الجمهورية الجزائرية الديمقراطية الشعبية
Popular Democratic Republic of Algeria
وزارة التعليم العالي والبحث العلمي
Ministry of Higher Education and Science Research
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Faculty of Natural and Life Sciences
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Department of Cellular and Molecular Biology

Order N:
Serial N :

END OF STUDY DISSERTATION

With a view to obtaining the Academic Master's degree

Subject: Biological Sciences

Specialty: Toxicology

THEME

Ankylosing Spondylitis: Etiology and Risk Factors

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Academic Year: 2024/2025

Acknowledgements

In the name of Allah, the Most Gracious, the Most Merciful.

All praise is due to Allah, Lord of the Worlds, who granted us the strength, patience, and guidance to complete this work. Without His mercy and divine assistance, this achievement would not have been possible.We pray that this humble effort is accepted as a sincere contribution in the pursuit of knowledge and truth.

We would like to express our deepest gratitude to our supervisor, Toumi Ikram, for their unwavering support, insightful guidance, and encouragement throughout the course of this research.Your wisdom and dedication have had a profound impact on both the academic and personal levels of our development. May Allah reward you for your efforts and generosity.

We also extend our sincere thanks to the honorable members of the examination committee, Pr. Djahra Aliboutlelis and Pr.Aouimeur Meriem , for taking the time to review and evaluate our work. Your insights and valuable feedback have greatly contributed to the refinement and quality of this research.

Our heartfelt appreciation goes to the faculty members of the Faculty of Natural and Life Sciences, Department of Cellular and Molecular Biology, University of Eloued .Your teaching, mentorship, and commitment to excellence have been a vital part of our academic journey.

To our beloved families, whose prayers, love, and sacrifices have been our constant source of motivation we owe you more than words can express. May Allah bless you and grant you the highest rewards in this life and the hereafter.

We also extend our sincere thanks to our friends and colleagues who have supported us with kindness, collaboration, and companionship along the way. Your presence made this challenging journey more bearable and meaningful.

Finally, to every seeker of knowledge, we ask Allah to bless your efforts and illuminate your path with wisdom and sincerity.

With gratitude and humility,
Kaddouri Hadda
Askri Hanadi
Othmani Maroua
Djaber Hana

Dedication

In the name of Allah, the Most Gracious, the Most Merciful.Most Merciful We, the authors of this Dissertation, humbly dedicate this work to the One who has granted us the strength, patience, and guidance to complete this journey Allah Almighty. Without His divine blessings and mercy, none of this would have been possible. All praise is due to Him, who grants success to whom He wills .

To our beloved families our parents and loved ones your unconditional love, endless prayers, and unwavering support have been the foundation upon which our efforts were built. May Allah reward you abundantly for your sacrifices and make this achievement a source of pride and joy for you.

To our respected supervisor Toumi Ikram, we extend our deepest gratitude. Your guidance, patience, and insightful advice have been invaluable. May Allah bless you for your dedication to teaching and mentoring.

To the faculty members of Natural and Life Sciences, thank you for being a part of our academic and personal development. Your knowledge and commitment have helped shape the people we are today.

To our dear friends and fellow students, your encouragement, cooperation, and companionship have lightened this journey. We are grateful to have shared this path with you.

And lastly, we dedicate this work to every seeker of knowledge. May Allah grant you ease in your pursuits and make knowledge a light that guides your path in this life and the hereafter.

With sincerity and gratitude,

Kaddouri Hadda

Askri Hanadi

Othmani Maroua

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Abstract

Ankylosing Spondylitis (AS) is a chronic autoimmune inflammatory disease that primarily affects the axial skeleton, especially the spine and sacroiliac joints. It typically begins in young adulthood and presents as inflammatory back pain and morning stiffness that improves with movement. The disease has been recognized since ancient times by scholars such as Bechterew, Marie, and Strümpell. Its symptoms are not confined to the musculoskeletal system, as it also manifests with extra-articular features such as uveitis, inflammatory bowel disease, psoriasis, cardiovascular and pulmonary disorders, osteoporosis, and kidney diseases. It leads to restricted mobility, loss of independence, and a significant decline in quality of life, particularly in advanced stages.

Genetic factors especially the presence of the HLA-B27 gene and its interaction with ERAP1 and IL-23R interact with environmental and lifestyle elements such as smoking, microbiome disturbances, and dietary habits to induce a prominent immune imbalance via the IL-23/IL-17 axis. This drives inflammation at tendon-bone attachment sites and leads to structural abnormalities. The relationship between chronic inflammation and an increased risk of certain cancers, such as hematologic malignancies and prostate cancer has become a recent research focus.

This dissertation presents a comprehensive overview beginning with the anatomy and vital functions of the musculoskeletal system, followed by an exploration of the disease mechanisms, contributing factors, and recent developments in metabolomics and genome-wide association studies (GWAS). It aims to provide a multidisciplinary perspective combining toxicology, immunology, genetics, and clinical sciences to deepen the understanding of the disease and improve patients' quality of life.

Keys Words: Ankylosing Spondylitis**,** Genetic factors**,** HLA-B27**,** musculoskeletal system**,** quality of life

Résumé

La spondylarthrite ankylosante (SA) est une maladie auto-immune inflammatoire chronique qui affecte principalement le squelette axial, en particulier la colonne vertébrale et les articulations sacro-iliaques. Elle débute souvent à un jeune âge et se manifeste par des douleurs dorsales inflammatoires et une raideur matinale s'améliorant avec le mouvement. La maladie est décrite depuis l'Antiquité par des savants tels que Bechterew, Marie et Strümpell. Ses symptômes ne se limitent pas au système musculo-squelettique, mais incluent également des manifestations extra-articulaires telles que l'uvéite, les maladies inflammatoires de l'intestin, le psoriasis, les troubles cardiaques et pulmonaires, l'ostéoporose et les maladies rénales. Elle entraîne une limitation de la mobilité, une perte d'autonomie et une nette diminution de la qualité de vie, surtout dans les cas avancés.

Des facteurs génétiques, notamment la présence du gène HLA-B27 et son interaction avec ERAP1 et IL-23R, s'associent à des facteurs environnementaux et liés au mode de vie, comme le tabagisme, les perturbations du microbiote et les habitudes alimentaires, pour provoquer un déséquilibre immunitaire marqué via l'axe IL-23/IL-17, entraînant des inflammations aux points d'attache des tendons sur les os et des déformations structurelles. Le lien entre inflammation chronique et risque accru de certains cancers, comme les hémopathies malignes et le cancer de la prostate, constitue un axe de recherche récent.

Ce mémoire propose une approche intégrée, débutant par une étude de l'anatomie et des fonctions vitales du système musculo-squelettique, poursuivant avec l'exploration des mécanismes pathologiques, des facteurs contributifs, ainsi que des avancées récentes en métabolomique et en études d'association pangénomique (GWAS). Il vise à offrir une vision multidisciplinaire combinant toxicologie, immunologie, génétique et sciences cliniques afin de mieux comprendre la maladie et d'améliorer la qualité de vie des patients.

Mots clés: La spondylarthrite ankylosante**,** facteurs génétiques**,** HLA-B27, système musculo-squelettique**,** la qualité de vie

ملخص

التهاب الفقار المقسط هو مرض مناعي ذاتي مزمن التهابي يصيب بشكل رئيسي الهيكل المحوري، خاصة العمود الفقري والمفاصل العجزية الحرقفية. يبدأ غالبًا في سنّ الشباب، ويظهر في صورة ألم ظهري التهابي وتيبّس صباحي يتحسن مع الحركة. وقد وُصف المرض منذ العصور القديمة من قبل علماء مثل بيختريف وماري وسترومبل. لا تقتصر أعراضه على الجهاز العضلي الهيكلي، بل تشمل مظاهر خارج المفصل مثل التهاب العنبية، أمراض الأمعاء الالتهابية، الصدفية، اضطرابات القلب والرئة، هشاشة العظام، وأمراض الكلى. كما يؤدي إلى تقييد الحركة، فقدان الاستقلالية، وانخفاض كبير في جودة الحياة، خصوصًا في الحالات المتقدمة.

تتداخل العوامل الوراثية لا سيما وجود الجين HLA-B27 وتفاعله مع ERAP1وIL-23R، عوامل بيئية ونمط الحياة، مثل التدخين واضطرابات الميكروبيوم والعادات الغذائية، لتؤدي إلى خلل مناعي بارز عبر محورIL-23/IL-17 ، يسبب التهابات في نقاط ارتباط الأوتار بالعظام وتشوهات هيكلية. وتُعد العلاقة بين الالتهاب المزمن وخطر الإصابة بأنواع معينة من السرطان، مثل سرطانات الدم وسرطان البروستاتا، أحد المحاور الحديثة للبحث.

تقدّم هذه المذكرة عرضًا متكاملًا يبدأ بتشريح الجهاز العضلي الهيكلي ووظائفه الحيوية، ثم ينتقل إلى استكشاف آليات المرض، العوامل المساهمة، والتطورات الحديثة في الأيض ودراسات الارتباط الجيني (GWAS) .وتهدف إلى تقديم رؤية متعددة التخصصات تجمع بين علم السموم، المناعة، الوراثة، والعلوم السريرية لفهم أشمل للمرض وتحسين جودة حياة المصابين به .

الكلمات المفتاحية: التهاب الفقار المقسط ، HLA-B27، العوامل الوراثية، تشريح الجهاز العضلي الهيكلي، جودة الحياة .

Summary

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Abbreviations

AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS HI	Assessment of SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life
AxSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BAS-G	Bath Ankylosing Spondylitis Global Score
BASMI	Bath Ankylosing Spondylitis Metrology Index
COWO	Closing–Opening-Wedge Osteotomy
CRP	C-reactive protein
CWO	Closing Wedge Osteotomy
DFI	Dougados Functional Index
DMARD	Disease-Modifying Antirheumatic Drugs
EQ-5D	EuroQol 5-Dimension health Utility index
ERAP1	Endoplasmic Reticulum Aminopeptidase
ERAP2	Endoplasmic Reticulum Aminopeptidase 2
ESR	Erythrocyte Sedimentation Rate
FA	Fatty Acids
GWAS	Genome-Wide Association Studies
HAQ-S	HealthAssessment Questionnaire for the Spondylarthropathies
HLA-B27	Human Leukocyte Antigen B27
HRQOL	Health-Related Quality of Life
IBD	Inflammatory Bowel Disease
IL-17	Interleukin 17
IL-23	Interleukin 23
INF-γ	Interferon gamma
KIR	Killer-cell Immunoglobulin-like Receptor
LILR	Leukocyte Immunoglobulin-like Receptor
MHC	Major Histocompatibility Complex
NF-Kb	Nuclear Factor kappa-light-chain-enhancer of activated B cells

NK	Natural Killer
NSAID	Non-Steroidal Anti-Inflammotory Drugs
OWO	Opening Wedge Osteotomy
PWO	Pedicle Subtraction Osteotomy (Posterior Wedge Osteotomy)
QOL	Quality of Life
SF-36	Short Form-36 Health Survey
SIJ	Sacroiliac joints
Th17	T helper 17 cells
TLR4	Toll-Like Receptor 4
TNF-α	Tumor Necrosis Factor alpha
WHO	World Health Organization

Introduction

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatological disease characterized by systemic inflammation **(Boonen et al., 2001; Zink et al., 2000).** It primarily affects the spine, peripheral joints, and entheses, ultimately leading to abnormal bone remodeling and ankylosis (bone fusion) **(Mauro et al., 2021).** AS most commonly begins in the second and third decade of life as persistent inflammatory back pain that can already be associated with significant loss of function, work disability and impaired quality of life early in the disease **(Boonen et al.,2001;Zink et al.,2000).**

As an autoimmune disease, AS develops through complex interactions between genetic background particularly the presence of HLA-B27 gene and environmental factors. Although significant progress has been achieved in the past decades, the etiology of AS remains unclear to some extent.To date, studies have revealed some factors that may be related to the occurrence of AS, including genetic background, immune reaction, microbial infection, and endocrinal abnormity**(Zhu et al.,2019).**

Regrettably, the pathogenesis of AS is still not fully understood, which limits the development of preventive, therapeutic, and interventional strategies for the disease. Wherefore, recognizing the etiology and the risk factors of AS is crucial for clarifying its pathophysiological mechanisms, predicting disease progression, and developing more effective strategies for early diagnosis and intervention **(Zhao et al., 2014; Han et al., 2018).**In particular, identifying toxic environmental or occupational exposures that may initiate or exacerbate the disease is a key area of interest within the field of toxicology. Toxicological research provides valuable insight into how certain chemical agents may influence immune system dysfunction, potentially contributing to autoimmune conditions like AS.Thus, exploring AS through a toxicological lens enables a more comprehensive, multidisciplinary understanding of its origins and contributing factors **(Zhao et al., 2014).**

Although ankylosing spondylitis is important healthcare and socioeconomic issue, its etiology and the contributing risk factors lacks the attention of researchers and scholars **(Zhu et al., 2019).**

Therefore, this dissertation aims to highlight the etiology and risk factors of ankylosing spondylitis and to fill this scientific gap. So, what is ankylosing spondylitis?What are its etiology and what factors contribute to its development?

Chapter I: Generality

I.Ankylosing Spondylitis

I.1.Definition

Ankylosing spondylitis (AS) or Bechterew's disease or Strümpell-Marie-Bechterew's disease is a chronic inflammatory rheumatic disease with pain and stiffness that affects the axial skeleton **(Sieper et al.,2015).**The disease often begins in the third decade of life and affects more men than women. It frequently results in stiffness, inflammatory back pain, and reduced mobility. The name has recently changed to axial spondyloarthritis (axSpA) based on the 2009 ASAS classification criteria to better include early disease, theoretically before the occurrence of bony structural damage **(Rudwaleit et al.,2009).** The sacroiliac joints (SIJ) are the primary site of initial damage, with the spinal column typically following. About one-third of patients have additional spondyloarthritis (SpA) symptoms, such as anterior uveitis. Psoriasis and inflammatory bowel disease are often linked to SpA. Comorbidities such as cardiovascular disease are a major cause of morbidity and mortality **(Haroon et al., 2015).**

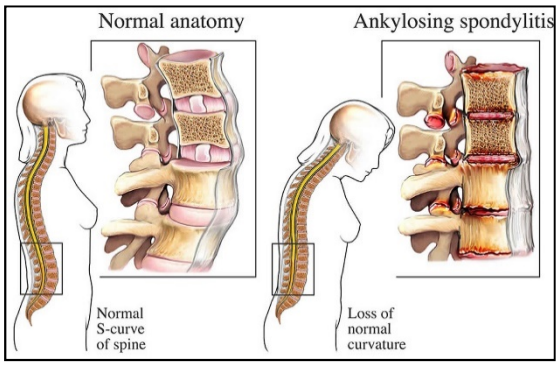

Figure 01: Comparaison of normal spine anatomy and ankylosing spondylitis **(https://www.healthdirect.gov.au/ankylosing-spondylitis).**

I.2.History: The first descriptions of ankylosing spondylitis

It is likely that the pharaohs such as Ramses II in ancient Egypt already had an inflammatory spinal disease **(Feldtkeller et al., 2003).**Today, the well-established association of AS with the MHC class I molecule HLA B27 is, however, less pronounced in some Arab countries **(Ziade,2017).**

In any case, the first scientific publication **(Connor, 1695)** can be attributed to the Irishman B. Connor (1666–1698), who was apparently confronted with an unusual skeleton in a cemetery that showed conspicuous signs of new bone formation due to AS **(Blumberg, 1958; Connor, 1692)** during his stay in Paris **(Keitel, 2012).**His publication in 1691 was his

MD thesis to the University of Reims.

At the end of the 18th century, publications from E. Sandifort (1742–1814), an anatomy professor at the Museum Anatomicum at the University of Leiden, included images of a patient with bone fusion suggestive of ankylosing spondylitis **(Sandifort,1793)** but the disease was not clearly mentioned.

Leonard Trask was an American born in 1805 who had a contortion of neck and spine during his late 20ies after an accident while horse riding. After numerous attempts at a cure, several further accidents resulted in a condition with an increasingly weird posture that led to loss of mobility and employment, but made him a lucrative curiosity. He was likely the first American patient with AS **(Jayson, 2003),** and his disease remained unresolved until his death in 1861, as reported in 1858 **(Trask, 1858)**.

The anatom and surgeon Sir Benjamin Brodie (1783–1862) became president of the Royal College of Surgeons of England when Henry Gray dedicated his work Gray's Anatomy to him in 1858. A typical clinical picture of AS is first described clinically in Chapter 5 of his book "Pathological and Surgical Observations on the Diseases of the Joints."**,(chaptre 12 Section 4, p. 353 ff.)** was published in 1850 **(Brodie, 1834; Holmes, 1898).**Brodie was also the first to describe iritis (anterior uveitis) as a complication of AS **(Spencer et al., 1980).**

Charles Hilton Fagge (1838–1883), a physician at Guy's Hospital in London, was the first medical professional to write about AS a few decades later. He detailed a case with 'simple synostosis' in 1877 **(Fagge, 1877; Bywaters, 1979).**

In an internationally well reputed textbook Adolf von Strümpell (1853–1925) who, at that time worked at the university of Leipzig,described cases of bodies with AS: his 'Lehrbuch der Speciellen Pathologie und Therapie der inneren Krankheiten' (two volumes, Leipzig 1883/ 1884) appeared in >30 editions and was translated into several languages **(Strümpell,1897;Keitel,2001).**

Like his colleague in St. Petersburg, Ivan Pavlov, the Russian neurologist Wladimir Michailowitsch Bechterew (1857–1927) promoted a scientific knowledge of psychological processes. In 1884, he won a scientific competition for an 18-month scholarship abroad, which brought him together with the leading minds in psychology and neurology in Berlin, Leipzig, and Paris where he hospitated at J.M. Charcot's neurologic department, and in Vienna. He joined St. Petersburg as a Professor of Neurology and Psychiatry in 1893. He was fired in 1913 for his political criticism, but he went on to found the Institute for Brain Research in 1918 following the October Revolution, which bears his name. He was asked to examine the very ill W.I. in 1922. Lenin who died in 1924. In 1927, he was when invited for

collegial assistance by Josef Stalin's personal physician; he remained in Moscow as chairman of the inaugural All-Russian Congress of Neuro-pathologists and Psychiatrists **(Keitel, 2002**). Before revealing his terrible diagnosis of severe paranoia, Professor Bretterew met with the General Secretary of the Communist Party of the Soviet Union (CPSU) for three hours. He was treated by two Russian secret service medics before passing away a day later.His body was cremated without autopsy, against the family's wishes **(Schuchart, 2020).** In his most cited publication **(Bechterew, 1893)** not all cases are believed to have had AS **(Ott, 1982; Leden, 1994).** Despite his belief that the neurological system was involved, the most common symptom in his final three cases—two of which were women over 50—was spinal stiffness, the most severe, a 39-year-old man**(Leden, 1994).**

The neurologist Pierre Marie (1853–1940), professor of anatomy at the university of Paris and successor of J.M. Charcot as head of neurologic department at the Hôpital Salpˆetri`ere in Paris, has also described AS cases **(Marie,1898;Keitel,2002).**In the following years AS was often referred to as Bechterew-Strümpell-Marie-disease **(Ott&Wurm,1957).**

I.3.Clinical manifestations

I.3.1.Symptoms

AS typically manifests its initial symptoms in late adolescence or early adulthood. The first symptom is usually a dull discomfort that starts slowly. The pain is generally felt deep in the buttock and/or in the lower lumbar regions and is accompanied by morning stiffness in the same area that lasts for a few hours, becomes better with movement, then goes back to normal with rest. Within a few months, the pain becomes bilateral, chronic, and typically worst at night. About 5% of patients presenting with chronic inflammatory back pain have AS or another SpA subset **(Crawford et al.,1995)**.The prognostic importance of inflammatory back pain lies in the likelihood of future progression to definite AS**(Mau et al.,1988).**

Bone discomfort may be the main complaint for certain patients, or it may coexist with stiffess or back pain. Some people develop hip and shoulder arthritis, frequently in the early stages of the condition. Asymmetric arthritis of other joints, predominantly of the lower limbs, can be present at any stage of the disease. Advanced disease is characterized by stiffness and pain in the neck **(Sieper et al., 2002)**.

