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Immunogenetic Aspects of Ankylosing Spondylitis

Hamza Altaf[1], Nageen Hussain[2], Muhammad Ahmed Saeed[3]

Institute of Microbiology and Molecular Genetics[1-2], University of the Punjab, Lahore

Rheumatoid, Centeral Park Medical College, Lahore[3]

Abstract

One of the common autoimmune diseases that mainly affect joints that make the bones immobile is Ankylosing Spondylitis (AS). It is a chronic inflammatory disease classified under spondyloarthritis. There are different types of AS depending on the site of inflammation. Symptoms and complications derived from this disease may vary from person to person. Studies have proved that patients with the HLA B27 positive gene, a part of the MHC class 1 molecule, are mainly involved in causing inflammation in the bony structure. Several hypotheses and meta-analyses explain the pathogenesis and autoimmunity towards cause AS. In addition to the HLA-B27 gene, other immunological, microbial, and endocrine factors along with cytokines and interleukins are involved in playing parts in causing inflammatory AS. The treatment of this disease involves pharmacological and surgical ways. The main aim of this review article is to give a view on immune-genetic aspects of Ankylosing spondylitis.

Keywords: Ankylosing Spondylitis, HLA, immunological factors, microbial factors, endocrine factors

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Coresponding author: Nageen Hussain.

Email: nageen.mmg@pu.edu.pk

Introduction:

Ankylosing spondylitis is a long-lasting provocative sickness that causes inflammation in the vertebral joints and makes the spine stiff. It is categorized as an autoimmune disease that mainly affects joints. Ankylosing spondylitis falls in the subtype of spondyloarthritis. Spondyloarthritis, a group of states with alike symptoms, is a type of arthritis that causes inflammation in the spine that mainly affects the back of the body. Painfulness can also occur in our back, eyes, rib cage, and neck in addition to making the neck stiff. The onset of this disease is in the late teens or 20s. [1] In AS, there is chronic soreness in the intervertebral joints and facet linkages of the backbone mainly due to an autoimmune response. As a backfire response against inflammation, the stiffness in the back and neck occurs because the body produces layers of tough fibrous bands around the bones of the spine. Ossification, a process in which the fibrous tissue turns into bone, starts. The result is the formation

of small bony outgrowths at the joint edges called ‘syndesmophyte’ that makes the spine immobile. Although AS mainly affects the neck and spine, it can also cause stiffness on other sites in the body for example hips, shoulders, and feet. AS is not a hereditary disease, which means it cannot be passed from one generation to another. [2]

The fusion of the vertebrae causes the flexibility of the spine to decrease and makes the posture curved. The attachment of the ribs also makes it difficult to breathe deeply. Men are thrice times more affected by ankylosing spondylitis than women [3]. 90% of white patients suffering from AS have an allele present in them which is the main cause of the fusion of vertebrae, this allele is named human leukocyte antigen B27 (HLA-B27). Depending on the ethnicity, AS is present in up to 10% of the overall populace [4].

AS began when a member of the Geological Museum staff in Cairo discovered crocodile remains. The crocodile remains were estimated to be at least 90,000 years old. Researchers discovered two fused vertebrae in these remains because these vertebrae had osseous tissues, which became the reason for fusion. Sir Armand Ruffer's repeated examinations of these remains led him to the conclusion that the fusion of a crocodile's vertebral column by pathological lesions is identical to the spondylitis deformity seen in humans today. This vertebral fusion disease has been identified in other animals as well. These animals include cave bears, sheep, ancient Egyptian oxen, scared monkeys, and Dinosaurs from the Mesozoic and Triassic periods. Following Sir Armand's conclusion, another researcher named Dr. Moodie commented on it in the 1930s. He stated that crocodiles, dinosaurs, giant wolves, cattle, horses, and tigers all had ankylosing spondylitis in their skeletons, which must have caused them pain and limited their movement. These discoveries demonstrated that AS existed before the evolution of humans. The first case was described in 1559 by a researcher from the University of Padua who described two skeletons with a spinal disease that could have been caused by ankylosing spondylitis. An Irish physician described the pathology of AS in a skeleton in 1693. He scribbled that the skeleton's vertebrae were so legitimately joined that they made up one, but there was a single uniform continuous bone. In his thesis, he emphasized that man must have had difficulty breathing due to rib joint fusion and difficulty bending and turning due to spinal fusion. During the latter half of the nineteenth century, AS was recognized as a distinct disease operation. Advances in radiology speed up the diagnosis of AS before it progresses to severe ankylosis. [5-6]

