (Westergren);
RF = rheumatoid factor;
SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count < 2,000/mm^3) + Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific.

We the authors will like to mention that the traditional and conservative management of osteoarthritis have been discussed threadbare in various textbooks of medicine as well as in the pages of reputed medical journals also. Here, we will attempt to throw light on futurist mode of therapy only.

FUTURE THERAPIES

Aggrecanase Inhibition: Proteases are responsible for the cleavage of aggrecan. Two such enzymes were found in particular tissues and named aggrecanase-1 and aggrecanase-2.[19, 20] These enzymes belong to the ADAMTS family and were further designated ADAMTS-4 and ADAMTS-5, respectively. Recent reports have shown that ADAMTS-5

is the predominant enzyme involved in the OA process.[21, 22] A selective inhibitor of aggrecanase and MMP-13 was recently reported.[23] This therapeutic approach may hold some promise for the future.

Gene Therapy: Several candidate genes have been identified as potential targets for the treatment of OA, [24-28] including a wide range of molecules such as cathepsin K, caspases, MMPs and cytokines.

Gene therapy controls the expression of a number of genes that are responsible for the synthesis of factors involved in cartilage degradation and/or those that promote cartilage repair.[29]

Studies have shown beneficial effects of using different in vivo gene therapy strategies with IL-1Ra in two OA experimental models.[30-32]

Strategies that are capable of stimulating cartilage anabolism and joint repair include the use of growth factors such as members of the transforming growth factor family, insulin-like growth factor IGF-1 and fibroblast growth factor, which were demonstrated to stimulate the formation of hyaline cartilage-like repair tissue. Transfer of these genes into OA joint cells, such as the chondrocytes, may represent an interesting therapeutic DMOAD option to repair cartilage lesions.

Targeting Synovial Inflammation:

Interleukin-1: Inhibition of the production/activity of IL-1 can be achieved by receptor blockade, neutralisation of the cytokine by soluble receptors or monoclonal antibody, blocking the formation of active IL-1, or inhibiting the IL-1 cellular signalling pathways, Recombinant human IL-1Ra, Anakinra, when injected subcutaneously, is safe and well tolerated in a diverse population of patients with RA.[33] However, its rapid clearance and variable accumulation in the OA joints has promoted the use of delivering IL-1Ra intra-articularly.

IL-1β is primarily synthesised as a precursor (pro-IL-1β), and must be cleaved by a cysteine-dependent protease, named IL-1β converting enzyme (or caspase-1), to generate the mature cytokine. It is also responsible for the cleavage and release of IL-18. Thus, inhibition of this enzyme will block activation of two very potent proinflammatory cytokines. IL-1β converting enzyme inhibitor was found to reduce the progression of joint damage in two experimental mouse models of OA.[34]

IL-1 activity is mediated by its binding only to type I receptor. After IL-1 binding to its type I receptor, there is induction of multiple phosphorylation-dependent signalling path-ways which includes the serine-threonine kinases of the mitogen-activated protein kinase family and nuclear factor-κB cascades. The mitogen-activated protein kinase superfamily is composed of at least three signalling pathways: The extracellular signal-regulated protein kinases, the c-Jun amino-terminal kinases or stress-activated protein kinases, and the p38 family of kinases.

An experimental in vivo study has reported a therapeutic effect of a specific extracellular signal-regulated protein kinase inhibitor, namely PD198306, in experimental rabbit OA.[35] Recently it was reported that phenyl N-tertbutyl nitrone, a spin-trap agent, down regulates IL-1-induced MMP-13 expression via the inhibition of the c-Jun amino-terminal kinase pathway in OA chondrocytes.[36]

The p38 inhibitor has anti-inflammatory effects in cartilage explants and in animal models.[37]

Orthokine: An alternative therapy, based on the intra-articular injection of autologous conditioned serum, is used in Europe. This product, known as Orthokine, is generated by incubating venous blood with etched glass beads. In this way, peripheral blood leukocytes produce elevated amounts of the interleukin-1 receptor antagonist and other anti-inflammatory mediators that are recovered in the serum. Considerable symptomatic relief has been reported in clinical trials of this product.[38]

Oncologists have taught us a lot. We have learnt not to lose hope and to keep on working towards the benefit of patients. We have seen the progress in the management of cancers – from no care, to palliative care, to definitive treatment, to cure. One of the earliest treatments described for cancer of breast was cauterization with the help of a burning branch of wood. This crude palliative care gave rise to more refined palliative care including treatments like lumpectomy, pain relief. Definitive care came in the form of more advanced radical surgery and radiotherapy. However, despite impressive gains, all treatments failed in late and widespread disease. Survival curves for different malignancies have shown that if malignancy is treated at stage 1, the prognosis is much better than if treated late in stage 4. A simple lumpectomy in stage I CA breast may cure the disease whereas complex radical mastectomy may not be sufficient for advance disease. Now, the emphasis is to screen for cancer and detect and treat it before it becomes a real disease. Currently, screening for CA cervix saves 5000 deaths in UK whereas only about 1000 die every year.

What have the rheumatologists picked up from the oncologists? - A strategy for the management of RA. This strategical shift from palliative therapy to definitive therapy includes (i) Use of combination disease modifying therapy, (ii) Early treatment, and (iii) Treat to target. The target in rheumatoid arthritis is set to "remission or very low disease activity. "Using this target, it has been possible to produce 65% remission rates using standard disease modifying anti-rheumatic drugs in the TICORA Trial (Grigor et al 2004). With anti-TNF drugs 40% remission is seen in MTX resistant patients. Rituximab produces another 15% remission in anti-TNF resistant patients. A combination of standard DMARD + anti-TNF in "early" patients may produce up to 90% remission.

Currently, accepted goal of management of osteoarthritis is "pain relief" with the use of paracetamol. It is recommended that NSAIDs should be used only when paracetamol does not work and should be used for the least possible time. All NSAIDs have a black box warning that they are harmful. If there is inadequate pain relief then opioids may be added to the treatment. The use of all other

medication available for treatment of osteoarthritis is disparaged upon. The other form of therapy that is acceptable is a total knee replacement surgery (TKR), which does take care of the pain in a bulk of the patients but is not suited for the Indian style of living of squatting and sitting on the floor. It is expensive and out of reach of most patients in the country. If 0.23 % patients of OA need TKR then total burden to the tax payer will be 1 lakh crore or more. Pain relief by paracetamol or TKR can be best described as palliative therapy.

Since pain relief and consequent improvement in function is the current target, it would be worthwhile to see the effect of various therapies on pain relief. Effect size for pain relief with different pharmacological treatment have been compared in a recent meta-analysis (Zhang et al, 2007). IA corticosteroid, glucosamine sulphate, chondroitin sulphate and COX-2 inhibitors have the best effect. This meta-analysis has shown that paracetamol as a treatment of pain relief is not worth it and neither any other medication provides optimum relief though some reach levels which are near the optimum relief.

CONCLUSION: Old age - the last but not the least and also the golden phase of the human life is beset by various problems including osteoarthritis. It has assumed greater proportion due to altered mode of life style now a days. The path to recovery from osteoarthritis has been brightened with the advent of newer modalities of therapy. The recent innovations in the therapeutic measures will be definitely a boon to the suffering humanity.

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