I.3.2.Extra‑articular manifestations

There are several extra articular manifestations of AS. Extra-articular manifestations vary widely in terms of both frequency and severity.The most common extra-articular

manifestations are represented by uveitis, bowel disease, lung, heart, skin, bone and kidney involvement**(Table01).**Many epidemiological studies have found higher incidences of extra-articular manifestations to be a consequence of uncontrolled systemic inflammation**(Elewaut &Matucci-Cerinic,2009).**Screening for extra-articular manifestations in patients diagnosed with AS is important to ensure appropriate management since treatment choices may be influenced by the existence of extra-articular symptoms.Clinical signs such as a painful red eye; diarrhea; skin/nail problems; and unexplained weight loss or fever are considered classical 'red flags' for further investigation**(El Maghraoui.20011).**

Table 01: Prevalence of extra-articular manifestations in ankylosing spondylitis**(El Maghraoui,2011)**

Extra-articular manifestations	Prevalence in %	[reference]
Anterior uveitis	20–30	**(Zeboulon et al., 2008)**
Inflammatory bowel disease	5–10	**(Rudwaleit & Baeten,2006)**
Histological inflammation of the gut	50–60	**(De Keyser &Mielants,2003)**
Lung abnormalities on high resolution CT	52	**(El Maghraoui et al.,2004)**
Heart conduction disturbances	3–33	**(Roldan,2008)**
Aortic insufficiency	6–10	**(Brunner et al., 2006)**
Psoriasis	10–25	**(Goupille, 2005)**
Renal abnormalities	10–35	**(Singh et al., 2007)**
Osteoporosis	11–18	**(El Maghraoui, 2004)**
Vertebral fractures	10–18	**(Ghozlani et al., 2009)**

I.3.2.1.Eye involvement

Inflammation of the uveal tract, the middle layer of the eye between the retina on the inside and the sclera, conjunctiva, and anterior chamber on the outside, is referred to as uveitis **(Munoz-Fernandez & Martin-Mola, 2006).** Patients with AS have a 20–30% chance of

developing uveitis during the course of their disease. Moreover, prevalence increases with disease duration. It is in about 90% of the cases anterior, acute and monolateral **(Zeboulon et al., 2008).**Clinically,it is characterized by painful red eye with photophobia, increased tear production and blurred vision. Inflammation occurs within the anterior chamber and may involve the uveal tract in either the iris or the ciliary body, with spillover of vitreous inflammatory cells into the space behind the lens. The initial episode is usually unilateral and begins with a minor eye discomfort prodrome that lasts for one to two days, followed by the development of noticeable redness and pain. There is a strong tendency for recurrence, which frequently occurs in the contralateral eye. Usually, uveitis goes away in two to three months without causing any lasting vision problems. It can develop into hypopion, synechia, cataract, and glaucoma if left untreated. Reduction of visual acuity is not exceptional.The pathogenesis of uveitis in spondyloarthropathies is still notwell understood.Acute anterior uveitis, themost frequent pattern associated with AS **(El Maghraoui, 2011).**

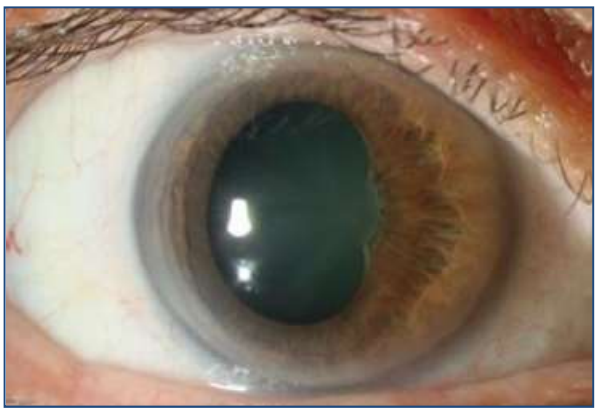

Figure 02: Iridocrystalline synechiae during anterior uveitis **(Gueudry, 2017).**

I.3.2.2.Gastro-intestinal tract involvement

A tight association occurs between joint disease and gastrointestinal inflammation.For instance, in susceptible people, peripheral arthritis may develop after a bacterial infection of the stomach caused by Shigella, Salmonella, Yersinia, or Campylobacter referred to as reactive arthritiswithin a fewdays to weeks after the onset of diarrhoea. Since reactive arthritis typically resolves on its own, it has long been thought to be a benign disorder. However, up to 20% of patients with reactive arthritis develop AS within 10–20 years. Crohn's disease or ulcerative colitis has been reported to be present in 5–10% of patients with AS **(El Maghraoui, 2011).**

Subclinical gut inflammation revealed by ileocolonoscopy was found in 25–49% of AS patients and microscopic lesions as detected by histological analysis of gut biopsies are found even more frequently than macroscopic signs of gut inflammation, with a prevalence of up to 50–60%**(De Keyser &Mielants, 2003).**In addition, up to 60% of patients with AS have asymptomatic IBD **(Mielants et al., 1987; Mielants et al., 1996).** In some cases, frank IBD will develop **(Mielants et al., 1996).**Furthermore, when investigated, remission of joint inflammation was always connected with a disappearance of gut inflammation. Conversely, AS is diagnosed in 3–10% of the patients with inflammatory bowel disease, although radiological evidence of sacroiliitis is reported to be present in 14–46% **(Rudwaleit &Baeten, 2006).**

I.3.2.3.Skin involvement

Between 10% and 25% of patients with typical AS had concurrent psoriasis lesions in different series. Five percent of psoriasis patients get involvement of the spine and SI joint. Patients with concomitant psoriasis tend to exhibit more peripheral joint involvement **(Goupille, 2005).** Additionally, compared to primary AS or AS linked to inflammatory bowel disease, association with psoriasis was evidently related with a worse course of the disease **(Lavie et al., 2009)**.Today, the three TNFα antagonists are registered for treating psoriasis and psoriatic arthritis (etanercept, infliximab, adalimumab) with similar reported efficacy **(Hoy &Scott, 2007; Gladman, 2008).** However, paradoxally between 1.5 and 5% of the patients may present an onset or exacerbation of psoriasis during treatment with the TNF-inhibitors **(Wendling et al., 2008).**

I.3.2.4.Bone involvement

Diffuse osteoporosis responsible for loss of bone strength is a well known feature of AS. The bone loss may be present early in the course of the disease and predominates at the spine .Late in the disease, vertebral fractures constitute a rare but non negligible source of morbidity and mortality related mainly to neurological compromise**(El Maghraoui,2011).**

Densitometric studies showed that a large proportion of AS patients (63%) are either osteopenic or osteoporotic affecting up to 59 and 18% of the patients with AS, respectively. A study found osteopenia and/or osteoporosis in about one-third of patients with very early disease and demonstrated worsening bone loss with advancing age and longer disease duration **(El Maghraoui et al., 1999).**In another study, used quantitative CT rather than dual

X-ray absorptiometry to evaluate lumbar spine bone mineral density in patients with AS.The results showed low bone mineral density in two thirds of cases. Although dual X-ray absorptiometry remains the standard of reference for studying osteoporosis, physicians must be aware that this technique overestimates spinal bone mineral density in patients with advanced AS, the reason being the presence of ossification at various spinal sites (syndesmophytes, vertebral ligament ossification, and facet joint fusion). Thus, dual X-ray absorptiometry is reliable at the femoral neck but not at the lumbar spine in patients with latestage AS where quantitative CT may be a good alternative **(El Maghraoui &Roux, 2008),** several studies reported a high prevalence (between 29 and 91%) of major neurological complications after clinical vertebral fractures **(El Maghraoui, 2011).**

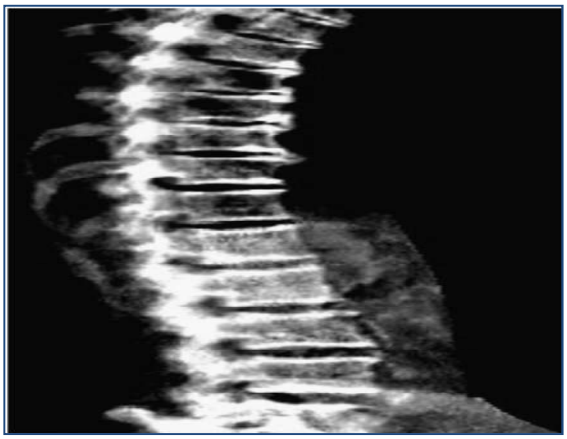

Figure 03: Example of vertebral fracture assessment using dual X-ray absorptiometry in a patient with ankylosing spondylitis **(El Maghraoui, 2011).**

I.3.2.5.Heart involvement

The prevalence of heart pathologies in patients with AS has been reported to be 10% to 30% **(Roldan, 2008).** Various studies indicate a higher rate of conduction disturbances, valvular heart diseases and cardiomyopathies in patients with AS when compared with the normal population **(Brunner et al., 2006).** Cusp retraction and aortic regurgitation may result from this sclerosing inflammatory process, which mainly affects the aortic root and the cusps of the aortic valve. In addition to the aortic root, the persistent inflammation may also affect the aortic muscle and elastic fibers, or it may spread into the ventricular septum and disrupt conduction wall and decrease its distensibility. The myocardium and endocardium may also be affected, though less frequently.As a result, heart conduction abnormalities like intraventricular, bundle-branch, and atrioventricular blocks have been often reported (3–33%).Because a longer QT time may be linked to HLA-B27, screening for it has been

advised.The heart valves can be impacted by a number of diseases; primarily the aortic valve (reported prevalence of aortic regurgitation varies from 6 to 10%) **(Brunner et al., 2006).**The spectrum of these structural changes is wide and can range from only minor thickening of the valves or nodules on the valves to severe regurgitation requiring surgical replacement of the affected valve. Clinical signs of cardiomyopathy were often associated with diastolic and/or systolic dysfunction of the ventricles **(O'Neill &Bresnihan, 1992).** Patients with AS were discovered to have a higher risk of heart failure and stroke as a result of these diseases. This is associated with a decreased life expectancy in this population **(El Maghraoui, 2011).**

According to available data, therapy may also increase the risk of cardiovascular disease. Elevated TNFα levels could play a significant part in the pathophysiology of AS endothelial dysfunction. Impaired coronary microvascular function was recently found in patients with AS, and correlated well with serum C-reactive protein and TNFα levels **(Caliskan et al., 2008).**A recent study demonstrated that patients with active AS have impaired microvascular endothelium-dependent vasodilatation and capillary recruitment in skin, which improves after TNFα-blocking therapy with etanercept **(van Eijk et al., 2009).**

It is important to remember, however, that NSAIDs remain the cornerstone in the treatment of AS and that with most NSAIDs, an increase in the thrombogenic risk must be expected **(Peters et al., 2004).** Furthermore, regardless of any inherent prothrombotic effects, NSAIDs and coxibs may induce or worsen hypertension, which in turn may lead to cardiovascular events **(El Maghraoui, 2011).**

I.3.2.6.Lungs involvement

Pulmonary abnormalities are also well documented in patients with AS **(El Maghraoui, 2005).**Nevertheless, the pathophysiology of pleuropulmonary involvement in AS is still unclear more than 50 years after the first description. The most likely explanation is a disease-specific inflammatory process whose course is parallel to that of the joint manifestations.The advent of high resolution computed tomography (CT) in the mid 1980s has permit to examine the entire lung parenchyma and pleura in many conditions with diffuse lung disease using a noninvasive method **(El-Maghraoui et al., 2003).**

It has never been determined how anti-TNF blockers affect interstitial lung fibrosis and other anomalies.But since these medications are increasingly frequently used for AS, this problem might become even more significant. Moreover, many recent case reports described contrasting effects on pulmonary fibrosis in patients with RA **(El Maghraoui, 2011).**

I.3.2.6.Kidney involvement

The incidence of renal abnormalities (including glomerulonephritis, particularly associated with deposition of immunoglobulin A (IgA)–containing immune complexes, renal amyloid deposition, microscopic haematuria, microalbuminuria and decreased renal function and creatinine clearance) has been shown to range from 10 to 35% in patients with AS. Amyloidosis is more prevalent in aggressive and active AS and in older patients with long-standing disease **(Singh et al., 2007).**There are, however, scant data on the prognostic significance of positive fat tissue aspiration in patients with AS without overt clinical signs of AA amyloidosis.TNF-inhibitors may help treat AA amyloidosis, according to several case studies **(Kobak et al., 2007).**

I.3.2.7.Physical involvement

Loss of spinal mobility, accompanied by limitations in flexion, lumbar spine extension, and chest expansion, is a primary physical finding. The limitation of motion is disproportionate to the degree of ankylosis because of secondary muscle spasms. Pain in the SIJs may be elicited with direct pressure or movement, but its presence is not a reliable indicator of sacroiliitis. There may be detectable inflammation of peripheral joints. Clinical signs of the disease can range from mild stiffness to a totally fused spine, with any combination of severe bilateral hip involvement, peripheral arthritis, or extra-articular manifestations. A patient's posture undergoes characteristic changes if a severe case goes untreated. The lumbar lordosis is destroyed, the buttocks atrophy, the thoracic kyphosis is exaggerated, and the neck may stoop forward **(Sieper et al., 2002).**

I.5.Pathophysiology

I.5.1.From injury to inflammation

I.5.1.1.Enthesitis and synovitis

As upright standing species, our lower limbs and lumbar spine are subjected to high mechanical stress. Stress can readily harm the connective portion (the enthesis) where the tendon or ligament attaches to the bone. This could be one reason why enthesitis, or inflammation of the entheses, typically happens at these locations, especially in axSpA. Entheses are structurally comparable to the growth plate (epiphyseal plate), where a continuous gradient from the uncalcified tendon to the calcified bone is formed by chondrocyte expansion and differentiation. They and their adjacent tissue synovium, named

'synovio-entheseal complexes (SECs)' **(McGonagle et al., 2012)**, are likely to represent a highly vulnerable part to inflammation.

I.5.1.2.Nonantigenic stimuli from cartilage

Modeled after human RA, the phenotype discovered in both CIA and CAIA mice may still offer some insights into the mechanism of AS development, as efforts to screen cartilage biomarkers for diagnostic and prognostic utility found that peptides derived from type II collagens are correlated with tissue destruction and AS severity **(Kim et al.,2005;Vosse et al.,2008).** It was suspected that type II collagen, the major component of hyaline cartilage, is a potential target antigen during the disease process **(Lee et al., 2000)**.

In AS patients, serum hyaluronic acid is also slightly elevated ($p = 0.04$) and is correlated with some clinical features, such as C-reactive protein (CRP) test, Schober's test, and the finger-to-floor distance**(Duruoz et al.,2008)**.The effect of hyaluronan in inflammation is related to its molecular weight; lower-molecular-weight hyaluronic acid has been reported to facilitate the immune response by binding TLR2 and TLR4**(Scheibner et al.,2006; Gariboldi et al.,2008)**, while higher-molecular-weight hyaluronic acid has been demonstrated to be anti-inflammatory through the CD44 signaling pathway(**Hashizume & Mihara,2010**).

I.5.1.3.Landscape of innate immunity in AS

In general, synovial infiltration and the proliferation of neutrophils and macrophages/monocytes are characteristics of AS. Compared to healthy persons, AS patients' hemograms exhibit higher neutrophil to lymphocyte ratios (NLR), platelet to lymphocyte ratios (PLR), and monocyte to lymphocyte ratios (MLR) **(Deng et al., 2020; Huang et al., 2018)**. ESR and CRP have favorable correlations with all of these characteristics, but MLR is thought to be a more accurate diagnostic metric than the others. Immunohistology also demonstrated shared features among non-RA SpA, including AS, PsA, ReA, and JIA, and CD163+ M2 macrophage and neutrophil counts were greater in synovial biopsies than in RA and HC **(Kruithof et al., 2005; Baeten et al., 2005)**. Apart from the frequently mentioned impact of increased inflammatory cytokines like GM-CSF or M-CSF, it has been proposed that monocytes can be produced in AS using a different technique Granulocyte and monocyte progenitors (GMPs), monocyte/DC progenitors (MDPs), and common monocyte precursors (CMPs) are the successive binary choices made in a classic monocyte differentiation paradigm precursors (CMPs).Furthermore, the epigenetic reprogramming-mediated modification of innate immunity may be long-lasting. In vaccine- or adjuvant-treated models,

this so-called "trained immunity" has been demonstrated; for example, mice given b-glucan (a PAMP that activates dectin-1) exhibit enhanced myeloid cell growth and enhanced proinflammatory cytokine production from monocytes **(Moorlag et al.,2020;Dos Santos et al., 2019).**

I.5.1.2.4.The IL-23/IL-17 axis

The significance of adaptive immunity is not always negated by nonantigenic immunological activation. On the other hand, the decrease in illness severity in immunocompromised mice validates the detrimental impact of activated lymphocytes, even though the IL-23/IL-17 axis has long been thought to play important role in AS development. According to the conventional model of the IL-23/IL-17 axis, Th17 cells release the inflammatory IL-17 3 family along with other cytokines like IL-22, TNFa, and IL-6, which are generated and sustained by IL-23. An increased level of IL-23 and IL-17 in a variety of AS patients indicates a widespread activation of this axis in AS **(Milanez et al., 2016; Chen et al., 2012)**. Other than Th17 cells, tissue-resident innate immunocytes, such as gdT17 cells and ILC3s, possess a comparable ability in secreting IL-17 and IL-22**(Sherlock et al.,2012; Cuthbert et al.,2017).**These cells are the innate equivalent of Th17 cells, and in animal models with IL-23 overexpression, they have been shown to promote SpA formation.

However, after achieving a favorable response rate in PsA and CD, IL-23 blockers failed to show efficacy in treating AS **(Yin et al., 2020; McGonagle et al., 2021)**. It has never been established if IL-23-driven IL-17 causes AS development, even though animal models have shown that it can trigger enthesitis and SpA **(Sherlock et al., 2012; Cuthbert et al., 2017**). Current evidence suggests that redundant IL-17-inducing pathways can account for the unclear link between IL-23 and IL-17 Cuthbert et al. Initially, it was shown that the Vd1 subset of gdT without IL-23R can release IL-17 and IL-22 when stimulated with phorbol myristate acetate (PMA) or anti-CD3/CD28 (which mimics TCR activation) **(Cuthbert et al., 2019**). This provides a method for the IL-23/IL-17 axis to be substituted. , it was shown that the Vd1 subset of gdT without IL-23R can release IL-17 and IL-22 when stimulated with phorbol myristate acetate (PMA) or anti-CD3/CD28 (which mimics TCR activation) **(Cuthbert et al., 2019).** This provides a method for the IL-23/IL-17 axis to be substituted. Prostaglandin E2 (PGE2), a major mediator of inflammation, is another possible IL-23-independent activator that is extensively found to be higher in AS patients, which led to the inclusion of the response rate to NSAIDs that prevent PGE2 production as a diagnostic criterion for AS. Human Th17 cells are long-lived inflammatory cells, with abundant

antiapoptotic gene expression as well as a stem-cel_llike phenotype (**Kryczek et al., 2001)**. Th17 population is more likely to be selfmaintained after differentiation, considering their remarkable capacity to proliferate in resistance to immunosuppression compared with Th0/1/2**(Crawford et al., 2020).**

I.5.1.2.Bone erosion and bone formation in AS

The repeated demonstration that TNF‑ blockade therapy in AS leads to dramatic suppression of symptoms, peripheral inflammatory swelling and reduced levels of acute phase reactants bears the promise that complete control of the as sequelae is possible. This hope is supported by the finding that cells in the sacroiliac joints of patients with as express high levels of TNF **(Braun et al., 1995).** In addition, in RA, TNF antagonists can prevent bone erosion at the synovial–bone junction **(Smolen et al., 2009).** This finding implies that bone loss and inflammation are related in RA. Nevertheless, TNF inhibition has been shown in clinical and animal trials to help regulate a large portion of inflammation and lessen the amount of bone-marrow edema on MRI control of entheseal bone erosion is less consistent; in particular, syndesmophyte formation continues unabated**(van der Heijde et al.,2008; van der Heijde et al.,2009).** Although there is some room for interpretation of these negative findings, it is commonly accepted that, in as, entheseal bone erosion and syndesmophyte formation are not completely coupled to inflammation or associated with RA-specific bone-destructive factors**(Schett et al.,2007; Lories et al.,2007; Maksymowych,2010).**

I.5.1.2.1.Bone-destructive factors in AS

To understand the pathogenesis of bone erosion and syndesmophyte formation in as, investigators need to focus on the pathology at the entheses **(Figure 04).** In clinical disease, the entheses affected most in as are the vertebral entheses. Examination of surgical specimens obtained from patients with long-standing as for bone destroying.