Ankylosing spondylitis is classified into three types. The first type is Axialspondyloarthritis (axSpA). It is an umbrella term for types of inflammatory arthritis that mainly affects the spine and sacroiliac (SI) joints, a joint that connects the lower spine to the pelvis. X-ray findings show it is typical of sacroiliitis. [7, 8]theSecond type is the non-radiographic ankylosing spondylitis. It is similar to axial spondylitis but damage to the joints is not visible on the X-ray.[9,10]The Third type is peripheral ankylosing spondylitis. The symptom of this spondylitis is inflammation in the tendons or joints outside the spine.[11] The joints that are most commonly affected are present in the hands, elbows, knees, shoulders, and feet. As compared, axSpA ductility and enthesitis are more common.[12]

Many observable symptoms are reported for AS. These symptoms may differ from patient to patient.[13] The most common

symptom of ankylosing spondylitis includes inflammatory back pain. Although spinal pain is the most normal symptom it can also begin in peripheral joints, especially in the case of women and children. Complications in result fromAnkylosing spondylitis. Common complications involved stiffness in the neck, and rib cage, decreasing lung capacity and its function, and inflexibility of the spine. Besides these complications,some other complications are involved with ankylosing spondylitis. These complications include eye swelling (uveitis), compression fractures, heart complications, and osteoporosis. Uveitis is the quick onset of eye aching, unclear vision, and sensitivity to bright light. During the early stages of AS, the bones of some people weaken. Weakened vertebrae can squeeze thus causing the vertebrae to fracture. Fractured vertebrae put pressure on the spinal cord and the nerves that pass through the spine. Aorta is also affected by AS. Inflammation in the aorta causes the aorta to become enlarged than the normal size that which damages the shape of the aortic valve in the heart. A condition in which bones become thin and are more likely to be fractured is known as osteoporosis. People having ankylosing spondylitis can develop osteoporosis [14].

Major Histocompatibility Complex (MHC) is referred to as Human Leukocyte Antigen HLA-B27. This gene is encoded on chromosome 6. It is abundant among cell types and is highly expressed in antigen-presenting cells. After translation and tertiary folding, HLA-B27 heavy chains form heterotrimeric complexes with β2-microglobulin (β2m) and intracellular peptides derived from self-proteins, viruses, and bacteria. [15]Genetic factors play a predominant contribution in provoking ankylosing spondylitis. The hereditary factors involved in triggering AS were first confirmed in families in 1961. 90% part in triggering AS is dominated by genetic factors. Different populations differently react toward the genes that provoke AS. The major gene involved in this is HLA B27. 90-95% of patients affected with AS are HLA B27 positive.

1-2% of HLA B27 positive populations develop AS. If there is an affected first-degree relative then this number may increase up to 15-20%. The risk may increase at 94%, 25%, and 4% for first-, second-and third-degree relatives respectively. HLA B27 positive patients have been shown lower average onset age, higher polymorphism, and compromised immunity as compared to HLA B27 negative ones. So far 100 subtypes have been reported especially of East Asian and Caucasian descent. Not only does HLA B27 alone play a part in developing AS other supporting factors also get involved like beta2 microglobulin. It is a non-covalent part of the MHC class 1 complex. Studies proved that it reduces HLA B27 protein misfolding and provokes arthritis, spondylitis in addition to intestinal inflammation. HLA B27 is only 20% involved in the genesis of AS. Other factors must be involved to get full onset to AS. Genetic difference between various ethnicities and regions indicates that other non-HLA gene factors must be involved in addition to HLA B27. In AS patients with HLA B27 negative genes, HLA B60 increases the disease susceptibility by 3-6 folds. An analysis in a Taiwanese population suggested that the interaction between HLA-B60 and HLA-B27 could be a better marker for the risk of AS susceptibility. For HLA-B27-negative AS, HLA-B7,HLA-B16, HLA-B35, HLA-B38 and HLA-B39 have also been associated with in various ethnicities with unknown mechanisms [16].

In 1973, relationship of HLA-B27 with ankylosing spondylitis was first portrayed for HLA alleles. This affiliation stays

perhaps the best illustration of an infection relationship with a hereditary marker. However, most HLA-B27-positive people stay healthy proposing that some other genes, both inside and outside the MHC, are associated with disease susceptibility [17]. Thus, *HLA-B27* may only account for perhaps 20 to 50% of overall genetic susceptibility to AS. Research has shown that 8 out of 100 people having HLA- B27 gene develop ankylosing spondylitis [18]. The harmony rate in monozygotic twins is 63%, and the risk in first-degree relatives is 8.2%. There is solid proof that diverse subtypes of HLA-B27 have specific qualities of association with AS in explicit populaces. About 100 HLA-B27 subtypes have been accounted for to date but the number is increasing rapidly. A large portion of them contrast from one another by a couple of amino acids, however these progressions are adequate to modify the molecules' peptide binding properties. The most common subtypes reported in association with AS are HLA-B*2705, B*2702, B*2704, B*2707 [19]

Some philosophies have been planned to clarify the molecular infective contribution of HLA-B27 in AS, together with the presentation of arthritogenic peptides, the abnormal folding of surface heavy chains, HLA-B27 misfolding, and improved intracellular bacterial existence. [20] As the name shows, the dominant paradigm hypothesis states that folded HLA B27 display peptides on its surface that resemble like microbial peptides which are recognized and targeted by autoreactive CD8+ T cells. These T cells then perform their contribution by causing cytotoxicity and chronic inflammation at that site as they attack these peptides displaying HLA B27.[21] Patients suffering from autoimmune diseases like reactive arthritis, ankylosing spondylitis, etc. are identified to have high specificity towards self-peptides in synovial fluid and peripheral blood. Another study revealed the sequence homology of vasoactive intestinal peptide receptor (VIPR) to Epstein-Barr virus derived epitope of latent membrane protein 2 (pLMP2) peptide (Figure 1.1). However, it was shown to have minimum cross reactivity between VIPR and EBV specific CD8+ T cells. [22]

HLA B27 homodimer hypothesis states that during endosomal recycling, heavy chain dimers of HLA B27 are expressed on cell surface. The two separate heavy chain homodimers are held together by disulphide bond in between cysteine resides at position 67, C67 without involving β2m. These heavy chain peptides bind to specific receptors displayed on the surface of NK cells, T lymphocytes and myelomonocytic cells and thus provoke an autoimmune response. This hypothesis gained weight by the discovery that HLA B27 positive patients have high amount of NK cells and CD4+ T cells that express a certain receptor KIR3DL2, a killer immunoglobulin-like receptor (KIR) that only HLA B27 homodimers can recognize (Figure 1.1). [23]

According to HLA B27 misfolding theory, the endoplasmic reticulum accumulates large amount of HLA B27 misfolded protein that triggers the inflammation. High concentration of misfolded HLA in endoplasmic reticulum invokes ER stress as a reaction in the form of generating a signal transduction pathway. ER chaperones (BiP) are accumulated as the reaction that promotes cytokine production which is recognized by macrophages thereby causing inflammation (Figure 1.1). The ER-overloaded response (EOR) to excessive membrane protein trafficking within ER involves activation of nuclear factor kappa B (NF-B) transcription, which can increase the manufacturing of proinflammatory cytokines such as YNF, IL-1 and IL-6 in certain cell types [24].

There is an assumed concept that inflammation to a part of body promotes new bone formation, a term called osteoproliferation. But there is no specific link found to be associated to osteoproliferation and inflammation. Though there is an ongoing debate on this association, there is a strong association between AS and Th 17 cells number as the later one releases cytokine upon inflammation. [25] Additionally, anti TNF therapy appears to have no effect on new bone formation in AS patients.It is highly likely that all of these mechanisms play some part in predisposing an individual to AS. Unfortunately, the precise contribution of HLA-B27 in pathogenesis remains unclear, but features that distinguish it from other genes and differences among its many subtypes have provided the basis for several putative explanations as to how it might predispose individuals to AS and mediate the disease (Figure 1.1). [26

Chronic inflammatory disease like AS involves many immune cells like DCs, macrophage, NK cells, etc that further produce various cytokines playing part in AS. A decrease in circulating CD1c+ DCs will increase the amount of CD-14 CD-16 mononuclear cells that in turn increase chemokine receptor 6 (CCR6) expression. All this together increase the production of IL-1B and IL-6 in patient. Moreover, it will trigger the Th-17 immune response and IL-17 production that causes inflammation and autoimmune disorder as observed in AS. Some studies observed that Th17 cells participate in the acute phase of inflammation. In AS patients, sacroiliac joint lesions are observed to contain large number of CD 68 positive macrophages or osteoclasts. The higher number of macrophages and NK cells are observed in the body of AS patients. But reduced activity of NK cells is due to high expression of NK cell-inhibitory receptor carcino-embryonic antigen-cell adhesion molecule (CEACAM1), thereby inhibiting NK cell activity [27].