Factors revealed that the collagenolytic proteinase cathepsin K is highly expressed in the in vading mono nuclear and multinuclear cells that attach to the surface of bones and intervertebral discs. These cells are probably osteoclasts. Another bone-destructive factor that has been identified, albeit in different cells, is the collagen degrading matrix metalloproteinase 1 (MMP1). Hence, cathepsin K and mmP1 are probably two of the bone destructive factors in AS **(Neidhart et al., 2009).** In contrast to RA synovitis, few cells in vertebrae affected by as express receptor activator of nuclear factor-κB ligand (RANKL) or MMP3 **(Walsh& Gravallese, 2010).**These findings confirm that the Osteoclastic activity is

the cause of the bone erosion pattern in as, which differs from the activities that take place in RA .Thus, it should come as no surprise that TNF inhibition stops bone degradation in RA patients but less so in AS patients **(Tam et al., 2010).**

I.5.1.2.2.Bone formation and how it is subverted in AS

We must talk about the physiology of bone development in order to comprehend the syndesmophyte production process in AS. The description of complicated systems that follows is somewhat simplified.In embryonic development, two bone-forming processes exist. Mesenchymal cells undergo chondrocyte differentiation prior to the creation of bone matrix in endochondral bone formation. Mesenchymal cells undergo direct differentiation into osteoblasts during the creation of membranous bone, which subsequently creates the bone matrix and its mineral component. Of these two, we know that at least the endochondral process occurs at the enthesopathy**(Lories et al.,2009).**Endochondral bone formation is controlled by two major molecular pathways, with some cross-talk between these, and each pathway has its own endogenous negative regulators Bone morphogenic proteins (BMPs), a family of growth factors and cytokines that are members of the transforming growth factor family, are primarily responsible for controlling the early phases of bone development β super family. Through the Smad (mothers against decapentaplegic homolog) signaling network, the different members of the BMP family act at different stages of chondrocyte differentiation **(Lories &Luyten, 2005).** This pathway is negatively controlled by endogenous inhibitors, such as noggin **(Winkler et al., 2004),** which is secreted by chondrocytes and the osteocytespecific protein sclerostin **(van Bezooijen et al., 2004**). A later stage of bone formation centers on the wingless (Wnt) family of glycoproteins, some members of which activate a complex of receptors on mesenchymal cells. Intracellular β-catenin rises as a result of this activation, and it then moves into the nucleus to cause Wnt-dependent cell differentiation into osteoblast-lineage cells. Wnt signaling is now recognized to be the "master regulator of bone remodeling" **(Schett et al., 2008) .**There are several endogenous suppressors of this Wnt-dependent pathway, one of which is Dickkopf-related protein 1(DKK1, which has been implicated as a suppressor of new bone formation in RA. DKK1 is activated by TNF and is readily detected in the sera and synovial of patients with RA **(Diarra et al., 2007)**. The lack of bone healing at inflammatory areas in RA may be mostly due to the presence of DKK1. By lowering DKK1 activity, TNF blockade may prevent bone loss in RA **(Tam et al., 2010).**

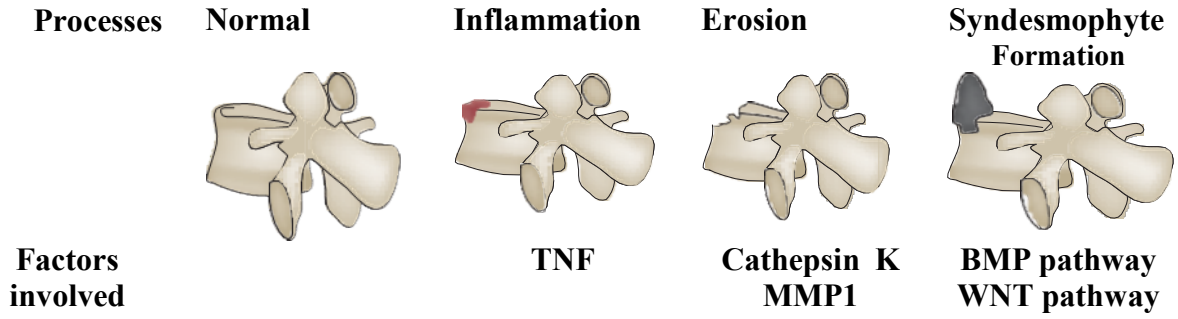

Figure 04: Pathology of entheses in ankylosing spondylitis**(Tam et al.,2010).**
Abbreviations: BMP, bone morphogenetic Protein; MMP, matrix metalloproteinase; TNF, tumor necrosis factor.

I.5.2.Extra-articular/musculoskeletal disease in AS

Although HLA-B27 has been implicated in several systemic and organ-specific signs of AS, the precise processes behind these manifestations are still unknown, as is the case with other aspects of AS pathogenesis. Shown to be associated with acute anterior uveitis (AAU) **(Chang et al., 2005).** However, one study reported that HLA-B27 negativity was associated with an increase in peripheral arthritis, dactylitis, and extra-articular manifestations including AAU **(Arévalo et al., 2018).**

According to one study, aortitis, acute anterior uveitis, and interstitial lung fibrosis can all result from aberrant IL-17 production, which is linked to HLA-B27 positive in AS.Extra-articular features of AS have been linked to pathogen-associated molecular patterns (PAMP), damage-associated molecular patterns (DAMPS).natural cytotoxicity triggering receptor 2 (NPC2), and CD336; however, further investigation is needed to fully qualify the pathophysiology of these phenomena **(Liao et al., 2022).**

I.6.Ankylosing spondylitis and cancer risk

I.6.1.Mechanisms of chronic inflammation and cancer development

TNF-α, IL-6, and IL-1β are examples of pro-inflammatory cytokines that are continuously released throughout a chronic inflammatory state, causing tissue damage and regeneration responses. Chemokines, cytokines, and prostaglandins can induce cellular malignancy **(Chang et al., 2017; Mantovani et al.,2008**) There are several ways that inflammation in the tumor microenvironment promotes tumor growth.It aids in the

differentiation and survival of tumor cells and promotes angiogenesis and metastasis **(Mantovani et al.,2008).** Research indicates that 20% of cancers are associated with chronic inflammation **(Chang et al., 2017; Lulin et al., 2024).**

I.6.2.The relationship between chronic inflammatory diseases (Rheumatoid Arthritis, Psoriasis, and Psoriatic Arthritis) and cancer

High inflammatory activity increases the susceptibility of patients with rheumatoid arthritis to lymphoma **(Feltelius et al., 2003).**Studies indicate that systemic lupus erythematosus (SLE) **(Lulin et al., 2023),**Sjogren's syndrome, and RA, due to chronic inflammation and immune dysregulation, have an increased risk of hematologic malignancies **(Alehashemi &Ward,2023).** Research shows that RA increases the risk of malignancies by 28% **(Deng et al., 2016).** Chronic microbial infections are also associated with cancer **(Lulin et al., 2024; Feltelius et al., 2003).** Common comorbidities of spondyloarthritis, such as psoriasis **(Mantovani et al., 2008)** and inflammatory bowel disease are related to fungal infections, which elevated malignancy risk **(Lulin et al., 2024).** However, studies indicate patients with psoriatic arthritis without increase cancer risk **(Vaengebjerg et al., 2020).**

I.6.3.The Association between ankylosing spondylitis and cancer

Patients with AS have an increased risk of bone cancer **(Chang et al., 2017),** thyroidgland cancer, multiple myeloma**(Chang et al.,2017; Alehashemi &Ward,2023; Deng et al.,2016),** leukemia**(Chang et al.,2017),** kidney cancer**(Feltelius et al.,2003),** prostate cancer**(Chang et al.,2017),** and non-Hodgkin lymphoma**(Chang et al.,2017; Alehashemi &Ward,2023; Deng et al.,2016).** There is no significant correlation with connective tissue cancer, brain cancer, testicular cancer, bladder cancer, skin cancer, gastrointestinal malignancy**(Feltelius et al. ,2003),** or respiratory malignancy**(Lulin et al.,2023).**The spine, which supports affects the lungs and digestive system, attaches to the head and neck, and joins the pelvis.Young guys are more likely to develop osteosarcoma and AS.According **(Chang et al., 2017),** chronic inflammation damages mineral plate 2 spaces and cartilage, and inflammation surrounding bones encourages the development of bone cancers(**Chang et al.,2017).**

The bone marrow within the spine is a hematologic tissue (**Lulin et al., 2023**), and chronic infection through bone marrow and edema in the bone marrow can be seen in both tumors and infections **(Wang et al., 2024),** increasing the likelihood of hematological cancers. Studies indicate that in patients with AS, IL-1, TNF-α, and IFN-γ causes the

proliferation of CD4+ T cells. The alteration of circulating memory CD4+ T cells changes the gastrointestinal microenvironment, transforming the immune response in the intestines into T-cell leukemia-like tumors. Research by Hemminki shows an increased incidence of multiple myeloma in Swedish patients with AS, suggesting that inflammation in patients with AS leads to hematologic malignancies. Patients with AS are more likely to develop hematologic malignancies if they have the HLA-B27 gene **(Chang et al., 2017).** Studies conducted in Taiwan and Korea suggest that male patients with AS are more likely to develop prostate cancer, possibly as a result of higher androgen levels. However, studies show that endogenous hormones are not related to prostate cancer **(Kelty et al., 2021).**

Chapter II:

Musculoskeletal System and Etiology of Ankylosing Spondylitis

I. Musculoskeletal System

I.1.Definition and functions

The musculoskeletal system, also known as the human locomotor system, is the framework of the body. It is controlled by the nervous system. It consists of bones (which make up the skeleton), muscles, tendons, ligaments, joints, cartilage, and other connective tissue that bind them together **(Murphy et al., 2018).** The purpose of this system is to support the body, facilitate movement, and protect the internal organs. Bones are also vital in the production of red blood cells.

The musculoskeletal system is dynamic and constantly remodeling itself to keep you healthy. Research shows that up to 40% of the musculoskeletal system's load-bearing capacity is lost within weeks of inactivity.The musculoskeletal system weakens with age (The musculoskeletal system undergoes many changes as people age), too, increasing the risk of injuries and musculoskeletal diseases like osteoarthritis. Regular exercise throughout your life is crucial for keeping your musculoskeletal system healthy.

The musculoskeletal system consists principally of bone, muscle, tendon, ligament, and articular cartilage tissue. These are arranged throughout the body to provide internal support and allow motion to occur. Their specific configuration, however, varies with the anatomic site by virtue of the types of loads these tissues experience and the movements that they are required to perform. As such, while the musculoskeletal sys-tem is governed by a set of underlying principles, there is a great deal of local variance throughout. This is why treatments for musculoskeletal injury and disease are divided into regions such as craniomaxillofacial, oral, shoulder and elbow, hand and wrist, hip and knee, foot and ankle, spine, and others .Among its many important functions, the musculoskeletal system**: (CDC Agency for Toxic Substances and Disease Registry. Musculoskeletal (muscles and skeleton)).**

- ❖ Gives your body shape.
- ❖ Supports the body's weight.
- ❖ Allows you to move.
- ❖ Shields vital organs from impact damage.
- ❖ Stores essential minerals like calcium and phosphorus, which are crucial for bone and cell maintenance.
- ❖ Produces red and white blood cells via bone marrow.
- ❖ Operates breathing (respiration) via muscle contractions.

I.2.Anatomy

The musculoskeletal system is an interconnected network of features that each boast their own structures, functions, and roles. To understand how the musculoskeletal system works as a whole, you will need to be familiar with its parts.

I.2.1.Skeleton

The skeleton consists of the bones of the body. For adults, there are 206 bones in the skeleton. Younger individuals have higher numbers of bones because some bones fuse together during childhood and adolescence to form an adult bone. The primary functions of the skeleton are to provide a rigid, internal structure that can support the weight of the body against the force of gravity and to provide a structure upon which muscles can act to produce movements of the body.

In addition to providing for support and movements of the body, the skeleton has protective and storage functions. It protects the internal organs, including the brain, spinal cord, heart, lungs, and pelvic organs. The bones of the skeleton serve as the primary storage site for important minerals such as calcium and phosphate. The bone marrow found within bones stores fat and houses the blood-cell-producing tissue of the body.

The skeleton is subdivided into two major divisions: the axial and appendicular **(Figure 05).**

☒ The axial skeleton forms the vertical, central axis of the body and includes all bones of the head, neck, chest, and back. It serves to protect the brain, spinal cord, heart, and lungs. It also serves as the attachment site for muscles that move the head, neck, and back and for muscles that act across the shoulder and hip joints to move their corresponding limbs.The axial skeleton of the adult consists of 80 bones, including the skull, the vertebral column, and the thoracic cage. The skull is formed by 22 bones. Also associated with the head are an additional seven bones, including the hyoid bone and the ear ossicles (three small bones found in each middle ear). The vertebral column consists of 24 bones; each called a vertebra, plus the sacrum and coccyx. The thoracic cage includes the 12 pairs of ribs and the sternum, the flattened bone of the anterior chest. Vertebral Column with Abbreviations:

- ✓ **Cervical:** C1 to C7; the first 7 vertebrae in the neck region.
- ✓ **Thoracic:** T1 to T12; the next 12 vertebrae that form the outward curvature of the spine.
- ✓ **Lumbar:** L1 to L5; the next 5 vertebrae that form the inner curvature of the spine.

- ✓ **Sacrum:** the triangular bone at the base of the spine.
- ✓ **Coccyx:** the tailbone.

☒ The appendicular skeleton includes all bones of the upper and lower limbs, plusthe bones that attach each limb to the axial skeleton. There are 126 bones in the appendicular skeleton of an adult.

Bone is made up of osseous tissue, which consists of special mature bone cells called osteocytes. The bones of the skeleton are of different shapes and sizes. They may be essentially flat, such as those found in the cranium and ribs. They also may be short, such as those in the wrist and ankles, or long, such as those found in the arms, legs, hands, and feet. Long bones have subparts that are named.

Bones undergo a process that is known as remodeling. Bone remodeling is a continuous process whereby old bone is gradually replaced by new bone. About 25% of trabecular bone and 3% of cortical bone are removed and replaced through the remodeling process each year. Most bones connect to at least one other bone in the body. The areas where bones meet bones or where bones meet cartilage are called articulations.

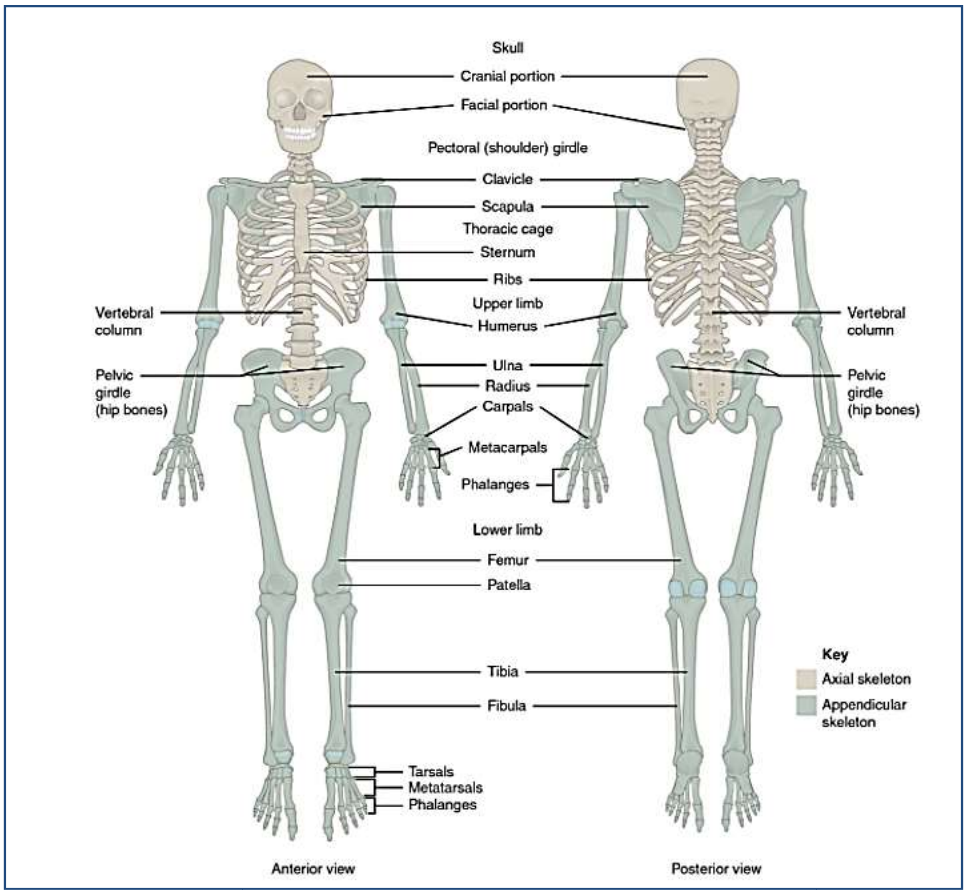

Figure 05: Axial and Appendicular Skeleton. The axial skeleton supports the head,

neck, back, and chest and thus forms the vertical axis of the body. It consists of the skull, vertebral column (including the sacrum and coccyx), and the thoracic cage, formed by the ribs and sternum. The appendicular skeleton is made up of all bones of the upper and lower limbs **(Betts et al., 2013).**

I.2.2.Muscle

This is one of the four primary tissue types of the body. The body contains three kinds of muscle tissue: skeletal muscle, cardiac muscle, and smooth muscle. There are two kinds of muscle that are part of the musculoskeletal system: skeletal muscles and smooth muscles. The third type of muscle, cardiac muscle, is not part of the musculoskeletal system.

- **Skeletal muscles are:**

✓ Bundles of contractile fibers, meaning that they move various parts of the body by contracting.

✓ Attached to bones and positioned in opposing groups around the joints. For example, muscles that bend the elbow are positioned opposite muscles that straighten the elbow.

✓ Controlled by the brain, operating voluntarily under a person's conscious direction.

- **Smooth muscles are:**

✓ Involved in certain bodily functions that are not under a person's control.

✓ Located around some of the arteries and contract to adjust blood flow.

✓ Located around the intestines and contract to move food and feces along the digestive tract.

✓ Controlled by the brain, but not voluntarily.

✓ The engagement of smooth muscle is based on bodily needs, not conscious control.

When you exercise, your skeletal muscles emit proteins called myokines that:

✓ Regulate body weight.

✓ Reduce inflammation.

✓ Suppress tumor growth.

✓ Increase insulin sensitivity.

I.2.3.Cartilage

The ends of the bone that form a joint are covered with a connective tissue called cartilage. Normal cartilage is smooth, flexible, and tough. Cartilage is composed of collagen, water, and proteins called proteoglycans. This elastic connective tissue is found at the ends of bones as well as in other locations such as the tip of the nose.

Cartilage serves to:

- ✓ Absorb shock during activities like running, jumping, and other forms of impact.
- ✓ Reduce friction with the movement of a joint, preventing bones from rubbing together.
- ✓ Enhance the resilience of bones and protect them from wearing down.

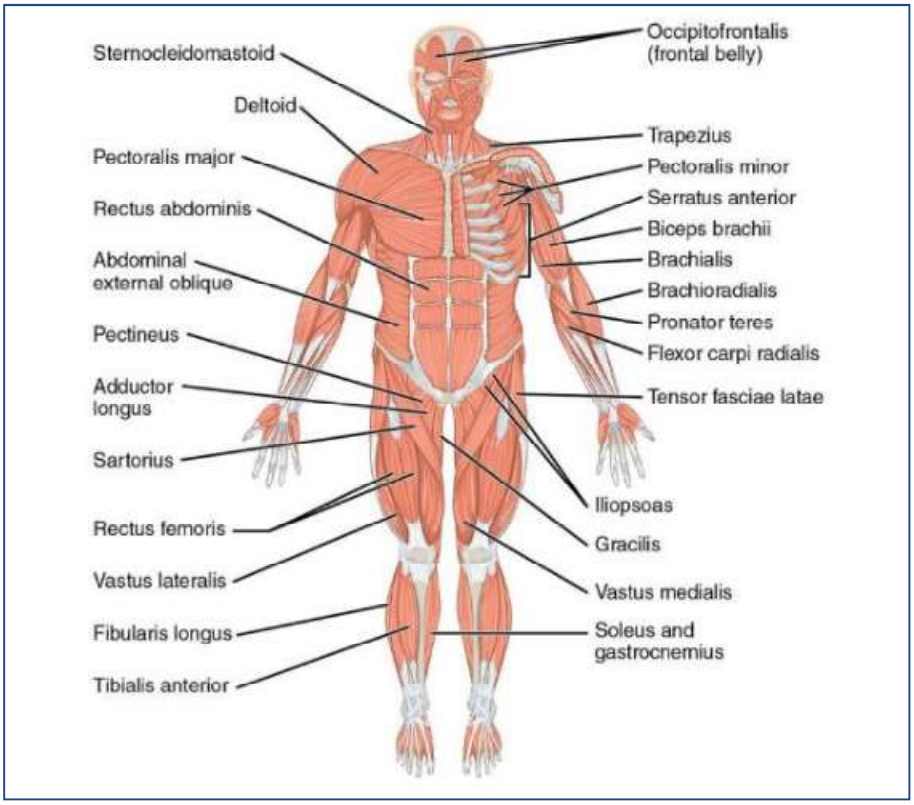

Figure 06: Major muscules of the body

Right side: superficial; left side :(deep anterior view)

I.2.4.Joints

These are also known as articulation and are any place where adjacent bones or bone and cartilage come together to form a connection.The joints are where the ends of two or more bones come together. While there are joints that do not move, such as the joints between

the plates of the skull, most joints are capable of facilitating movement. There are two types of joints that facilitate movement: synovial joints and cartilaginous joints.

Synovial joints are:

- ✓ The most common joint in humans.
- ✓ Able to slide without friction, due to the slippery, lubricated cartilage that covers the ends of each bone at the joint.
- ✓ Numerous in form and include ball-and-socket, condyloid, gliding, hinge, pivot and saddle joints. The elbow joint and hip joint are examples of synovial joints.

Cartilaginous joints are:

- ✓ Completely united by cartilage where the two bones meet.
- ✓ More rigid than synovial joints. Cartilaginous joints lack a joint cavity, which limits their movements. The pelvis is an example of a cartilaginous joint.
- ✓ Able to withstand high-impact activities like running and jumping due to the cushioning cartilage provides.

Joints are enclosed in a joint capsule which has a lining (synovium). Cells of the synovium produce synovial fluid which nourishes the cartilage and helps to reduce friction during movement.

I.2.5.Ligaments

Ligaments are tough, fibrous bands of tissue that connect bone to bone. They are composed of collagen and elastic fibers, which give them a rubberband-like stretchability.