Interleukin 17 (IL-17) which is basically a proinflammatory cytokine that helps to contribute in the progression of a number of inflammatory infections. T helper 17 cells are one of the most common sources of IL-17, but T cells, neutrophils, mast cells and natural killer (NK) cells, may also be implicated. Because it intervens the release of IL-6 as well as IL-8, the activity of IL-17 is well recognized to play a contribution in numerous aspects of acute inflammation. Based on the disclosures that reveal that IL-17 advances cartilage degradation in a mouse model [25], the contribution of IL-17 in rheumatic infections has been discovered. Dendritic cells (DC) may deliver an arthritogenic peptide originated from pathogenic microorganisms or self-antigens to THO cells, which may play a contribution in AS. NK cells lead to the release of IL-17 that recognize HLA-B27 homodimers and the differentiation of these T cells may be impacted by the mast cells, causing them to differentiate into TH17 cells which are engaged in aggravation by chemicals which includes IL-6 and IL-8.[28]

CD4+ T cells are delivered as naive CD4+ cells into the periphery after selection in the thymus, where they develop into different types of effector T cells. Th1 and Th2 are the earliest T cell subtypes, each with its own master transcription factors and cytokine production pattern [29]. The Tregs were the next to arrive. The main physiological effector role of these cells is assumed to be the immunity against extracellular bacterial and fungal infections. Th17's effector actions are intervened by the secretion of cytokines such IL-17 A (the lineage's hallmark cytokine), IL-17 F, and

IL-22. A mixture of cytokines, which includes IL-1, IL-6, TGF-, and IL-23, induce Th17 differentiation. IL-23, on the other hand, is regarded as the major driver of Th17's pathogenic potential, as it promotes the expression of the crucial transcription factor ROR-t.[30]

Several studies have been conducted to investigate the contribution of various immune cells which play a role in the pathogenesis of AS, including CD4+ T cells that produce IL-17, which are somehow linked to autoimmune illnesses, notably inflammatory autoimmune diseases [31]. Mast cells injected into SpA synovial joints boosted IL-17 expression, supporting the concept that they could be a wellspring of Th17 production [32]. Furthermore, Th17 cells have been implicated in the promotion of the inflammatory process in AS. Th17 cells have been found in comparatively much higher quantities in the AS patients' peripheral blood, implying that they may play a contribution in inflammation. IL-17 and IL-23 levels in the serum of AS patients have also been reported to be elevated. Studies have revealed that the anti-TNF medication lowers levels of IL-17 and Th17 cells in individuals with AS, implying that Th17 cells have a contribution in inflammation and AS. However it is accepted that aggravation invigorates new bone development, no solid link between inflammation and osteoproliferation has yet been established; additionally, inflammation and new bone formation can occur in different places, and anti-TNF therapy appears to have no effect on new bone formation in AS. Notwithstanding the way that the connection among inflammation and new bone formation is still debated, there is a definite link between AS, Th17 cell numbers, and the latter's cytokine release, suggesting that the latter plays a key part in the inflammatory process seen in AS.[33]

A GWAS study in 2007 emerged with the idea of involvement of IL-23 and IL-17 in AS. In humans; IL-23, TGF-β, and IL-1β may trigger the differentiation of Th17 cells, among other inflammatory cytokines, and IL-17A, IL-17F, IL-22, IL-26, and CCL20 are further generated by differentiated immunocytes. If there is an alteration doing in this pathway of IL-23/IL-17, it may lead to diseases interrupting immunological procedures like in psoriasis, rheumatoid arthritis, IBD, etc. Furthermore, IL-17 and IL-23 go about as significant cytokines for psoriatic arthritis and axSpA. Experimentations have proven that serum levels of IL-23 and IL-17108 and the presence of IL-17+ cells is higher in the facet joints of the AS patients. Differentiated T lymphocytes in ankylosing spondylitis generates IL-17 which afterwards triggers the osteoclast activation, in this manner suppressing bone regeneration. In addition, lymphocytes on its exposure to IL-23 results in the production of IL-22, to stimulate osteoproliferation [34].

Regulatory T cells (Tregs) intervene the peripheral tolerance by effectively smothering effector T cells and repressing tissue damage which is immune mediated. In the beginning, Tregs were distinguished on their tendency to express CD25, however presently these are portrayed by the expression of FoxP3, which is an intracellular transcription factor [35]. They work by keeping up with immune tolerance and prohibiting diseases which lead to inflammation. Likewise, they have been involved in maintaining the balance of pretty much every adaptive immune response. and, similarly in inflammatory responses, by utilizing suitable mechanisms that restrain designated cell populaces [36].

On account of AS, some examinations have been completed to measure the levels of Tregs present in the patient's peripheral

blood; notwithstanding, low rates of Treg cells have been accounted for the peripheral blood, and in the synovial fluid of patients with AS, proposing a lopsidedness among Tregs and the adaptive immune response. Besides, when compared to the healthy subjects, the AS patients which were basically treated with anti-TNF therapy exhibited almost similar levels of Treg. These experimental evidences recommend a potential capability of Tregs in causing AS, and imbalance of Th17/Tregs has been expected in playing an innovative part in AS [37].

NK cells act as a borderline in innate and adaptive immunity towards AS. The main contribution played by NK cells is first line defence towards different pathogens but they are also involved in provoking some autoimmune response. The expression of CD56 and absence of CD3 promotes NK cells. In an anti-inflammatory response like as in AS, there is high quantity of circulating CD3- CD56+. An NK inhibitory receptor KIR3DL1 is recognized by the protein HLA B27. Signal transduction leads the phagocytic activity of NK cells. Several surface receptors of NK cells are also get activated like NKp44+ and NKp46+ in AS patients. In addition, there is high production of IL-22. Altogether, it will trigger an autoimmune response in AS patients as compared to people with normal NK cell amount. Metanalysis and immunogenetic studies also proved a strong association of several receptors like that KIR2DL1, KIR2DL5, KIR2DS5, KIR3DS1, and KIR3DL1 to be associated to HLA B27 in an autoimmune response in AS patients.[38]

several non-MHC genes that are involved in the activation of T lymphocytes associated with AS including RUNX3, EOMES, ZMIZ1, IL7, TBX21, and IL7R. Run related transcription factor 3 (3 RUNX3) involved in regulating the expression of lineage specific genes, linked to many autoimmune diseases like psoriatic arthritis and AS. Previous studies have revealed a connection between the RUNX3 polymorphism rs11249215 and AS in Caucasian, 99 Han Chinese118 and Korean populations,119 and rs4648889 has been related to reduced RUNX3 expression in AS. Polymorphism of molecules such as programmed cell death 1 (PDCD1), encoding PD-1, or T lymphocyte antigen 4 (CTLA-4), encoding CTLA-4, have been shown to influence the susceptibility to AS [39].

AS share common immunological and genetic bases with IBD, anterior uveitis, psoriasis and other diseases. In the peripheral blood of AS patients and healthy HLA-B27-positive controls, the levels of T cells secreting tumor necrosis factor (TNF)-α and interferon (IFN)-γ were reportedly lower. CD8+ T cells in AS patients tended to secrete more IL-10. HLA-B27 transgenic rats failed to developfeatures of SpA in a germ-free environment, which changed when commensal bacteria were introduced into the germ-free models, suggesting possible interactions between HLA-B27 and the microbiome. The gut microbiome, including Lachnospiraceae, Veillonellaceae, Prevotellaceae, Porphyromonadaceae, and Bacteroidaceae, showed significant differences in AS patients compared with that in healthy controls. Studies proved that Klebsiellapneumoniae has been shown to be a triggering factor in autoimmune AS, acting as an opportunistic pathogen. Klebsiellapneumoniae has an indirect influence in provoking ankylosingspondolytis along with HLA B27 gene. Moreover, if there is compromised immunity due to gut infection, the immune response would be intense and long lasting.[39]