Ligaments:

- ✓ Surround and support the joints, allowing movement in specific directions.
- ✓ Ensure the bones in a joint do not dislocate or twist too much.
- ✓ Contain sensory nerves that monitor data from movements, and help regulate the stiffness of joints based on that data.
- ✓ Ligaments are particularly vulnerable to damage caused by overuse, trauma, and disease. While they are capable of self-healing after an injury, the process tends to be slower compared to muscles and bones.

I.2.6.Tendons

Tendons are similar to ligaments, except rather than connecting bone to bone, tendons

connect muscle to bone. These tough, fibrous bands of tissue are primarily made of collagen.

Tendons primarily perform the following functions :(**Thorpe& Screen., 2016)**

- ✓ Absorb the forces that muscles generate upon impact.
- ✓ Evenly transfer those forces to bones.
- ✓ Protect muscles from injury.
- ✓ Tendons are usually found within a sheath (the tendon sheath), which allows them to move friction-free. A tendon sheath has two layers: the supportive and protective fibrous tendon sheath, and the synovial sheath, which produces synovial fluid to lubricate joints.

II. Etiology of ankylosing spondylitis

II.1.Genetic factors

II.1.1.HLAB27

Human Major Histocompatibility Complex (MHC) class I is also known as Human Leukocyte Antigen (HLA) and is one of the many surface proteins present on all nucleated cells and platelets in the human body.MHC I plays a role in antigen presentation to cytotoxic T cells via the T Cell Receptor (TCR) (**Tsukazaki& Kaito, 2020).**

Genetic factors contributing to development of AS have been recognised since 1961 leading to the discovery of the HLAB27 gene in 1973**(Zhu et al., 2019).** There is significantly higher concordance between monozygous twins and dizygous twins with AS rates of 63% and 23–27% respectively **(Zhu et al., 2019; Tsui et al., 2014).** HLA B27 belongs to the MCH class I receptor family. There are 4 domains of this molecule as depicted in Figure. Regions α1 and α2 are located at the top of the protein where antigen binding occurs. The α3 heavy chain is located adjacent to the cell surface partially penetrates the cell membrane. The 4th domain is the β2 microglobulin which is covalently associated with the rest of the HLA B27 molecule **(Sharip&Kunz, 2020).**

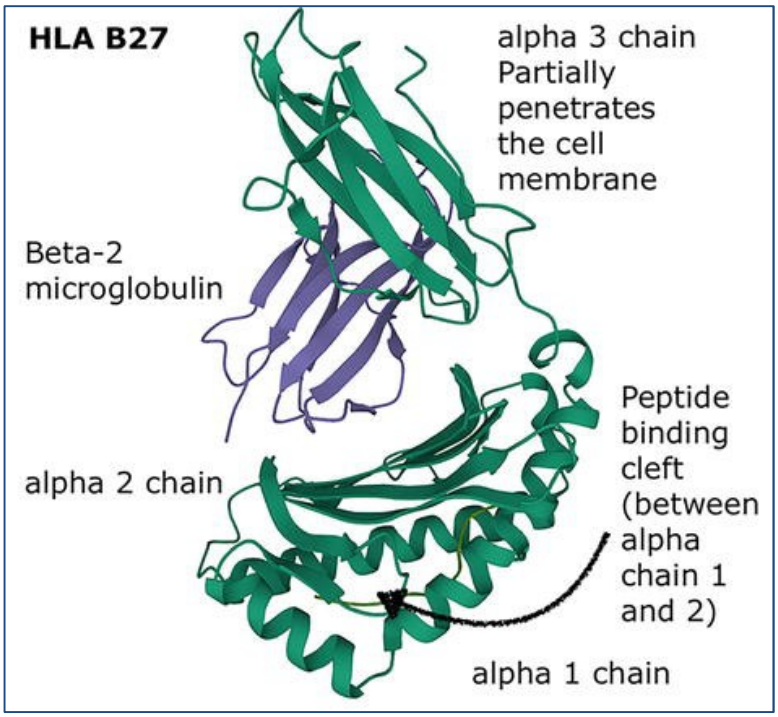

Figure07 : HLA B27 protein structure **(Sehnal et al., 2001; Berman et al.,2000).** Three main features distinguish HLA B27 from most other HLA class I molecules.

1. Glutanine is substituted for methanine located at the 45 position.
2. The second feature is an unpaired cysteine (Cys67). This feature enables formation of homodimers and oligomers of free heavy chains which are thought to contribute to development of AS and is discussed in more detail later on in this chapter.
3. Thirdly there is a Lys residue at position 70 that increases reactivity of the cysteine at position 67.

Extensive polymorphism of HLAB 27 results from the considerable variability of the heavy chain component of the protein **(Madden et al., 1991).**

Studies show 90–95% of AS patients are HLA-B27 positive.The chances of developing AS for an individual with an HLA-B27 gene is 1–2%. This percentage increases to 15–20% for those who have a first degree relative with AS. The relative risk of developing AS for an individual with a first degree relative who has AS is 94%, for a second degree relative 25% and for a third degree relative 4% (**Zhu et al.,2019**).

HLA B27 is a polymorphic gene with around 223 subtypes thus far identified **(Sharip&Kunz, 2020).** HLAB2705 is more prevalent in affected Caucasians, HLAB2704 is associated with affected Han Chinese whilst HLAB2702 is associated with affected people of

Mediterranean ethnicity **(Zhu et al., 2019).** HLA B2705 and HLA B2704 are the predominant subtypes in the South Indian population **(Haridas et al., 2018).** Inuit and native Alaskans have the highest rates of HLA B27 in the world and correspondingly the highest prevalence of AS **(Doğan et al., 2022).**

II.1.1.1 Pathogenesis

HLA-B27, basically belonging to the MHC-I surface protein encoded by the MHC B gene on chromosome 6, is the most essential gene that predisposes an individual to AS. HLA-B27 presents peptide antigens to T immunocytes of the human body defense process and is considered to be significantly linked to AS and associated inflammatory diseases.

The connection between HLA-B27 and AS has not yet been fully elucidated, although it is widely accepted that the entire intracellular process of HLA-B27 formation needs to be considered. There are some prevailing theories regarding the mechanism, including: the hypothesis of arthritogenic peptide, misfolding hypothesis, the hypothesis of molecular mimicry, as well as the hypothesis of the cell-surface HLA-B27 homodimer. Founded on the antigenic peptide presentation role of HLA class I molecules**.**

The arthritogenic peptide hypothesis postulates that structurally exclusive peptide-MHC complexes can directly initiate HLA-B27-specific autoimmune responses by relying on the primary structure of antigen peptides. Some microbial peptides are similar to self-peptides in body tissues and can activate the response of certain HLA-B27-specific CD8+ T lymphocytes. The T lymphocytes react with these HLA-B27-peptide complexes, leading to autoreactivity and autoimmune disease (**Faham et al., 2017; Wolfgang et al., 2004).**

The molecular mimicry hypothesis posits that the antigenic components of infectious bacterial pathogens partially resembling or cross-reacting with HLA molecules can stimulate CD8+ T lymphocytes, followed by responding to one HLA-B27 relevant self-peptide or the peptides directly produced by HLA-B27**(Antoniou et al.,2011)**This hypothesis is largely based on previously identified amino acid structures of homologous origin between the HLA structure and specific sequences and previous results depicting cross-reactions among the HLA and some bacterial antigens **(Zhang et al.,2018) .**

HLA-B2702, have been found to exhibit a relatively lower rate of correct folding procedures compared with those of HLA-B2706 and HLA-B2709, which are generally not considered associated with AS **(Chen et al.,2017).** Due to cysteine residue C67 and other

reasons, HLAB27 tends to fold slower than other HLA alleles, and without proper folding, these defective HLA-B27 proteins continually gather in the ER**.** Improperly folded HLA-B27 proteins accumulate in the ER and activate autophagy and the interleukin (IL)-23/IL-17 pathway **(Colbert et al., 2009).** Reover, these misfolded molecules can interfere with ER function, leading to ER stressand even triggering the pro-inflammatory endoplasmic reticulum unfolded protein response (ERUPR), which further activates the IL-23/IL-17 pathway **(Colbert et al.,2009; Turner et al.,2005).** However, conflicts also exist regarding whether the HLA-B27-activated ERUPR occurs in AS patients. The increased production of IL-23 without significant ERUPR induction occurs in macrophages in AS **(Zeng et al., 2011) .**The disease related polymorphisms of the ERAP1 or HLA-B27 locus would not change the ER stress intensities of AS. which also remained controversial in other studies conducted later.14 One possibility is that HLA-B27 misfolding results in autophagy and triggers the IL-23/IL-17 pathway instead of ERUPR **(Kenna et al.,2015)**.Further research is required for illumination of the connection of ERUPR and HLA-B27 during the development of AS.

HLA-B27 heavy chains tend to form homodimers without β2m via the disulfide bonds of the cysteine at C67 **(Chen et al., 2013).** The dimeric HLAB27 complexes, mostly found in the gut and synovium of patients, may contribute to the genesis of AS and some other SpAs. These HLA-B27 dimers could occur on antigen-presenting cells, thus stimulating IL-23 receptor + T lymphocytes to produce IL-17**(Ranganathan et al., 2017).** The hypothesis of cell-surface HLA-B27 homodimer formation suggests that HLA-B27 dimers might contribute to the development of AS. HLA-B27 homodimers have been linked to receptors expressed on natural killer (NK) immunocytes, myelomonocytes and lymphocytes. The binding is realized via killer cell immunoglobulin-like receptors (KIRs) and leucocyte immunoglobulin-like receptors (LILRs), thus acting in the processes related to autoimmune disorders **(Allen et al., 2001; Tam et al., 2010).** The 3 immunoglobulin domains and the long cytoplasmic tail 2 (KIR3DL2) receptor expressed by certain increased immune cells, including NK cells and Th17 cells, can recognize cell-surface HLA-B27 homodimers via a greater affinity than that with the classic HLA-B27 heterotrimers **(Bowness et al.,2011; Chan et al.,2005)**. The binding of KIR3DL2 with HLA-B27 homodimers was revealed to stimulate the survival and differentiation of KIR3DL2+CD4+ T lymphocytes in patients with SpA **(Giles et al., 2012; Wong-Baeza et al., 2013).** Compared to KIR3DL2− lymphocytes, these T cells significantly increase cytokine output, including IL-17, TNF-α and INF-γ **(Bowness et al., 2011).** These findings suggest that the aberrant HLA-B27 homodimers function in AS pathogenesis.

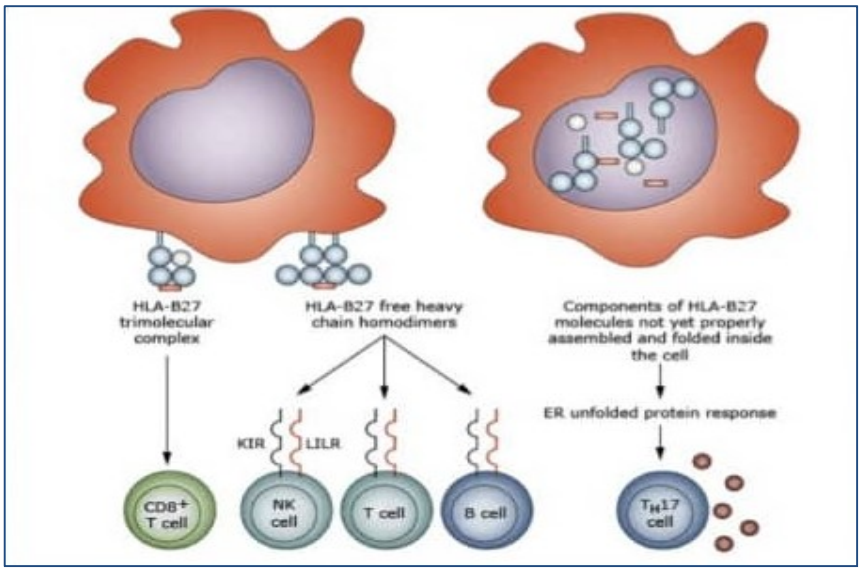

Figure08: Three different HLA-B27 structures and hypotheses as to how they might induce disease processes in ankylosing spondylitis **(Tam et al., 2010).**

Other HLA B genes have been recognised in association with development of AS including: HLA-B730 HLA-B16, HLA-B35, 31, 32 HLA-B38 and HLA-B3933. These genes have been identified across a variety of ethnic groups and are associated with HLA-B27-negative AS, although the mechanism is not yet clear **(Zhu et al., 2019).**

An HLA-C amino-acid variant in addition to HLA-B*27 confers risk for ankylosing spondylitis in the Korean population.The four amino-acid positions of HLA-B and -C account for most of the associations between AS and MHC in the Korean population. This finding updates the list of AS susceptibility loci and provides new insight into AS pathogenesis mediated by MHC class I molecules **(Kim et al., 2015).**

II.1.2.ERAP1 ERAP2

ERAP genes are located on chromosome 5q15 in opposite orientations. The ERAP1 gene spans 47,379 base pairs and includes 20 exons, while the ERAP2 gene covers 41,438 base pairs and contains 19 exons **(Cifaldi et al., 2012).** Both genes are polymorphic; in particular, the ERAP1 sequence exhibits over 40,000 single nucleotide polymorphisms (SNPs) in both the intron and exon regions. In contrast to ERAP1, non-synonymous alterations affecting the amino acid sequence of ERAP2 appear to be rarer; indeed, only 11,097 SNPs have been documented, so far **(Zhang et al., 2020).**

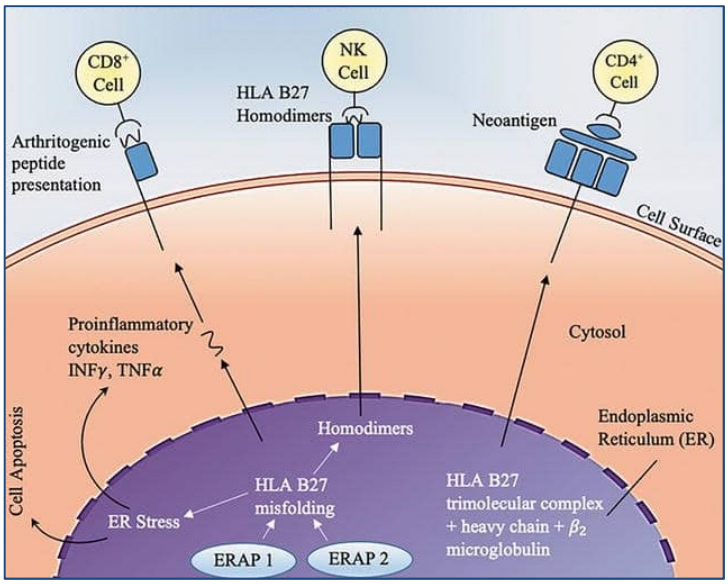

Figure09: Proposed theories on the role of HLA B27 & ERAP genes in pathogenesis of ankylosing spondylitis **(alexander,2023).**

II.1.2.1.Pathogenesis

ERAP1 and ERAP2 previously identified aminopeptidases were recognized as genetically related to AS vulnerability, including ERAP1 (coding for endoplasmic reticulum aminopeptidase 1 (ERAP1), ERAP2 (coding for ERAP2) (**International Genetics of Ankylosing Spondylitis Consortium,2013;Wellcome Trust Case Control Consortium,2007)**.Recent research has indicated that gene-to-gene interactions among HLA-B27 and ERAP1 and subsequent abnormal peptide presentation are likely relevant to the development of AS **(International Genetics of Ankylosing Spondylitis Consortiumb,2013;Graham et al.,2007).**A case-control association study revealed that protective genetic variants were associated with reduced function of ERAP1 and ERAP2 and suppressed MHC-I expression on the cell surface**(International Genetics of Ankylosing Spondylitis Consortium, 2013)**. ERAP1 and ERAP2 variations may also reduce the speed of HLA-B27 folding by affecting the amount of relevant peptide accessible, thereby increasing ER stress and AS development.Both ERAP1 and ERAP2, genes at chromosome 5q15, participate in trimming peptides in the ER to nine amino acids for antigen presentation by HLA-I molecules such as HLA-B27 **(Kanaseki et al.,2006).** In addition to the processing and presentation of antigens, ERAP1 can still trim several cytokine receptors on the cell surface, such as IL-1R2, TNFR1, and IL-6Rα, thus reducing their ability to conduct signals to cells, and the latter further affects inflammatory processes **(Cui et al.,2002)**. These two genes are involved in the development of AS and other diseases. ERAP1 is reportedly associated with

HLA-B27− and HLA- B40positive AS **(Kanaseki et al., 2006).**While ERAP2 is related to HLA-B27+ and HLA- B27− AS **(Robinson et al., 2015)**.

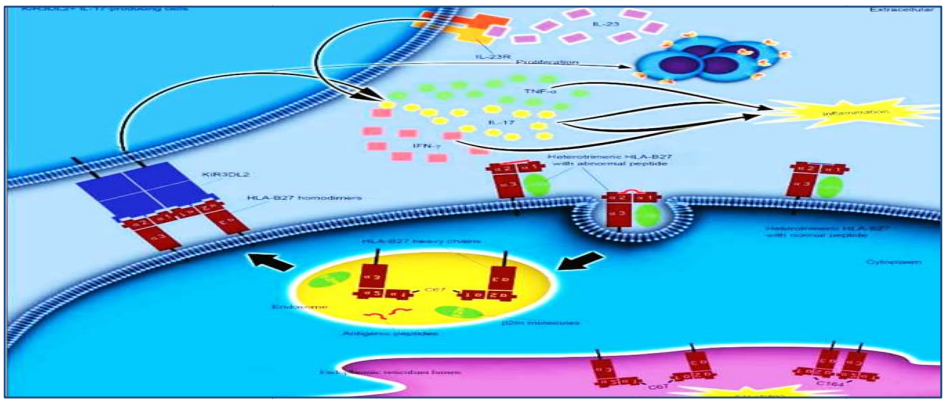

Figure 10: Various functions of ER resident and cell surface HLA-B27 **(Chen et al., 2017).**

II.1.3.IL23R IL17 Th17

Th17 cells are a subset of T helper cells, developmentally distinct from Th1 and Th2 cells, which produce IL-17 together with other proinflammatory cytokines, such as IL-6, IL-22, IL-26, interferon (IFN)-γ and tumour necrosis factor (TNF)-α **(Park et al., 2005).** Of these, IL-17 subsets A and F and IL-26 are considered to be the most specific to the Th17 response **(Yen et al., 2006).**

IL-17 has been shown to enhance T cell priming and to stimulate various cell types, including fibroblasts, endothelial cells, macrophages and epithelial cells, to produce proinflammatory mediators (such as IL-1, IL-6, TNF-α and chemokines). IL-17 has been shown to function principally during the effector phase of an inflammatory response **(Piper et al., 2014).** Interestingly, the development of murine Th17 cells from native T cells has been shown to be inhibited by IFN-g and IL-27 (Th1 response cytokines), and by IL-4 and IL-25 (also known as IL-17E; associated with Th2 responses) (**Yen et al., 2000),** confirming its distinction from the other T cell subsets. IL-22 and granulocyte–macrophage colonystimulating factor (GM-CSF) can be produced by Th17 cells or by related but probable Th populations **(Oppmann et al.,2000)**

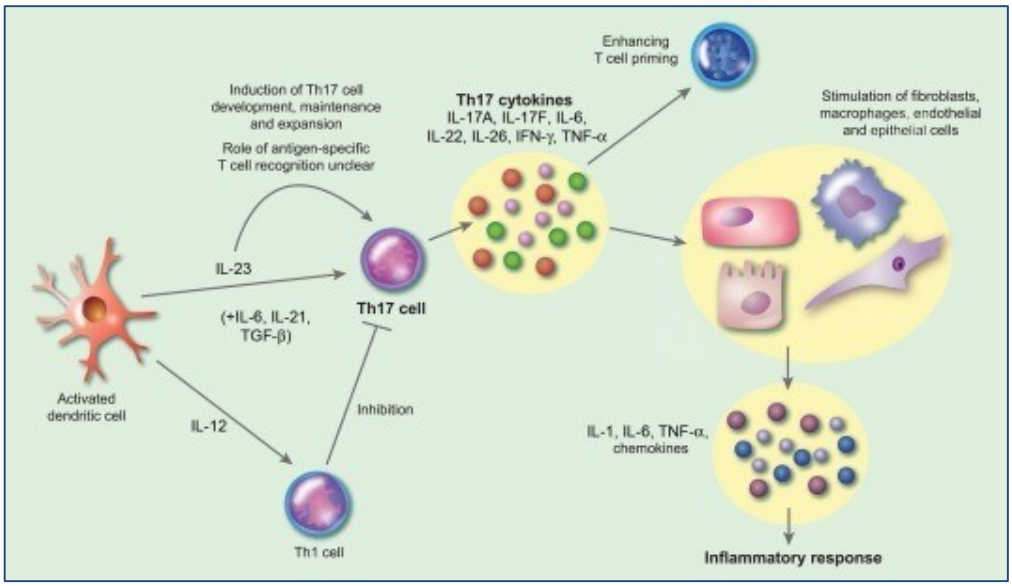

Figure 11: Interleukin (IL)-17/IL-23 pathway **(Jethwa et al., 2015).**

II.1.3.1.Pathogenesis

In AS, the first indication of IL-23/IL-17 relevance came from a GWAS study in 2007 that identified an IL-23 receptor (IL-23R) SNP related to AS pathogenesis **(Consortium et al., 2007)**. In humans, the differentiation of Th17 cells may be triggered by IL-23, TGF-β, and IL-1β, among other inflammatory cytokines, and the differentiated immunocytes further generate IL-17A, IL-17F, IL-22, IL-26, and CCL20**(van den Berg et al.,2013).**

Dysfunction of the IL-23/IL-17 pathway was identified in many diseases related to human immunological procedures, including psoriasis, IBD, rheumatoid arthritis and SpA **(Mahmoudi et al.,2017).**Additionally, IL-17 and IL-23 act as major cytokines for axSpA **(Paine & Ritchlin,2016).**

In AS, differentiated T lymphocytes can generate IL-17 and then trigger osteoclast activation, thus suppressing bone regeneration. Moreover, lymphocytes can produce IL-22 when exposed to IL-23 to stimulate osteoproliferation (**Babaie et al.,2018).**This contradictory process may explain the coexistence of erosion and formation of bone for patients with AS.