Many hormonal and endocrine factors detected to be associated with AS. A study

on 22 AS positive patients showed a lowered testicular testosterone level, high luteinizing hormone level, estradiol/testosterone level and slightly increased estradiol level. A high difference is observed in hormonal level in between AS positive menstruating and menopausal women compared to healthy women. More observational findings, such as male preponderance, starting at a young age, and an increase in the frequency of first manifestations following pregnancy, suggest that sex hormones play a role in AS. In patients with AS, low levels of sex hormones, particularly dehydroepiandrosteronesulphate (DHEAS), may also contribute to bone loss. A study of the low-dose adrenocorticotropic hormone (ACTH) test (LDST) found that the cortisol increment in AS patients was considerably lower than in controls (20.0 4.4 vs 24 2.2 microg/dl, P 0.001). Subclinical glucocorticoid deficit in AS patients demonstrated a disrupted hypothalamic-pituitary-adrenal (HPA) axis, implying that the endocrine system is involved in the pathophysiology of AS. [40]

Human genome organization nomenclature committee has currently accepted the term ERAP1. ERAP1 belongs to the M1 family of metallopeptidases and is a zinc aminopeptidase (46). There are two prime isoforms of the ERAP1. ERAP1-a is the longer isoform while the second isoform which is ERAP1-b is the shorter as compare to ERAP1-a. ERAP1-b is present in greater amount than ERAP1-a (47). With the help of functional outlooks, we can explain the association of ERAP1 SNPs with AS. There have been three biological functions of ERAP1 that are known. It's first function is in the endoplasmic reticulum in which it act as a molecular ruler, cutting peptide antigens to suitable length. At first complex proteins in the cytosol are broken down into peptide fragments up to 25 amino acids this reaction is aided by proteasome complex (33).

Secondly the breakdown of receptors present on the surface of cell by proinflammatory cytokines such as IL-1R2 (50), IL-1Ra (51), TNFR1 (52) is done by endoplasmic reticulum aminopeptidase 1. Therefore, any defect in the ERAP1 will lead to either in the increase or decrease in the cell surface receptors which are available for these cytokines and ultimately increasing the susceptibility against AS (53). Lastly, ERAP1 is involved in the macrophage activation which is induced by lipopolysaccharide (LPS) and interferon (IFN)-*γ (54).* In 2007, Welcome Trust Case-Control Consortium (55) and Australo-Anglo-American Spondylarthritis Consortium (WTCCC/TASC) reported the first confirmed association of ERAP1 with AS. 14,500 nonsynonymous SNPs were used to determine the *ERAP1* association in AS. This was the first non-*MHC* gene for which a decisive AS-association was observed (34).

Maintaining the normal position and relieving pain of patient is the only aim of treatment. Non-steroidal anti-inflammatory medications and TNF alpha inhibitors are mainly used for this purpose. The baseline treatment for patients having active AS, there must be a dose that selectively inhibit cyclooxygenase 2. That's why the use of NSAID treatment is persuaded but continuously using it would prove a blessing in disguise with hypertension and depression. For an adult treatment, there is use of two kinds of NSAID and each is given for over minimum two weeks with maximum tolerated dosage. However, the lowest effective dosage is to be recommended [35].

NSAIDs drugs should be chosen keeping in mind the patient's history, risk factors, etc.

Good results after NSAID drugs involve relief in pain and inflammation. However, if the treatment isn't going in a good direction, analgesics, especially opioid like drugs must be followed. With high disease active patients, treatment with TNF is advised. Other doses like IL-17 inhibitor or other TNFi must be administered in case of failure to treatment with TNF. It's a 3-month long treatment and if no improvement is seen, second TNFi is to be considered and treatment should be changed. Another way of treating AS is to use local injections of glucocorticoids for rapid pain relief in different joints. But long-term use of systemic glucocorticoids somehow increase the risk for osteoporosis, insulin resistance and hyperlipidemia. That's why short-term high doses seem to be effective (50 mg/day). Ankylosing spondylitis, if left untreated, can cause spinal deformity and immobility. Corrective osteotomy and stabilisation is a common surgical procedure for adult patients with kyphosis and hip arthritis. Despite the fact that this process has a 4% mortality rate and a 5% rate of permanent neurologic sequelae. This surgery has been shown to help prevent natural progressive deformity processes, reduce pain caused by muscle fatigue, improve disability, restore global balance and horizontal axis of view, and improve respiratory and digestion function. [36].

Ankylosing spondylitis is a painful disease. Though the full effective treatment isn't available for it but maintaining the posture and relieving the pain is the main concern behind its therapy. Severity depends on different factors. Many genes play their part if go switched on due to an autoimmune response. Other than genetic factors, several immunological factors are also involved in triggering this autoimmune disease. If AS go untreated, it will cause the inflammation to get even worse as a result the joint fuses and bone gets immobile.

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