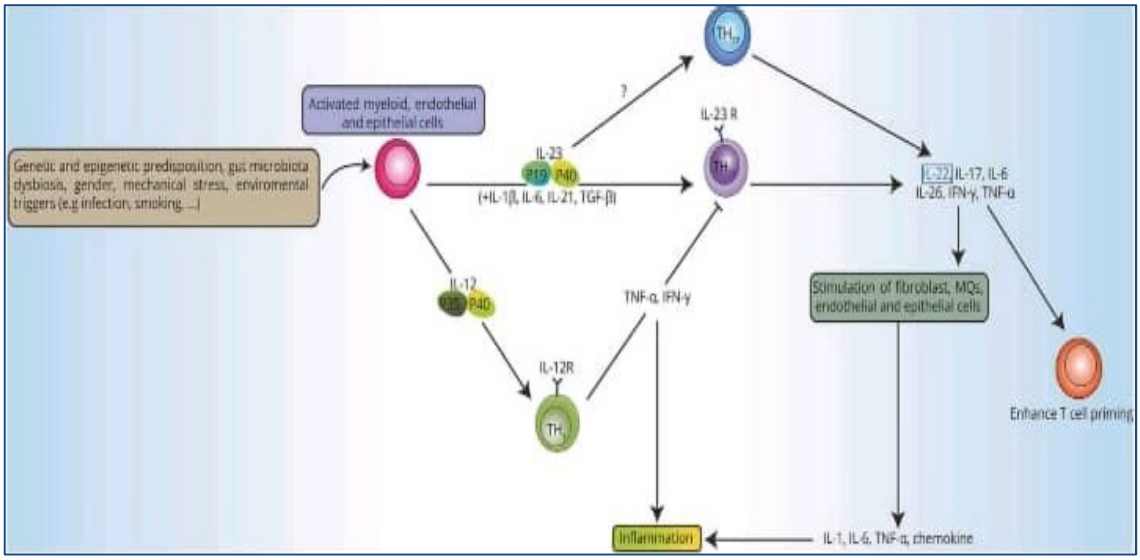

Figure12: IL-23/17 pathway in AS pathogenesis **(wei et al., 2019).**

II.1.4.Gene–gene interactions and pleiotropy

There are significant gaps in knowledge about gene–gene interactions and the development of AS. However, certain links have been established. For example, a Taiwanese population study is suggestive of an interaction between HLA-B60 and HLA-B27 as a marker for the risk of AS susceptibility **(Zhu et al., 2019).** The combination of HLA B60 with HLAB 27 increases chances of developing AS by 3–6 times. HLAB27 interacting with ERAP1 gene is thought to contribute to development of AS **(Evans et al., 2011).**

Pleiotropy in AS has been investigated. A number of pleotrophic gene loci have been identified **(Bowness et al., 2011).** DNA methylation genes 3a and 3b (*DNMT3A, DNM3TB)* are recognised in genomic imprinting and X-chromosome and have been studied in cross-gene studies. Their relationship with haematopoietic stem cell development and UBE2 activation (a family of genes also known to be associated with AS) supports the hypothesis of involvement in male predominance in AS, which remains currently remains unexplained **(Bowness et al., 2011).**

FUT2 encodes fucosyl transferase, a gene which controls secretion of blood group antigens into body fluids. This gene is known has a major effect on the gut microbiome and is thought to contribute to AS **(Costello et al., 2015).**It is likely that further research will illuminate several ways in which gene–gene interactions contribute in AS pathogenesis.

II.2.Immunological factors

AS is one type of seronegative spondyloarthritis, which is usually associated with

chronic inflammation involving DCs, macrophages, NK cells and adaptive immune cells **(Rezaiemanesh et al., 2018).** These immune cells produce various innate cytokines that play a crucial role in the development of AS, as shown in **(Fig.13).** Human DCs located in lymphatic and nonlymphatic organs are divided into CD1c positive (conventional DC1) or CD141-positive (conventional DC2) subsets **(O'Keeffe et al., 2015; Guilliams et al., 2014).** Another group of DCs, called plasmacytoid dendritic cells (pDCs), exhibit a plasma cell-like appearance and can produce CD56+, HLA-DR, derived dendritic cell antigen 2 (BDCA-2), Toll-like receptor 7 (TLR7), CD123, and TLR9 and can be distinguished from monocytes and conventional DCs by the lack of CD14 and CD11c expression **(Zang et al.,2014; McKenna et al.,2005).** In addition to their function in the inborn and adaptive immune processes, these cells participate in B cell-mediated humoral immunity **(McKenna et al., 2005).** Previous studies have shown elevated production of IL-1B and IL-6 in AS patients compared with that in normal subjects because a decrease in the number of circulating CD1c+ DCs increases the quantity of CD14-CD16+ mononuclear cells, which mediates the activation of CC chemokine receptor 6 (CCR6) expression **(O'Keeffe et al.,2016).** These processes trigger the Th17 immune response and IL-17 production, which are involved in autoimmune and inflammatory responses and are associated with clinical manifestations of AS **(Zambrano-Zaragoza et al., 2013; Talpin et al.,2014).**

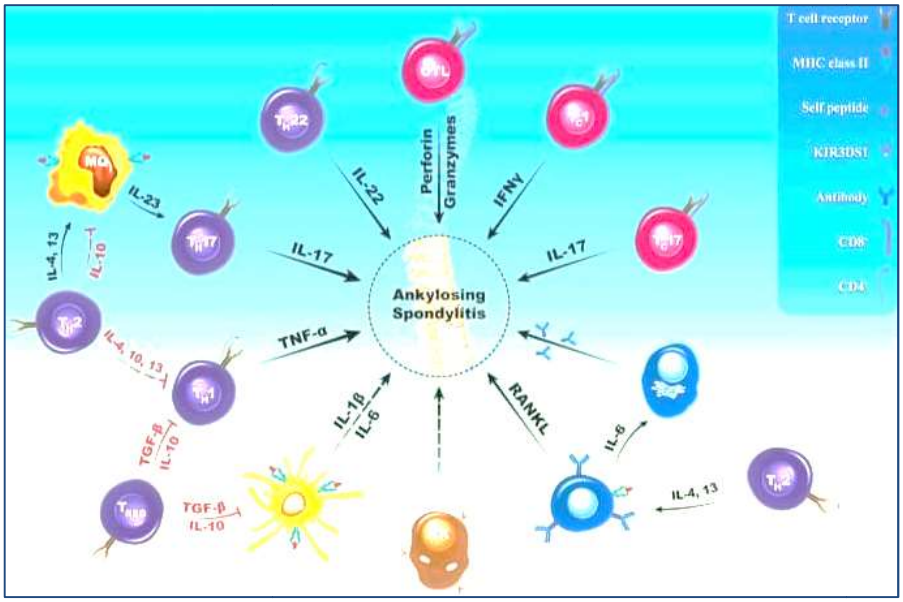

Figure13: Immunocytes are involved in the initiation, evolution, and regulation of AS **(wei et al., 2019).**

II.3.Metabolomics

Studies on metabolomics have gained attention in recent years. This has relevance to

understanding pathogenesis, diagnosis and response to treatment in AS **(Rizzo et al., 2022).** They show a range of findings in AS patients including altered pathways of tryptophan metabolism **(Berlinberg, 2021).** Other studies revealed significant alterations in unsaturated fatty acids (FA), linoleic acid, alpha-linolenic acid, FA degradation, and FA biosynthesis pathways **(Doğan et al., 2022).** Another study revealed down regulation of the Vitamin D3 metabolite (23S, 25R)-25-hydroxyvitamin D3 26, 23-peroxylactone. The ratio this vitamin D metabolite versus vitamin D binding protein serum levels was shown to be altered when compared with healthy controls **(Fischer et al., 2012).**

II.4.Sex hormones

Until recently it was thought that a relationship between male gender and presence of AS existed, given males account for the majority of AS patients, however recent literature demonstrates a more homogenous sex prevalence of AS **(Rusman et al., 2018)**.Although this is true, females with AS have different phenotypical disease due to different immunological, hormonal, and genetic responses **(Rusman & van Vollenhoven, 2018).**

Despite this these recognised relationships, the role of sex hormones and biologic gender in AS pathogenesis remains poorly understood **(Jo et al., 2020).** This is complicated by conflicting evidence in research to date **(Odeh et al., 2019)** with a lack of robust study design to date **(Gooren et al., 2000).**

However, some reports on variations of sex hormones in AS patients compared with controls imply that increased androgen levels in both males and females possibly contributes to disease development **(Rusman et al. ,2020).** Patients who are HLA-B27 were originally reported to have higher levels of testosterone **(Jame al., 1991).** However, a study with small sample size revealed a decreased testicular testosterone reserve, elevated luteinizing hormone level, and inversion of the normal estradiol/testosterone ratio and increased estradiol level **(Zhu et al., 2019).** In female studies reports show that patients with active AS have significantly.

II.5.Diet and lifestyle factors

Currently evidence on the relationship between AS and diet is extremely limited and inconclusive. This is mainly due to studies being small, single studies with moderate-to-high risk of bias, and insufficient reporting of results as reported by one systematic review **(Macfarlane et al., 2018).**No prospective cohort studies of dietary risk factors for the development of AS exist, however one report suggested that a change in dietary habit from a

high protein, low-starch diet to a Westernised high-starch diet among the Inuit population of Alaska and Canada whose populations also express high percentages of HLA B-27, possibly explain an increased incidence of AS in this population **(Rashid et al .,2015).** Other studies have suggested adoption of a "Westernised" diet is a contributing factor to development of AS **(Popa et al., 2022).** The patients with AS were breastfed less compared with healthy controls **(Montoya et al., 2016).** Breast feeding could potentially affect the development of AS through microbiome and other immunological factors.

Smoking is associated with increased cumulative spinal structural damage in patients with AS **(Akar et al., 2018)** as well as higher disease activity, inflammatory markers and functional disability **(Farouk et al., 2021).** Whether smoking induces AS is unclear.

Alcohol consumption is associated with spinal structural progression in patients with axial spondyloarthritis and appears to be dose related according to one Korean study **(Min et al., 2019).** These researchers demonstrated an increase of syndesmophyte progression over a two-year period.

II.6.Periodontal Pathogens and AS

Anti–P gingivalis and anti–Prevotella intermedia antibody titers were higher in patients with SpA than in healthy people **(Rinaudo-Gaujous et al., 2014).**Sulfasalazine is an effective antibiotic treatment for AS **(Dougados et al., 1986).** When reviewing the literature **(Van der Linden et al., 1984)** randomized controlled studies that focused on sulfasalazine use were found **(Dougados et al., 1986; Clegg et al., 1999)**. However, long-term use results in drug resistance. It is more effective for the peripheral signs than the spinal symptoms of AS **(Clegg et al., 1999).**

Periodontal pathogens are responsible for the development of AS in genetically susceptible individuals. This finding should guide the development of more comprehensive and efficacious treatment strategies for AS**.**

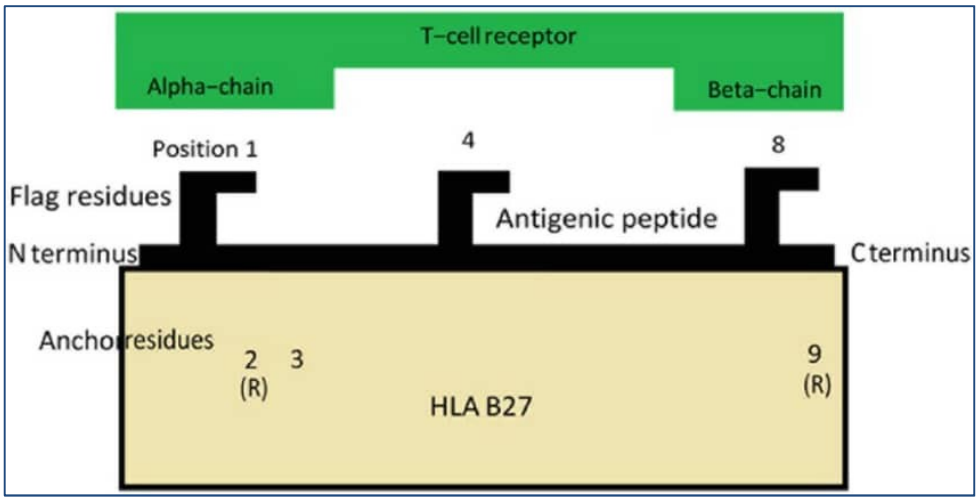

Figure 14: Antigen presentation in ankylosing spondylitis .The potentiality and actuality of gut-joint migration **(Departement of physical medicine and rehabilitation et al., 2017).**

III. Genome-wide association studies (GWAS)

Genome-wide association studies examine the whole genome for regions where DNA sequence variation is associated with the phenotype of the trait being explored. It builds on the common disease common variant hypothesis, that common disorders are likely to be influenced by common genetic variation and that each variant has a small effect that combine together to cause disease. This hypothesis-free genetic association study is most frequently performed on genotyping array, where thousands of individuals can be genotyped at hundreds of thousands to millions of sites of variation with the aim of identifying the genetic differences between groups of individuals. This method has been widely used in the study of common complex human traits to identify genomic regions on chromosomes that identify the genetic markers of that trait.

III.1. GWAS in AS

GWAS have been employed in AS in order to identify the multiple associated variants to the disease. Multiple published studies exist that investigate AS in European cohorts **(Ellinghaus et al., 2016; Evans et al., 2011)** 1 and have identified more than 100 genetic associations **(Brown, 2018, Li and Brown, 2017).** The use of this hypothesis free technique has led to the discovery of unsuspected pathways and biological mechanisms, including aminopeptidases and the IL-23/IL-17 pathways, which prior to this form of investigation had not been implicated in disease. Also; comparison across immune-mediated disease hits has contributed to the idea of a shared genetic background amongst diseases.

Most of these associations are yet to be explained biologically but understanding the mechanisms that have led to these associations is of great importance in understanding the causes of this complex disease. Further work is required to fine-map these associations, identify the causative genes and variants driving the association signal, and experimentally show their impact on function and how this contributes to ankylosing spondylitis.

Chapter III:

Risk Factors, Diagnosis and Treatement

I.Risk factors

I.1.Genetic Factors

Genetic factors have been acknowledged as crucial in the genesis of AS. Since the identification of hereditary components of AS in families in 1961, the relationship between genetics and AS has been a constant issue of discussion. The 1973 discovery of the major histocompatibility complex (MHC) class I allele HLA-B27 makes it one of the most significant genetic variables **(Brewertonet al., 1973).** Over 86% of Hispanic patients with AS and 85 to 95% of White and Han Chinese patients have HLA-B27 positive **(Jamalyaria et al., 2017; Reveille et al., 2019).**Although only 8% of the general population **(Reveille et al., 2009).** In fact, only approximately 5% of HLA-B27– positive individuals in the general population have SpA **(Akkoc & Khan, 2005).**In the Middle East and North Africa, and in American Black patients, the prevalence of HLA-B27 among patients with AS ranges from approximately 50 to 84% **(Reveille et al., 2009; Ziade, 2017).** AS cases that do not involve HLA-B27 comprise > 10%, and twin concordance rates are not 100% HLA-B27-positive monozygotic twins (17 of 27 patients) and dizygotic twins (4 of 15 patients) had respective concordance rates of 63% and 27% **(Brown et al., 1997).** Nonetheless, HLA-B27 is still thought to be a significant factor that is strongly linked to the onset of AS, especially for the size and severity of bone marrow edema lesions in the sacroiliac joints in early disease **(Coates et al., 2008).** The HLA-B27 family has 231 protein subtypes, spanning from HLA-B*27:01 to HLA-B*27:232, and 328 alleles, exhibiting a significant degree of genetic variability (the subtype HLA-B*27:22 was found to be in error and was withdrawn); these subtypes differ from each other in only a few amino acids, which may alter the peptide-binding specificity of the molecule **(Galocha &López de Castro,2010; Allele Search,2020).** The most common HLA-B27 subtype, the ancestral subtype HLA-B*27:05, is distributed ubiquitously worldwide, is found in all races and ethnicities, and is strongly associated with AS **(Reveille et al., 2009; Dashti et al., 2018; Cortes et al., 2015).** Specific populations have other HLA-B*27 subtypes that are positively associated with AS such as the “major” or most common subtypes HLA-B*27:02 (in people of European, Chinese, and Mediterranean or Northern African ancestry), HLA-B*27:04 (in Eastern Asia and China), HLA-B*27:07 (in Western Asia), and HLA-B*27:15 (derived from HLA-B*27:04 and found in China). Other HLA-B27 subtypes are rare, representing amino acid substitutions derived from HLA-B*27:05 and its major subtypes Studies show that those positive for specific HLA-B27 subtypes have an increased risk of developing AS and specific AS manifestations, including peripheral joint involvement **(Cortes et al., 2015; Lin & Gong, 2017).**The role that HLA-

B27 plays in the pathogenesis of AS is a subject of much investigation. Six mechanisms have been proposed:

1. Presentation of an “arthritogenic” peptide **(Faham et al., 2017).** Major Histocompatibility Complex (MHC) class I molecule HLA-B27 displays endogenous peptides, including those from bacteria, viruses, cancer, or "self" peptides that have been broken down intracellularly in lysosomes.to the αβ T cell receptor on CD8+ T lymphocytes or to the killer immunoglobulin (KIR) receptor on natural killer (NK) cells. Despite a great deal of work that has gone into identifying a peptide specific for SpA, this has proven to be an elusive target. That said, CD8+ T lymphocytes have a role in AS pathogenesis, and recent data do suggest AS patients have a reduced cytotoxic CD8+ T cell profile in their peripheral anenrichment in the inflammatory joint, as well as blood **(Gracey et al., 2020).**
2. HLA-B27 heavy chains have the rather unique tendency to misfold in the endo/; plasmic reticulum (ER) compared to other HLA-B alleles. HLA-B27 misfolding (i.e., incorrect folding and loading of peptides) has been postulated as one reason for genetic susceptibility **(Navid et al., 2021)**. One study demonstrated that the AS-associated HLA-B27 subtypes B*27:02, B*27:05, and B*27:07 differed from the non–AS-associated B*27:06 and B*07:02 alleles by a greater tendency to accumulate in intracellular ER-derived vesicles, at high expression levels examining cells from SpA patients or HLA–B27/human β2-microglobulin (hβ2 m)–transgenic rats **(Jeanty et al.,2014;Jah et al.,2020).** ER-associated heavy chain degradation and a proinflammatory unfolded protein response are the outcomes of this misfolding and the buildup of misfolded HLA-B27 heavy chains in the ER, which activates the innate immune response and upregulates proinflammatory cytokines such as interferon gamma and interleukin (IL)-23, as well as other cytokines, especially those in the T helper 17 (Th17) pathway **(Navid et al., 2020).**
3. HLA-B27 heavy chains have a striking tendency to self-adhere and form homodimers by virtue of having a cysteine residue at position 67 in the « 1 domain (and elsewhere). These homodimers have been detected at the cell surface and are recognized by KIR and leukocyte immunoglobulin-like receptors. How and if homodimerization affects predisposition to AS is unclear, especially in that HLA-B27 subtypes that are associated with AS (HLA-B*27:02, B*27:04, B*27:05, B*27:07) and those not disease-associated (B*27:06, B*27:09) share this property, with the exception of B*27:03, which does not efficiently-self adhere **(Indumathy et al., 2019).**

4. People who are HLA-B27 positive show changes in the intracellular invasion and destruction of arthritogenic bacteria. This is especially seen for reactive arthritis, where impaired intracellular killing of causative microorganisms has been described, leading to intracellular bacterial persistence and upregulated cytokine production **(Sahlberg et al., 2012)**. HLA-B27 itself, either free B27 heavy chains or homodimers (or peptides produced from them) or the trimolecular complex of B27 heavy chain, α2 microglobulin, and peptide are identified as antigenic by the T cell receptor (or peptides bound therein) on CD4+ T lymphocytes, generating an autoimmune response **(Boyle et al., 2001).**
5. People who are HLA-B27 positive have a changed microbiota, which affects their vulnerability to disease (explained below).

I.1.1.MHC genes other than HLA-B27

Though considerably less so than HLA-B27, other HLA-B alleles have also been linked to AS risk.Studies on Whites, Han Chinese, and Blacks have shown that the development of AS is negatively correlated with HLA-B*07, B*35, and B*57 and favorably correlated with HLA-B*40. Peripheral versus axial spondyloarthritis is more likely to develop in those with HLA-B*15 **(López-Larrea et al., 2002).** HLA-B*14:03 may make West Africans who are HLA-B27-negative more susceptible to AS **(Londono et al., 2015).** African Americans did not exhibit this subtype. In a large global imputation investigation, HLA-A*02:01 was found to be independently associated with AS susceptibility**.** DNA sequencing implicated the MHC related gene MICA in a large cohort of White American patients with AS and confirmed in a Han Chinese cohort **(Zhou et al., 2014).** However this was a much larger imputation research did not confirm this **(Cortes et al., 2018).** In a study of Taiwanese patients, HLA-C alleles were also linked to AS **(Wang et al., 2017).** However, after accounting for linkage with HLA-B27, this was not observed in a larger cohort of American White patients **(Reveille et al., 2019).** The correlations between AS and MHC class II alleles, such as HLA-DRB1, and particularly with alleles at HLA-DPA1 and DPB1 were more convincing **(Castro-Santos et al., 2013; Huang et al., 2020).** Most likely, linkage to HLA-B27 haplotypes explains correlations with additional MHC loci, including TAP and TNF **(Qian et al., 2017; Ma et al., 2013).**

I.1.2. Non-MHC genes

Genome-wide association studies have identified and characterized the role of > 100

susceptibility genes or loci outside the MHC locus genes for AS, Crohn's disease, ulcerative colitis, and psoriasis, which are summarized in. Especially important are the genes endoplasmic reticulum aminopeptidase 1 (ERAP1) and interleukin 23 receptor (IL23 R); ERAP1 is more frequently identified in patients with AS who are HLA-B27 positive than in those who are HLA-B27 negative.Gene chip and genomewide association studies have revealed AS susceptibility genes, including ERAP1, which are compiled in Supplemental **(Reveille et al., 2010; Lin et al., 2011).** A recent study that compared 2752 AS patients with acute anterior uveitis (AAU) with 3836 AS patients without AAU is noteworthy since it found new connections between the two conditions **(Huang et al., 2020).** A major achievement of these studies relates to the identification of important biological pathways that are likely responsible for AS pathogenesis. New therapeutic targets have been found as a result of this identification.

Understanding genetic differences in AS pathogenesis may allow better patient and treatment matching.

I.2.Gut microbiota and associated factors

Given what is now known about the pathophysiology of AS, it is highly probable that the microbiome contributes, particularly in individuals who are predisposed genetically. Current human research as well as those conducted in animal models support this. Arthritis developed as a result of commensal bacteria like Bacteroides vulgatus being introduced into the transgenic mice **(Rath et al., 1996).**

Furthermore, SpA symptoms appeared after the HLA-B27-transgenic rats were moved from their sterile environment to a regular rat colony. In a cross-sectional study assessing the relationship between disease activity and infections among Mexican patients with different forms of SpA, more infections were found to occur among those with HLA-B27 positivity, particularly enteric infections **(Martínez et al., 2004).** Thus confirming that microbial infection and genetics play a part in the development of AS. By changing the gut flora and exhibiting a distinct and divergent array of peptides in the gut, HLA-B27 may increase vulnerability to AS by creating a microenvironment that leads to microbial imbalance, inflammation, and subsequent overproduction of IL-23 and other proinflammatory mediators **(Rosenbaum & Davey, 2011).** an effect that is even seen in HLA-B27 positive "healthy controls"**(Asquith et al.,2019).**Additionally, gut permeability is increased among patients with AS and their first-degree relatives as well as in experimental animal models, which perhaps allows for a greater systemic exposure to potentially pathogenic gut microbes .In this

regard, Paneth cells, a subset of specialized secretory host-defense epithelial cells located in the small intestines, have been shown to secrete IL-23 and activate key IL-23 responsive cells such as group 3 innate lymphoid cells (ILC3), γδ T cells, and mucosal-associated invariant T (MAIT) cells, whichrecirculate from the gut to sites of inflammation important in SpA pathogenesis, such as the entheses **(Ciccia et al.,2009).** The gut microbiome Several families of gut bacteria have been associated with AS development in humans, including Lachnospiraceae,Prevotellaceae, Rikenellaceae ,Porphyromonadaceae, Ruminococcaceae, and Bacteroidaceae **(Costello et al.,2015).** and these AS-associated microbial families have been connected to intestinal inflammation markers such as fecal calprotectin levels, but not to other clinical indicators **(Klingberg et al., 2019).**211 Chinese people's gut microbial DNA was examined in a metagenomics study, which revealed that patients with AS had higher loads of Prevotella melaninogenica, Prevotella copri, and Prevotella sp. C561, and decreases in Bacteroides spa. Remarkably, patients with AS acquire the Bifidobacterium species, which is frequently seen in probiotics **(Wen et al., 2017).** Another study, again in Chinese AS patients, confirmed previous reports of gut dysbiosis in AS, and TNFi therapy was correlated with a restoration the perturbed microbiome that was observed in untreated AS cases compated to that of healthy controls **(Yin et al.,2020).**

Asymptomatic intestinal inflammation, usually involving the terminal ileum, is also known to occur in a large proportion of patients with AS (57 to 70%) and is especially apparent in those with peripheral arthritis, again suggesting a link between the gut and AS **(Mielants et al., 1988).** However, no evidence of an exact connection of AS with subclinical gut inflammation has been found to date **(Klingberg et al., 2016).**

Gut mucosal immunity has been linked to the overproduction of IL-23 by Paneth cells that line the small intestine's epithelium. Among patients with AS and Crohn’s disease, a marked upregulation of IL-23 p19 transcripts was observed in the terminal ileum, suggesting an association between polymorphisms in the IL-23 receptor and gut inflammation **(Ciccia et al., 2009).** Gut-induced protection through nursing: To present, only one study has looked at AS patients' breastfeeding histories. According to this retrospective case-control study, breastfeeding may prevent the onset of AS **(Montoya et al., 2016).** Patients with AS were breastfed less often than healthy controls. Patients with AS and HLA-B27 positivity were breastfed less often than their siblings who did not have AS as well as unrelated, healthy controls, which suggested that breastfeeding may reduce the occurrence of AS in families, maybe due to intestinal factors in breastfed individuals.

I.3.Infections

When an elevated fecal carriage was discovered in patients with "active" disease, Klebsiella pneumoniae was linked to the pathophysiology of AS **(Ebringer et al., 1977).** Patients with HLA-B27 positive were found to have reduced in vitro lymphocyte response to Klebsiella antigens in a subsequent investigation **(Seager et al., 1979).** However, no one else was able to validate these preliminary findings **(Warren et al., 2002).**Nevertheless, molecular mimicry between Klebsiella (and other enterobacteria) capsular antigens and HLA-B27 was proposed with the discovery of cross-reactivity between antigens in several Gram-negative microorganisms and lymphocytes of patients who were HLA-B27 positive **(Ebringer, 1983).** Additionally, compared to HLA-B27-positive controls, SpA patients were found to have a higher frequency of antibodies to a homologous area shared by Klebsiella nitrogenase and HLA-B27 **(Schwimmbeck et al., 1987).** This implied that AS is an autoimmune reaction against HLA-B27 that was first triggered by K. pneumoniae nitrogenase proteins. Nevertheless, independent confirmation of this discovery was not possible **(de Vries et al., 1992).** Other reports postulated that active AS was characterized instead by elevated IgA antibodies to various enterobacteria in both AS and AAU regardless of HLA-B27 status **(Mäki-Ikola et al., 1986).**Raising doubts about the molecular mimicry theory.

Alternatively, modification by a Klebsiella K43 plasmid-derived soluble cell wall factor of specific MHC-associated gene products was implicated in the pathogenesis of the HLA-B27–linked arthropathies, which likewise could not be confirmed by others **(Trapani & McKenzie, 1985; Ngo et al., 1984).** Research on AS patients or their family members with familial AS, whether they are affected or not, has not shown a particular K. pneumoniae antibody response for AS. By the mid-2000s, there was a lack of a convincing, continuous tale linking Klebsiella to the severity or susceptibility of AS, which sparked interest in more research on the subject.to wane; however, there has been a recent systematic review, a report demonstrating Klebsiella protein antibody responsiveness persisting in patients with AS **(Puccetti et al., 2017).** And another addressing the popularity of “low starch” diets, as well as “anti-Klebsiella” dietary supplements **(Rashid et al., 2015).** Al beit with little evidence of their effect on disease activity.Notably, recent research on the gut microbiota has not validated earlier findings linking Klebsiella to the gut **(Stone et al., 2004).** Infections during childhood hospitalization in a Swedish national case-control study, childhood hospitalization (with infections) was associated with later development of AS The study included 2453 patients with AS and 10,257 control subjects, of whom 17.4% and 16.3%, respectively, had been hospitalized with an infection before 17 years of age **(Lindström et al.,2016).** While

tonsillitis and respiratory tract infection rates were higher in AS patients than in controls, appendicitis was linked to a lower risk of AS. No correlations were found between AS and any other kind of illness.

I.4.The Participation of oxidative stress in pathogenesis of AS

A disruption in the equilibrium between the generation of reactive oxygen species (free radicals and non-free radicals) and antioxidant defenses is known as oxidative stress. Oxidative stress is a phenomenon harmful to DNA, as evidenced by its numerous damages in the course of action of reactive forms of oxygen **(Kiranatlioglu-Firat et al., 2023).**

The stimulation of the cell membrane during phagocytosis activates NADP oxidase, which catalyzes the formation of the superoxide anion O2−. Superoxide dismutase (SOD) is responsible for converting this radical into singlet oxygen and hydrogen peroxide **(Alfadda et al., 2012; Belenguer-Varea, 2020**). The reaction between the superoxide radical and H2 O2 produces a hydroxyl radical. These three compounds are called reactive oxygen species (ROS) and play a significant role in inflammatory processes.

Superoxide anions are produced in greater quantities at the site of inflammation in inflammatory disorders. An important mechanism of action of oxidative stress is the disruption of redox signaling, causing molecular damage that inevitably affects angiogenesis, inflammation, and the function/activation of dendritic cells, lymphocytes, and keratinocytes **(Bushnell et al., 1990).** The onset and course of inflammatory diseases in the osteoarticular system, such as ankylosing spondylitis, can be significantly influenced by ROS. The body produces toxic end products from the gradual oxidation processes of unsaturated fatty acids, such as malondialdehyde (MDA), which is a sign of lipid peroxidation and advanced oxidation protein products (AOPP) **(Damavandi et al., 2019).** By activating the vital TNF-α and NF-κB pathways, MDA and AOPP, respectively, might act as secondary mediators to worsen damage and quicken the progression of the illness. For the inflammatory process associated with AS **(Aslani et al., 2018).** The overproduction of free radicals and weakening of mechanisms for their neutral- ization are two of the causes of the development of the inflammatory process in ankylosing spondylitis. The toxic accumulation of metabolites first leads to functional impairment and then the destruction of the structure of the cell membrane in cells, resulting in inflammation.

I.5.Hormones

Since the presence of HLA-B27 and AS varied by sex, an etiological link between

endocrine factors and AS was postulated in early 1973 **(Schlostein et al., 1973).**Testicular function and a decrease in testicular testosterone were identified in a study involving 22 participants with AS. (T) Reserve, elevated luteinizing hormone (LH) level, estradiol/ testosterone ratio (E2: T) inversion and slightly increased estradiol (E2) level **(Tapiaserrano et al., 1991).** The results in studies of ovarian function have also indicated sex hormone differences in menstruating and meno-pausal AS patients compared with those in matched healthy controls **(Jimenez et al., 1990).** It is reported that estradiol levels in patients with active AS are significantly lower than those in patients with inactive AS in the menstruation period. More observational results, such as male predominance, peak onset at young age and increased number of first manifestations after pregnancy, imply that sex hormones play a role in AS **(Gooren et al.,2000).**Low levels of sex hormones, especially dehydroepiandrosterone sulfate (DHEAS), may also contribute to bone loss in patients with AS **(Aydin et al., 2005).** adrenocorticotropic hormone (ACTH) test (LDST) showed that after low-dose ACTH, the cortisol increment was significantly lower in AS patients than in controls (20.0 ± 4.4 vs 24 ± 2.2 microg/dl, $P < 0.001$)**(Kebapcilar et al.,2010).** The subclinical glucocorticoid deficiency indicated an impaired hypothalamic-pituitary-adrenal (HPA) axis in AS patients, suggesting the involvement of the endocrine system in AS.

I.6.Mechanical stress

An enthesitis-based model for the pathophysiology of SpA was initially put up by McGonagle and associates, according to which disease may result from interactions between biomechanical elements and the innate immunological response **(McGonagle et al., 2001).** In a mouse model in which a 69-base pair deletion comprising the tumor necrosis factor (TNF) AU-rich elements (ARE) yielded TNFΔARE-mutant mice with chronic inflammatory arthritis and Crohn's disease, mechanical stress was found to be involved in the development of enthesitis in the Achilles' tendon, where hind limb unloading could efficiently prohibit the development of enthesitis in those sites. In more recent work **(Cuthbert et al., 2019).** Examining human spinal entheseal tissue, Vδ1 and Vδ2 subsets of T lymphocytes were shown to be tissue resident cells with inducible IL-17 a production and that the Vδ1 subset does so independently of IL-23 R expression.

It is commonly known that individuals with AS who work in physically demanding tasks are more likely to suffer from a temporary or permanent work handicap, particularly in jobs that need dynamic flexibility (i.e., the ability to repeatedly bend, stretch, twist, or reach), because patients with AS tend to have more functional limitations than those whose past jobs

required little or no dynamic flexibility **(Ward et al., 2008).** This conclusion was supported by a recent study that found blue-collar workers had a greater radiographic progression of AS than white-collar workers **(Ramiro et al., 2015).** This would suggest that a young patient with AS, in evaluating his/her future employment, consider avoiding those with physically demanding tasks.

I.7.Gender at birth

Despite the equivalent prevalence of HLA-B27 between men and women **(Reveille et al., 2009).**AS reportedly affects more men than women (approximately 2:1 ratio, although this varies greatly between studies), and this gender disparity is not seen in nr‑axSpA, where there is relatively equal proportion of men and women, or even a female preponderance **(Reveille et al., 2012).** Male gender has been implicated as a risk factor for progression from nr-axSpA to radiographic axSpA, but this has not been examined in longitudinal studies. There also exists a gender-at-birth difference in the severity of AS, the type of clinical manifestations, and response to treatment. A Swedish study reported the higher prevalence of anterior uveitis among men with AS vs women and of peripheral arthritis and psoriasis among women with AS vs men **(Exarchou et al., 2015).** Furthermore, men with a family history of AS are at a higher risk of developing AS than both women with a family history and men without a family history of AS **(Lin & Gong, 2017).** The differences observed in men are, in part, due to genetic factors predisposing them to AS development, and to immunological and lifestyle differences (e.g., smoking, diet).

The onset of AS is reportedly earlier among men than among women, which leads to a more rapid diagnosis **(Park et al., 2018).** However, women experience more delay in receiving an AS diagnosis. Additionally, according to the Bath Ankylosing Spondylitis Disease Activity Index and Ankylosing Spondylitis Disease Activity Score, men have lower disease activity and higher quality of life (Ankylosing Spondylitis Quality of Life Questionnaire) but have worse spinal mobility (Bath Ankylosing Spondylitis Metrology Index) and a more severe radiographic involvement (Bath Ankylosing Spondylitis Radiology Index). In terms of the clinical signs of AS, women typically experience a higher prevalence of dactylitis, enthesitis, and peripheral arthritis than males **(Landi et al., 2016).**

Women also report lower response rates to anti– TNF treatment than men. However, data appear conflicting. In a small prospective cohort study (N = 216) using data from the Outcome in AS International Study, no gender-at-birth–attributable differences in physical function or disease activity over time were discovered, although men had more severe

radiographic damage **(Webers et al., 2016).** This confirms earlier findings showing that men with chronic AS experienced more severe radiographic alterations than women.

Despite this, men report a better quality of life than women over time. Furthermore, there has been evidence of a clear sexual dimorphism in the immune system's activation status in AS patients, namely in the Th17 axis, which may help to explain clinical gender-related abnormalities.Among men and women with AS **(Gracey et al., 2016).** This dimorphism may suggest gender-specific AS treatment.

Other genetic differences (IL-22 copy number variants, rs11428092 and rs10208769 in USP34, and IRGM) have also been observed between the genders.

I.8.Social and environmental and lifestyle factors

Older siblings Having older siblings was strongly associated with greater risk of developing AS and birth weight below 3000 g, but not low birth weight (i.e., < 2500 g), was weakly associated with the risk of AS development. The results of this one study are inconclusive and require confirmation and replication in additional cohort **(Lindström et al., 2016).**

The importance of environmental factors in the etiopathogenesis of diseases of the osteoarticular system has been noted. It is suggested that elements easily absorbed by bone tissue, e.g., cadmium, lead, Diseases of the osteoarticular system, such as osteoarthritis, rheumatoid arthritis, and osteoporosis, may be influenced by strontium and aluminum. Numerous factors, including systemic and multi-organ alterations, influence the osteoarticular system's ability to operate properly **(Jeka & Murawska, 2009).**

Calcium functions as a secondary messenger in inflammatory processes. Its abnormal deposition in the extracellular matrix, occurring during dystrophic or repair processes, is the basis for ectopic calcifications in bone and extraskeletal spaces.AS is thought to be crucial for calcium absorption since it frequently coexists with non-specific intestinal inflammation and microbiological abnormalities. The aforementioned comorbidities lead to the inhibition of the expression of Ca transporters, including calbindin D9 K, which in turn impairs intestinal calcium absorption **(Huybers et al., 2008).** Furthermore, it has been demonstrated that AS patient neutrophils have elevated intracellular calcium, which may support lipid peroxidation, apoptosis, and caspase 3 and 9 activation. Additionally, in individuals with AS, the total blood 25(OH) D levels and the inverse relationship between serum vitamin D levels and the Bass Ankylosing Spondylitis Disease Activity Index may be significantly impacted by differences in continents and ethnicities. Therefore, it is advised that people with AS increase their

vitamin D intake by taking dietary supplements or by being exposed to sunlight. This is implemented to enhance overall quality of life and lessen the intensity of clinical symptoms **(Chen et al., 2022).** Magnesium is another crucial mineral that is a part of the proteins in nervous tissue. Because it affects the development of AS and plays a part in the process of bone mineralization, its significance cannot be overlooked. It is responsible for the proper absorption of calcium in the bones, regulates the transport of this element, activates the ossification process, stimulates bone-forming cells to incorporate calcium into the bone structure, and also prevents pathological calcium deposition in soft tissues **(Zhang et al., 2019).** Increased phosphorus concentrations lead to the release of calcium from the bones, thus increasing its content in the blood. In addition to interfering with bone mineralization processes, this causes hypercalcemia, which triggers inflammatory responses.

Neovascularization, which is essential for the onset and progression of rheumatoid synovitis, can be inhibited by selenium. An incorrect concentration of selenium in the blood is an important factor for the osteoarticular system. In the course of conditions like AS or RA, deficiencies may result in autoimmune alterations in the joints **(Deyab et al., 2018).**

One of the most crucial components of the natural antioxidant barrier is zinc .A lack of this component may cause proinflammatory processes to be triggered and the antioxidant defense to deteriorate. Reduced zinc assimilation in arthritis results in extracellular matrix degradation, immune system alterations, increased inflammation, and Zn-mediated disturbance of the Th1/Th2 balance.In Th17, and a loss in PMN phagocytic activity **(Goggs et al., 2005).**

Inhalation exposure to cadmium is thought to be a trigger for the pro-inflammatory activation of macrophages. According to some theories, this causes lung nodules to develop, which in turn triggers and releases a particular type of RA. Additionally, vanadium activates the NF-κB signaling pathway **(Chen et al., 1999).**

Smoking cigarettes and e-cigarettes—Current smoking (but not a history of smoking) appears to be a risk factor for AS and is linked to disease activity level in those with AS. Given the established pro-inflammatory and pro-oxidative effects of smoking, particularly in relation to the development of disease in a genetically susceptible individual, this is not surprising. Nr-axSpA into AS While there are no data on e-cigarette users with AS, a mouse model of arthritis revealed that nicotine made inflammatory arthritis worse. Indicating that e-cigarettes and other products containing nicotine may be harmful to people with AS. Research conducted by Min et al. found a substantial correlation between alcohol consumption and the advancement of spinal structural damage in individuals with axial spondyloarthropathies.

These findings suggest that alcohol consumption may have a deleterious impact on the development of spinal structural damage in individuals with axSpA **(Min et al., 2019).** Du et al. investigated the impact of occupational exposure on ankylosing spondylitis. The study examined the effects of three different work arrangements: heavy lifting, working in shifts, and primarily standing or walking. It showed that there is no direct link between AS and the type of work exposure. The other important factor that may affect AS patients is the quality of their sleep. A fatty diet and prolonged exposure to air pollution have been associated with worse disease outcomes in AS patients **(Soleimanifar et al., 2019).** The study confirmed that an insufficient consumption of omega- 3 polyunsaturated fatty acids and fiber was linked to elevated (SpA) activity.

II.Diagnosis

II.1.Types of doctor diagnoses and treats ankylosing spondylitis

The diagnosis of ankylosing spondylitis is often made by a rheumatologist, a doctor specially trained to diagnose and treat arthritis and related conditions of the musculoskeletal system. However, a person with ankylosing spondylitis may require treatment from multiple different types of doctors because the condition can affect different sections of the body **(NIAMS, 2013).** These may include:

- ✓ An ophthalmologist, who treats eye disease.
- ✓ A gastroenterologist, who treats bowel disease.
- ✓ A rehabilitation professional or physical therapist who oversees stretching and exercise routines.
- ✓ A physical examination and medical history play a major role in the diagnosis of ankylosing spondylitis. Radiologic tests and lab tests may be used to help confirm a diagnosis, but both have some limitations**.**

II.2. Diagnostic and classification criteria for ankylosing spondylitis

All criteria for AS, SpA and axSpA published to date are not diagnostic but classification criteria. The first criteria developed in Rome **(Ball et al., 1963).**Were already fairly strong, as they covered the SIJ imaging, physical examination, and history with an early indication of inflammatory back pain. Additionally, the conditions permitted to include imaging negative patients. The next changes of the criteria were made in New York in 1966 which focused even more on the radiographic criterion, before the evaluation study by Moll &

Wright in 1973 and the modification proposed by van der Linden in 1984 **(Van der Linden et al., 1984).** Interestingly, Moll and Wright proposed quantitatively weighting the criterion since limited chest and back mobility were found to be too particular and too non-specific, while thoracolumbar discomfort was found to be excessively sensitive and non-specific. Since the sacroiliac joints were normal in less than 1% of patients with classic AS, the authors of the 1984 New York criteria contended in the discussion that radiographic sacroiliitis is a condition sine qua non for the diagnosis of AS according to the most recent suggestions. However, they stressed that sacroiliitis is not restricted to AS, but may also be found in psoriatic arthritis, Reiter's syndrome, and even in rheumatoid arthritis. The authors concluded that criterion of pain in the dorsolumbar spine lacks specificity, and the chest expansion criterion is too insensitive. However, the Rome criterion of low back pain for >3 months was found to be very useful **(Ball et al., 1963).** The current study showed that the clinical history as screening test for AS had only moderate sensi- tivity. It was suggested that the Rome pain criterion be used in place of the New York pain criterion as a modification of the New York criteria. The clinical criteria for 'inflammatory back pain' first published in 1977 **(Calin et al., 1977).** Include age at onset (<40 years) and chronicity (> 3 months). They are further distinguished by lower back stiffness in the morning lasting more than 30 minutes, subtle onset, and improvement by exercise, not by rest. A modification of this definition was included in the 1984 modified New York criteria and also in later proposals. In 1974, Moll and Wright published the first paper that introduced the idea of SpA as "seronegative spondarthritides" **(Moll et al., 1974).** They proposed to put these seven entities together: AS, psoriatic arthritis, reactive arthritis, arthritis associated with Crohn's disease and ulcerative colitis, as well as Whipple's disease and Behcet's syndrome.The first attempt to broaden the spectrum of AS was by Amor and almost in parallel the activity of the European Spondylarthropathy Study Group (ESSG) developing criteria for what is now called spondyloarthritis. All SpA signs, including axial manifestations, lower extremity polyarthritis or seronegative oligoarthritis, dactylitis, and other undifferentiated SpA cases, were to be included. Crucially, heel pain due to enthesitis as already shown in 1970 by J. Ball when giving his Heberden Oration and later stressed again in an MRI study by D.McGonagle **(McGonagle et al., 1998).** However, the two major entry

- **Medical History**

The medical history involves answering questions, such as the following:

1. How long have you had pain?

Where specifically is the pain in your back or neck? Are other joints affected?

2. Do you have other problems; such as eye problems or fatigue?
3. Does anyone in your family have back problems or arthritis?
4. Have you recently suffered from a gastrointestinal illness?
5. From your answers to these questions, your doctor can begin to get an idea of the diagnosis **(NIAMS, 2013).**

- **Physical Exam**

During the physical exam, the doctor will look for signs and symptoms that are consistent with ankylosing spondylitis. These include pain in the heels, chest, sacroiliac joints, pelvis, and/or along the spine. Your doctor may ask you to move and bend in different directions to check the flexibility of your spine and to breathe deeply to check for any problems with chest expansion, which could be caused by inflammation in the joints where the ribs attach to the spine. In milder cases or in the early stages, clinical symptoms may be inconspicuous. In addition to palpating and stressing, a clinical examination should assess chest expansion, lateral lumbar flexion, and forward lumbar flexion (Schober's test, > 5 cm flexion is normal) the sacroiliac joints**.** The peripheral joints should also be examined for evidence of synovitis or enthesitis. Patients should be assessed for the presence of extra-articular manifestions of disease, including anterior uveitis (which occurs in up to 40% of patients), aortic incompetence, cardiac conduction disturbances, and pulmonary fibrosis **(NIAMS, 2013).**

- **Radiologic Tests**

✓ **X ray**

Sacroiliitis is the hallmark of the disease. The bottom portion of the sacroiliac joints is where changes typically take place. Bony erosions, sclerosis, and the joint's apparent enlargement may occur after the joint first seems blurry and fuzzy. Complete bony fusion may occur in longstanding disease. Marginal vertebral body erosions, squaring of the vertebral bodies and the development of bone bridges or syndesmophytes between neighboring vertebrae are examples of alterations seen on spinal radiography. Spinal osteopenia is prevalent and spinal ligament osseification is possible. In severe longstanding disease, almost complete fusion of the vertebral column may occur (“bamboo spine”) Plain radiographs may be normal in early disease however, it may take years of inflammation to cause damage that is

visible on x rays.Plain X ray showing bilateral sacroiliitis in a patient with ankylosing spondylitis **(Slobodin et al., 2012; Braun et al., 2018).**

- ✓ **X-ray computed tomography (CT)**

Sir Godfrey Newbold Hounsfield (1919 – 2004), a British electrical engineer, shared the 1979 Nobel Prize for Physiology or Medicine with Allan MacLeod Cormack, a South African American physicist (1924–1998) for developing the diagnostic technique of CT **(Cormack, 1963; Cormack, 1964).** In the Hounsfield scale, which is a quantitative assessment of radiodensity used to evaluate CT scans and is measured in Hounsfield units (HU), his name is "immortalized." MacLeod Cormack mentioned after having received the award: 'it is not much of an exaggeration to say that what Hounsfield and I know about medicine CT is a promising method to detect pathologic changes in the spine such as syndesmophytes in AS patients **(Diekhoff et al.,2017).** Radiation exposure has historically been the largest disadvantage, however low dosage approaches appear to significantly lessen this issue.

- ✓ **Magnetic resonance imaging (MRI)**

MRI may allow for earlier diagnosis, because it can show damage to soft tissues and bone before it can be seen on an x ray Magnetic resonance imaging of the It has been demonstrated that sacroiliac joints are more responsive to sacroiliitis than either computed tomography or conventional radiography. MRI is beneficial in identifying early inflammatory lesions, bone marrow edema, sclerosis, fatty lesions, and enthesitis, especially at the sacroiliac joints **(Sieper et al., 2002).** Additionally, it is renowned for its sensitivity, which makes it the best imaging modality for detecting symptoms including morning stiffness, inflammatory back pain, and potential involvement of peripheral joints **(Maksymowych, 2004).** It typically impacts the sacroiliac joints and spine, creating a bamboo spine. However, MRI is very expensive.Short tau inversion recovery or coronal STIR Magnetic resonance imaging demonstrating unilateral sacroiliitis on the right.

- ➢ **Lab Tests**
- ❖ **The HLA-B27 gene**

The main blood test for ankylosing spondylitis is one to check for the HLA-B27 gene, which is present in the majority of Caucasians with ankylosing spondylitis About 90-95% of white western European patients with ankylosing spondylitis have the tissue human leukocyte antigen B27 (HLA-B27), compared with around 8% in the general population,

(Reveille,2011). Though prevalences vary in different populations. The relationship is complicated since HLA-B27 has multiple subtypes, not all of which are harmful, and other genes other than HLA-B27 are also involved. Patients who are genetically susceptible are likely to be affected by an unidentified environmental component that causes the disease. Also, the gene is found in many people who do not have ankylosing spondylitis, and will never get it. Still, when the gene is found in people who have symptoms of ankylosing spondylitis and/or x-ray evidence of ankylosing spondylitis, this finding helps support the ankylosing spondylitis diagnosis **(Brown, 2010).**

- **Inflammatory markers**

Erythrocyte sedimentation rate ESR or C-reactive protein CRP.The first test measures how quickly red blood cells settle in a test tube within one hour. The greater the inflammation in the body, the faster the sedimentation rate Normal range for women: approximately 0–20 mm/hour For men: 0–15 mm/hour The second test, CRP, is a protein produced in the liver and rises rapidly in acute or chronic inflammation. It is more accurate than ESR. Normal range Less than 5 mg/L in most laboratories, but not all, patients with ankylosing spondylitis will have elevated levels of C reactive protein and erythrocyte sedimentation rates. Levels of inflammatory markers are less useful for monitoring disease activity in ankylosing spondylitis than they are in other inflammatory conditions such as rheumatoid arthritis, and may relate more to disease activity in peripheral joints shoulder joints and the cartilage between the ribs and the breastbone than axial disease.A normocytic normochromic anaemia may be present, particularly in patients with active disease **(Wu et al., 2021).**

Each person's diagnosis of AS may or may not include normal acute-phase reactants (APRs) (such as CRP and ESR) **(Mukai & Morita, 2022).** In inflammatory diseases like AS, APRs markers of inflammation are often high. However, each patient experiences an increase in APRs to a different extent.

- **Artificial Intelligence**

In the diagnosis and treatment of a wide range of illnesses, including autoimmune diseases like ankylosing spondylitis (AS), artificial intelligence (AI) has emerged as a legitimate tool.RA diagnosis achieved an excellent accuracy by incorporating clinical, serological, and radiological data, Utilizing AI techniques; the prediction, diagnosis & expecting the prognosis of the AS patients are possible. A real-time intelligent diagnosis is

possible by using smartphone-captured photos. Their model had achieved a good predictive value as compared to classical models of diagnosis (**Dhall et al., 2024).**

III.Treatment

Ankylosing spondylitis has no known cure, although certain therapies can lessen its symptoms and perhaps stop it from getting worse. Treatment typically consists of a mix of self-help techniques, exercise, and medication. In some cases, surgery may be used to repair some of the joint damage caused by the disease **(NIAMS, 2013).**

III.1.Medications are used to treat ankylosing spondylitis

- **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

These drugs relieve pain and inflammation improves spinal pain, peripheral joint pain, and function in ankylosing spondylitis. Are examples of NSAIDs Diclofenac, ibuprofen, naproxen, Indomethacin, Celecoxib, Etoricoxib All NSAIDs work similarly by blocking substances called prostaglandins that contribute to inflammation and pain. However, each NSAID is a different chemical, and each has a slightly different effect on the body **(Sieperet al., 2016).**

Diclofenac is a non-steroidal anti-inflammatory drug derived from phenylacetic acid from the arylcarboxylic acid group. It has the following properties Analgesic verb Antipyretic action Anti-inflammatory action **(Kroon et al., 2012).**

Ibuprofen is a non-selective cyclooxygenase inhibitor, inhibiting both COX-1 and COX-2. Its analgesic, antipyretic, and anti-inflammatory effects are primarily mediated by inhibiting COX-2, which reduces the synthesis of prostaglandins that mediate inflammation, pain, and swelling It is taken orally or intravenously, and begins to work within about **(Smolen et al.,2018).**

Indomethacin is a nonsteroidal anti-inflammatory drug, commonly used as a fever reduce, pain reliever, and to reduce stiffness and swelling. It works by inhibiting the action of prostaglandins molecules that cause these symptoms **(Wanders et al., 2005).**

- **Cyclo-oxygenase-2 selective inhibitors (COX-2 inhibitors)**

Celecoxib is a reversible, highly selective inhibitor of the COX-2 cyclooxygenase isoform. Celecoxib inhibits the conversion of arachidonic acid to prostaglandin and this selectivity theoretically allows celecoxib and other COX-2 inhibitors to reduce inflammation and pain while minimizing gastrointestinal adverse reactions (such as peptic ulcers) that are common with nonselective NSAIDs **(Wanders et al., 2005).**Etoricoxib that belongs to the selective COX-2 inhibitor class, which is considered the safest class for the stomach.

All NSAIDs can have significant side effects, and for unknown reasons, some people seem to respond better to one NSAID than another. The decision on which NSAID to use should be on an individual patient basis taking into account risk factors, particularly for gastrointestinal and cardiovascular disease. Analgesics, including paracetamol and opioids, may be considered when NSAIDs are contraindicated or not tolerated **(Ward et al., 2016).**

- **Corticosteroids**

These potent anti-inflammatory medications are comparable to the cortisone our systems produce. Doctors may administer corticosteroids directly into the afflicted joints to provide immediate, albeit transient, comfort if NSAIDs are unable to reduce inflammation in patients with ankylosing spondylitis. Injections are not administered in the spine, but rather to the hip, knee, or sacroiliac joints. A recent study reported that AS patients achieved relief from signs and symptoms after short-term treatment with high doses of glucocorticoids (50 mg/day) **(Haibel et al., 2014).** Intravenous methylprednisolone is occasionally used in severe unresponsive cases, but this use may decline with the availability of tumour necrosis factor inhibitors.

- **Disease-Modifying Antirheumatic Drugs (DMARDs)**

These medications regulate the ankylosing spondylitis disease process in various ways. For ankylosing spondylitis, methotrexate and sulfasalazine are the most often prescribed DMARDs. Sulfasalazine is a sulfa drug, a derivative of mesalazine, formed by linkingsulfapyridine and salicylate with an azo bond Sulfasalazine and its metabolite, 5-aminosalicylic acid (5-ASA), are poorly absorbed from the gastrointestinal tract. Therefore, their primary mode of action is thought to be in the intestine **(Rashidian et al., 2016).** Methotrexate formerly known as amethopterine, is a chemotherapy drug and immunosuppressant It can be given orally or by injection **(Fairbanks et al., 1999).**

- **Biologic agents**

✓ **TNF-alpha (Tumor Necrosis Factor Inhibitors)**

Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab pegol Members of this relatively new class of medications are genetically engineered to block proteins involved in the body's inflammatory response. All work by suppressing a protein called tumor necrosis factor-alpha (TNF-α), and are often effective for relieving symptoms when NSAIDs or other treatments are not. These drugs are taken by intravenous infusion or injection **(Aderka et al., 1989).**

Disease activity markers that continue to exceed certain cut-offs (BASDAI ≥ 4 or AS Disease Activity Score (ASDAS) ≥ 2.1) over time are considered to indicate an inadequate response to TNFis. The ASDAS has superior cut-offs and a better representation of the inflammatory state than the BASDAI. It is important to employ biological agents in accordance with their indications, contraindications, and patient comorbidities **(Gaoet al., 2012).**

✓ **Interleukin-17 inhibitors**

When AS patients fail to respond to the first TNFi, treatment with a second biologic should be advised.The different biologics can be an IL-17 inhibitor (IL-17 i) or a different TNFi **(Lie et al., 2011).**IL-17 A is a proinflammatory cytokine that is involved in normal inflammatory and immune responses and also plays a key role in the pathogenesis of AS. Three human IgG monoclonal antibodies that target IL-17 A are approved for use in AS and active non-radiographic axial spondyloarthritis: secukinumab; ixekizumab; and bimekizumab, which also targets IL-17 F **(Baeten et al., 2015).**

✓ **Janus kinase inhibitors**

JAKs are intracellular tyrosine kinases that affect a range of intracellular activity, including the production of inflammatory cytokines. The JAK family contains four JAKs: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Two JAK inhibitors, upadacitinib (Rinvoq) and tofacitinib (Xeljanz) are approved by the FDA for treatment of active AS in adults who have an inadequate response or are intolerant to one or more TNFi. Both are available as extended-release tablets **(Deodhar et al., 2022).**

Upadacitinib, a JAK1-selective inhibitor, was approved by the FDA for use in AS in

2022 15 mg taken orally once daily **(Baraliakos et al., 2023).**

Tofacitinib, which inhibits JAK1 and JAK3, was approved by the FDA for use in AS in December 2021 Twice daily (orally) at a dose of 5 mg. Approval was based on data from a phase III, randomized, double-blind, placebo-controlled trial in patients who had an inadequate response or intolerance to 1 or more TNFi. At 16 weeks, the percentage of patients achieving an ASAS20 was significantly higher with tofacitinib than with placebo **(Deodhar et al., 2021).**

- ✓ **Ayurvedic treatment for AS**

The holistic approach of Ayurvedic therapy for autoimmune illnesses, such as ankylosing spondylitis, has drawn attention. The publications that are offered emphasize several therapeutic approaches for autoimmune disorders; however, they do not specifically address Ayurvedic therapy for AS **(Bottini et al., 2015).** The Basis of Ayurveda in the Management of Autoimmune Diseases: Ayurveda emphasizes regulating the body's energy, or doshas, in order to treat illness. This all-encompassing strategy may alleviate AS symptoms by managing pain and inflammation through the use of herbal remedies and dietary changes. Certain Ayurvedic medicines, like turmeric and ashwagandha, are well known for their anti-inflammatory qualities, which may help with AS symptoms**.** Treatment regimens typically include Panchakarma treatments, oral Ayurvedic medications, and lifestyle modifications. Common Ayurvedic drugs include Ekangveer Ras, Sameera Pannaga Rasa, and Panchatikta Ghrita Guggulu **(Singh &Rajoria, 2016).** The cases reported improvements in disease activity scores, quality of life measures, and AS symptoms after receiving Ayurvedic treatment. One study discovered that symptoms had vanished and inflammatory indicators had reverted to normal after a one-year follow-up **(Shetty et al., 2024).** Although these case reports show promising results, there are drawbacks, including a limited sample size and no control groups.

Ⅲ.2.Drug treatment strategy for ankylosing spondylitis patients

- ✓ **Diet and exercise help**

Everyone benefits from a nutritious diet and regular exercise, but those who have ankylosing spondylitis may find it especially beneficial.A healthy weight is crucial for easing the strain on aching joints, even if there isn't a special diet for those who have ankylosing

spondylitis. There is some evidence that omega-3 supplements may lessen the activity of ankylosing spondylitis, despite the fact that the benefits of these fatty acids have not been thoroughly investigated in this population.In people with ankylosing spondylitis **(NIAMS, 2013).**

Sleep disorders and depression. Exercises (muscle strengthening exercises) are important to maintain or improve spinal mobility and physical fitness as well as to reduce pain and are included in evidence-based recommendations for the management of AS2, in addition to aerobic training **(Carter et al., 1999).**

Resistance exercises are currently used in several studies **(American College of Sports Medicine, 2009).** They can be performed using free weights, resistance bands or weight machines. Exercise that use the Swiss ball differed from other resistance exercise because it recruits the muscles responsible for spine stabilization during movement **(Escamilla et al., 2010).** Musculoskeletal and cardiovascular safety of resistance training have also been demonstrated, even in the face of co-morbidities.Muscle strengthening exercises have been studied in five other trials in AS patients. In these studies, the strengthened muscles were the legs, trunk, arms, back and abdominal exercises **(Fernandez-de-Las-Penas et al., 2005).**

It is suggested that resistance training using unstable surfaces, like a Swiss ball, can increase patients' functional capacity since it influences other physical fitness such as balance and proprioception. The purpose of this study was to assess the impact of Swiss ball muscle strengthening exercises on the functional ability of patients with AS, with a secondary focus on muscle strength, disease activity, spinal mobility, walking performance, and quality of life **(Hidding et al., 1993).**

Exercises that increase range of motion enhance flexibility and mobility while easing joint stiffness. If the spine is painful and/or inflamed, exercises to stretch and extend the back can be helpful in preventing long-term disability. Many people with ankylosing spondylitis find it helpful to exercise in water **(NIAMS, 2013).**

III.3.Surgery

Complete joint replacement could be a possibility if ankylosing spondylitis results in significant joint deterioration that makes it difficult to perform daily tasks. This entails taking out the injured joint and replacing it with a metal, plastic, or ceramic prosthesis. The knee and

hip are the joints that are most frequently replaced. Hip abnormality is commonly recognized by rheumatologists in AS patients and affects approximately one-fourth to one-third of AS patients **(Vander et al., 2010).** Proposed by the ACR, based on evidence, arthroplasty is the best treatment option for patients with advanced hip arthritis and severe hip pain who often would otherwise experience progressive limitations in mobility and reliance on opiates **(Ward et al., 2016).** Improvements in medical care that postpone the time from disease beginning to total hip arthroplasty (THA) may be the reason for the notable drop in the annual trends of THA among AS patients **(Bloom et al.,2017).** Although THA has been well studied, it may be a challenging operation for people with AS. According to recent findings, THA can have positive outcomes, significantly enhancing hip joint function and reducing discomfort without posing serious risks **(Xu et al., 2017; Xu et al., 2013).** Heterotopic ossification (HO) prophylaxis, intraoperative management techniques, implant selection, and surgical time are still controversial. Concomitant severe hip and spinal deformity is particularly challenging to treat, and there is no consensus on which deformity to repair first **(Bisla et al., 1976; Kim et al., 2012).** Prior to THA, some people advocate that a spinal osteotomy should be performed to reduce the risk of hip dislocation **(Tang et al., 2014).** Others agree with the assertion that a THA performed first would contribute to placement of the patient in a stable prone position to facilitate corrective spine osteotomy (**Kim et al., 2012).** Another debate has been focused on the superiority of cementless or cemented components in AS patients. For AS patients with severe osteoporosis who should undergo revised total hip replacement (THR), cemented prosthetic components are advised in order to guarantee a proper fit of the prosthesis to the canal **(Joshi et al. ,2002; Tang et al .,2000; Kim et al.,2012).** Additionally, the failure rate of THR using cemented components (5%) is lower than that of THR with cementless components (28%). On the other hand, cementless prostheses are recommended for AS patients, particularly those who are young and do not have major proximal femur morphological abnormalities, as this approach can lessen the challenge of future revisions while allowing bone ingrowth to enhance the durability of the implant **(Bhan et al. ,2008 ; Lee et al.,2017).** In very rare cases, a procedure called osteotomy may be used to straighten a spine that has fused into a curved-forward position. This surgery involves cutting through the spine so that it can be realigned to a more vertical position. Hardware may be inserted once the bones have been straightened to keep them there while the spine heals.With more than 30% of AS patients suffering from thoracolumbar kyphosis **(Kubiak et al., 2005).** Corrective osteotomy and stabilization are very common in surgical procedures and are recommended under certain conditions, such as adult patients suffering severe kyphosis or advanced hip

arthritis. This procedure has a perioperative mortality rate of 4% and permanent neurologic sequelae rate of 5% **(van Royen et al., 1999).** It has been demonstrated that this operation helps to improve disability, prevent the natural processes of progressive deformity, reduce pain from muscular exhaustion, and restore the horizontal axis and global balance. Of view, and improving respiratory and digestion function **(Allouch et al., 2018).** There are two basic types of osteotomy treatments used to address kyphotic deformity: closing-vs. openingwedge osteotomy (CWO/OWO) procedures.In 1945, Wilson et al**.** First presented poly-segmental wedge osteotomy (PWO) in 1949, this was improved by Zielke in the 1980 s **(Chen, 1988; Püschel& Zielke, 1982).** Correction was achieved via multiple CWOs in the posterior lumbar spine to generate a rather harmonious opening of the anterior disc spaces with tempered posterior shortening spanning. Zielke and his coworkers, different from the former procedure, advocated PWO with internal fixation using Harrington rods, laminar hooks, and later transpedicular screws. Scudese and Calabro originally presented monosegmental CWO in 1963 **(Scudese& Calabro, 1963).** And thoroughly developed by Ziwjan in 1982 and Thomasen in 1985 during this procedure, the posterior elements of one vertebra, in combination with the posterior wedge of the vertebral body, are resected to achieve correction by passive extension of the lumbar spine. Similar to PWO, internal fixation is also needed to enhance immediate stability. In this technique, correction is achieved. On the other hand, CWO appears to have better postoperative satisfaction and complication rates than either OWO or PWO **(Thiranont & Netrawichien, 1993).** Based on these three surgical procedures, surgical approaches for treating kyphosis have been consistently developed. Closing–opening-wedge osteotomy (COWO), particularly beneficial in cervical spine surgery, was first introduced by Kawahara et al .to overcome some limitations and simultaneously combines the benefits of CWO and OWO. Similar to CWO, posterior column resection is carried out with the wedge's tip at the vertebral midsagittal region. A plane is osteotomized anteriorly from this point parallel to the endplates or the anterior cortex is fractured and the anterior column is opened during osteotomy closure. At follow-ups ranging from 2.2 to 7.5 years, it has been demonstrated that this technique reduces localized kyphosis from an average of 67 to 18°. Similar outcomes have been reported by Ji and Bourghli; additionally, all patients tolerated spinal cord shortening and aorta lengthening well. Regarding the incidence of spine fractures, it is estimated to be 4 times greater in patients with AS than in the general population, largely because of the combination of rigidity and osteoporosis that develop in these patients **(Finkelstein et al., 1999).** In addition to standard AS treatments, these steps may also help ease inflammation and pain:

- Eat a nutritious diet: Fried foods, processed meats, and foods high in fat and sugar can have an inflammatory effect.
- Anti-inflammatory diets, such as the Mediterranean diet, may help fight inflammation.
- Maintain a healthy weight: Obesity and excess weight put pressure on joints and bones.
- Limit alcohol consumption: Drinking too much alcohol can weaken bones and increase the risk of osteoporosis.
- Stop smoking: Tobacco use accelerates spinal damage and intensifies pain. Your provider can help you quit smoking.

Chapter IV:

Impact of Ankylosing Spondylitis on HRQOL and SQOL

I. Health -related quality of life

I.1.Definitions

I.1.1.Health

Different definitions of health have been promoted during the last decades and the meaning has changed over the years **(Larson, 1999; Leonardi, 2018).** How we define health might have implications for clinical practice, policy making, and healthcare services **(Leonardi, 2018).**

The WHO definition of health as, '…a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' **(WHO, 1948)**

The definition has been criticized for stating that health and disease cannot coexist, even though some studies report that people with severe chronic diseases have reported their QOL as being equal or superior to people with no chronic disease **(Wahl et al., 2005).** Therefore, in 1984, a WHO discussion document proposed moving away from viewing health as a state, towards a dynamic model that presented it as a process or a force. The new suggestion was:

'The extent to which an individual or group is able to realize aspirations and satisfy needs, and to change or cope with the environment. Health is a resource for everyday life, not the objective of living; it is a positive concept, emphasizing social and personal resources, as well as physical capacities.' **(WHO, 1984)**

This definition of health is a resource for living and incorporates both social and personal resources as well as physical capacities **(WHO, 1984).** The definition is in line with the approach and philosophy of care as Treat- to- target in patients with axSpA. So far, no new attempts for a definition have reached consensus **(Leonardi, 2018).**

I.1.2.Quality of Life in a health context

As for health, many definitions of QOL have been suggested and it can mean different things for different people **(Fayers & Machin, 2016, p. 4; Post, 2014).** However, there is agreement that QOL is a multidimensional concept, which in different contexts may comprise different characteristics, meanings, and perspectives, including multiple aspects of people's lives, such as good health, comfort in relationships, material comfort, and safety. Other aspects of QOL are the opportunity

to learn, creative expression, the opportunity to help and encourage others, and socializing in all stages of life **(Fayers & Machin, 2007; Spilker, 1996).** The World Health Organization defines QOL as

'An individual's perception of their position in life in the context of the culture and Value systems in which they live and in relation to their goals, expectations, standards And concerns.' **(WHO, 1997)**

I.1.3.Health-related quality of life

Health-related quality of life is a subjective and multi-dimensional concept **(Rohde et al., 2025)** under a broad term of "quality of life" that has been introduced to healthcare since 1970s **(Jaeschke et al.,1989;Richard et al.,2018;Shim et al.,2018).** It is an important patient-reported outcome that can be used in both clinical settings and research **(Yüksel& Christensen, 2025).** That reflects the impact of illness and treatment on a person's perception of his/her daily life **(Kotsis et al., 2014; Skevington et al., 2004).**

HRQoL captures the composite impact of symptom burden, patient-perceived disease severity, treatment side effects, and healthcare interactions on physical, psychological, social and financial well-being as well as the degree of ease with which one is able to participate in important life areas (family, work/school, social, hobbies)**(Saketkoo et al ., 2021)**and may be affected by educational level, family support, employment status, and duration as well as the treatment of the disease and coping with the disease **(Özgül et al., 2006).**

Health-related quality of life, while infrequently considered a primary endpoint in clinical trials, may represent the singular outcome reflecting patient priorities when living with a health condition **(Saketkoo et al., 2021).**

I.2.Measures of health related quality of life applied in Ankylosing Spondylitis

I.2.1.Generic instruments

I.2.1.1.Euro QoL Visual Analogue Scale

EQ-VAS thermometer is a single self-reported global question asking respondents to rate current health on a VAS with end points labeled best imaging

health (100) and worst imaging health (zero) **(EuroQol Group, 1990).** It is part of the European Quality of Life instrument. The EQ-VAS is likely underused and under investigated in axSpA. The instrument is easy to administer and provides a summary of overall health that is close to the patient's experience. The advantage of being implicit might be considered at the same time a disadvantage, because underlying factors driving the scores remain unclear .Although end-of-scale aversion is a known limitations of the VAS; the instrument is reliable and sensitive to change **(Kiltz et al., 2020).**

I.2.1.2.Short Form-36 and Short Form-12

SF-36 is a generic questionnaire **(Ward, 1998; Ariza-Ariza et al., 2003),** widely used patient-reported outcome measure that assesses health-related quality of life across various populations, including both healthy individuals and those with medical conditions **(Zanoli et al., 2006)** such as ankylosing spondylitis**(Ware et al.,1994).**

It consists of eight subscales that assess the burden of disease on physical functioning, role-physical, bodily pain, mental health, role-emotional, social functioning, vitality, and general health perception **(Garrett et al., 1994).** Domain summary scores range from 0 to 100, where higher scores indicate greater levels of functioning and/or better health status. The main components of SF-36 are subscores for physical and mental health.The scale scores are calculated by summing responses across scale items and then transforming these raw scores to a 0 to 100 scale **(Busija et al .,2011).** Recall period depends which form is being used (standard 4 week, acute form 1 week) **(Boonen et al .,2008;Davis et al .,2007;Braun et al .,2007).**

This questionnaire is self-administered by patients, or it can be administered by a trained interviewer in person or via telephone. It typically takes about 5-10 min to complete **(Zhang et al.,2012).**Many studies consistently showed that in patients with axSpA the PCS and MCS are reduced when compared with the general population**(Boonen et al .,2008;Davis et al .,2007;Braun et al .,2007).**Overall, the SF-36 demonstrates good psychometric properties. However, its validity has been questioned because presence of severe floor and ceiling effects indicates that it does not capture the full range of health experiences in rheumatologic settings. The SF-12 is a shortened version that contains 12 of the original questions and from which a

physical and mental component summary score can be calculated **(Jenkinson & Layte, 1997).**

I.2.1.3.Measure of Health-Related Quality of Life (15D)

The 15D questionnaire is a generic, multidimensional, standardized evaluation tool of HRQOL that can be used primarily as a single index measure but also as a profile utility measure**.**This questionnaire captures the health status by assessing 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity **(Sintonen, 2001).**Each dimension is assessed by one question using five response categories. A single utility index score is obtained by incorporating population-based preference weights to the dimensions **(Stavem, 1999; Stavem et al., 2005).**The utility scores fall between 0.0 (being dead) and 1.00 (no problems on any dimension).Regression analyses were performed to impute missing values in accordance with the guidelines published by the developer of the questionnaire **(Sintonen, 2001).**The questionnaire has been tested thoroughly for psychometric properties in other studies, within several countries, including Norway **(Sintonen, 2001; Stavem, 1999).** And it has favourable validity and reliability (**Sintonen, 2001; Saarni et al., 2006).**

I.2.1.4.Health Assessment Questionnaire (HAQ)

This tool was used to measure physical disability. The questionnaire comprises 20 questions about the performance of physical activity over the last week and covers Eight areas: dressing and getting ready, arising, eating, walking, personal hygiene, Reach,grip,and common daily activity. Each item has a four-level response scale from 0 to 3, where 0 is no difficulty, 1 is some difficulty, 2 is much difficulty, and 3 Indicates inability to do the activity **(Fries et al., 1980).**

HAQs are used frequently to measure physical disability in patient groups. The questionnaire has established validity and reliability, internationally and in Norway **(Bruce & Fries, 2003; Uhlig et al., 2005).**

I.2.2.Disease-specific instruments

I.2.2.1.Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

BASDAI is a self-reported questionnaire developed by a multidisciplinary team, including patients, as a new approach in defining disease activity for AS patients in the last week by six questions about**(Garrett et al .,1994)** the level of weakness and fatigue, the severity of pain and swelling in the spine and other joints, the degree of sensitivity to touch, especially in the enthesis areas, the degree of discomfort after waking up, and the duration of morning stiffness**(Ay et al .,2004;Calin et al .,1999;Garrett et al .,1994;Karkucak et al .,2010).** Each question has a score from 0 (nothing to report) to 10 (the most negative answer) in the other end, this is a numerical ranking scale **(Garrett et al., 1994).** The average of the scores obtained from the final two questions is taken and summed with the scores of the other four questions. BASDAI score is obtained by dividing the total score by five. Where the scores of four and above indicate that the patient is in the active phase of Ankylosing spondylitis**(Ay et al .,2004;Calin et al .,1999;Garrett et al .,1994;Karkucak et al .,2010).**

BASDIA has been found to be negatively associated with some domains of the SF-36 **(Yang et al., 2016; Salaffi et al.,2009; Machado et al., 2011).**This scale reported good test-retest reliability (the Turkish version) and it was developed and validated by Garrett et al. It is a rapid and simple instrument and sensitive in detecting treatment-related changes **(Garrett et al., 1994).** Therefore, it has been translated into several languages, including Norwegian **(Fayers &Machin, 2016).**

I.2.2.2.Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a 10-item self-report questionnaire used to evaluate the functional capacity in performing daily activities over the last week **(Calin et al., 1994)** of patients with ankylosing Spondylitis**(Calin et al .,1994;Gur Kabul et al.,2021;Ozer et al.,2005).**It consists of eight visual analogue scales dealing with physical function and two scales reflecting the patient's ability to cope with daily activities **(Zochling & Braun, 2007).** Based on prompts for the following 10 activities, patients are asked to mark the difficulty of completing these activities by marking them on a 10 cm long scale. The activities include putting on socks or close-fitting clothes, bending to pick

up objects, reaching for items from a higher place, standing up from a chair without armrests, getting up from lying on the floor, standing for 10 min without discomfort, climbing 10–15 steps, looking backward, engaging in physical activities, and completing a day of household and work tasks **(Abdal et al., 2021).** Each item is scored from 0 (easy) to 10 (impossible) with a total score generated by calculating the mean of the 10 items **(Calin et al., 1994).** The BASFI is also quick and easy to apply – it takes maximum 100 seconds to complete this index **(Ruof & Stucki, 1999; Calin et al., 1994; Moncur, 2003)** and it has acceptable test-retest reliability and internal validity and is sensitive to change (Turkish version) **(Zochling,2011)** and it has shown better comparative responsiveness than other functional indices widely used in AS.

I.2.2.3.Bath Ankylosing Spondylitis Patients Global Score (BAS‑G)

This tool was used to measure the effect of axSpA on a patient's well-being over the past week and the past 6 months through a self-administered questionnaire, consisting of two questions **(Jones et al., 1996).** Each question has a numerical rating scale range of 0 (the most positive) to10 (the most negative). It was tested for reliability, validity and sensibility in the original and Swedish versions **(Jones et al.,1996;Waldren&C.H,1999).**It was translated and validated into Norwegian by the medical company MSD-Norway, using standardized translation procedures according to an international cross-cultural translation manual**(Fayers &Machin,2016).**

I.2.2.4.Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL)

This self-reported questionnaire is an18-items binary response scale. They include impact of AS on sleep, mood, motivation, coping, activities of daily living, independence, relationships, and social life. Scores range from 0-18 with higher scores indicating poorer quality of life **(Doward et al .,2003).**The total score is the sum of the individual, dichotomous responses **(Jenks et al .,2010)**(yes or no)**(Duruöz et al .,2007).** The questionnaire has been demonstrated to be feasible, reliable and to have content and convergent validity in patients with axSpA **(Jenks et al., 2010)** (e.g. The Serbian ASQoL has demonstrated good psychometric properties and reliability for assessing quality of life in r-axSpA patients) **(Zlatkovic‑Svenda et al., 2025).** And

the reliability and validity of the Turkish version of this questionnaire has been verified by Duruoz et al. **(Duruoz et al., 2008).** Patients need between 2 and 16 minutes to complete the questionnaire and it takes less than 1 minute to score the results **(Zochling, 2011).**

I.2.2.5.Ankylosing Spondylitis Disease Activity Score (ASDAS)

The ASDAS is a new composite index with continuous measurement properties developed by the Assessment of Spondyloarthritis International Society group for Assessing AS **(Lukas et al., 2009).** It determines disease activity, using the scores (on a scale of numerical measure of 0–10) of back pain, duration of morning stiffness, global assessment by the patient, pain/swelling in peripheral joints and also the C-reactive protein doses (mg/L) or erythrocyte sedimentation rate (mm/h). The values are put into an equation to obtain the final score **(Machado et al., 2011).** It combines five single disease activity variables in such a manner that it optimally conveys information, resulting in one single score with better validity, enhanced discriminative capacity, and improved ability to detect change as compared to separate variables**(Lukas et al .,2009;Pedersen et al .,2011).**ASDAS was developed in two versions. These versions included the same variables, with the exception for the acute phase reactants, CRP or ESR, but with slightly different weighting **(Lukas et al., 2009).**

According to the treat-to-target **(Smolen et al .,2018)**and the ASAS/EULAR management recommendations for axSpA**(Van der et al .,2016),** the CRP-based ASDAS is the preferred instrument for the assessment of disease activity in the process of making decisions on modification of axSpA treatment inclinical routine, with ASDAS-ESR as an alternative in case CRP is not available .Although both ASDAS versions demonstrated a high level of agreement when they were developed, it has been suggested that they might not be interchangeable **(Van der Heijde et al., 2009).** During the 2010 ASAS workshop in Berlin, Germany, upon presentation of results and discussion**(Machado&Pedro ,2016),** the ASAS group has established cut-off values (1.3, 2.1, and 3.5) to classify patients into four distinct disease activity states **(Machado et al.,2011; Machado et al.,2018)**and two improvement scores were chosen by consensus**(Machado&Pedro ,2016)** : disease activity states: inactive disease (ID)Lower than 1.3, low disease activity (LDA)1.3–2, high disease activity

(HDA) 2.1–3.5 and very high disease activity Higher than 3.5 (VHDA) **(Sandoval &Fernández-Ávila,2023)** and two improvement scores :minimal clinically important improvement(MCII) and major improvement **(Machado&Pedro ,2016).**

Table 02: Presents the formula to calculate ASDAS score with PCR or ESR **(Sandoval & Fernández-Ávila, 2023).**

ASDAS-CRP	0.12 × Back Pain + 0.06 × Duration of Morning Stiffness + 0.11 × Patient Global + 0.07 × Peripheral Pain/Swelling + 0.58 × Ln (CRP + 1)
ASDAS-ESR	0.08 × Back Pain + 0.07 × Duration of Morning Stiffness + 0.11 × Patient Global + 0.09 × Peripheral Pain/Swelling + 0.29 × √(ESR)

- ASDAS, Ankylosing Spondylitis Disease Activity Score
- √ (ESR), square root of the erythrocyte sedimentation rate (mm/h)
- Ln (CRP + 1), natural logarithm of the C-reactive protein (mg/L) + 1
- Back pain, patient global, duration of morning stiffness, and peripheral pain/swelling assessments use a visual analog scale (from 0 to 10) or a numerical rating scale (from 0 to 10).
- Back pain, BASDAI question 2: “How would you describe the overall level of AS neck, back, or hip pain you have had?”
- Duration of morning stiffness, BASDAI question 6: “How long does your morning stiffness last from the time you wake up?”
- Patient global: “How active was your spondylitis on average during the last week?

I.2.2.6.Assessment of Spondyloarthritis International Society Health Index

The ASASHI is a health index developed for AS patients based on the core set of the International Classification of Functioning, Disability and Health (ICF), aiming to evaluate the actual life status of ankylosing spondylitis patients **(Kiltz et al.,2014; Kiltz et al .,2013).** It includes 17 items**(Rudwaleit et al .,2011)** covering pain, maintaining a body position, moving around, toileting, energy and drive, motivation, sexual functions, driving, community life, handing stress, recreation and leisure, emotional functions, washing oneself, economic self-sufficiency, sleep, and handling stress .Patients self-assess each domain by selecting “agree,” “disagree,” or “not

applicable." A score of 1 is assigned for each domain marked as "agree," with a total score calculated from the 17 domains. A score of 0 represents the best outcome, while 17 represents the worst **(Alonso et al., 2022).** Threshold values were determined (good functional ability, <5 points; poor functional ability, >12 points) to differentiate between poor, moderate, and good functional ability. An improvement of greater than or equal to three points (smallest detectable change) in an individual patient is considered to be larger than measurement error and thus points to true change **(Kiltz et al., 2018).** The ASAS HI also includes a nine-item contextual factor set (environmental factors only). Its reliability and validity have been confirmed **(Rudwaleit et al., 2011).**

I.2.3.Health Utilities

I.2.3.1.The generic EuroQoL five dimensions health utility index

The EQ-5D is a generic preference-based questionnaire **(Rabin &Charro, 2001)** .It provides societal preferences for health states across five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression **(EuroQol Group, 1990).** This index uses a utility-weighted scoring system that has been derived from extensive studies with different countries **(Gignac et al., 2011).** The higher values of EQ-5D indicate better health, with 1 representing perfect health, 0 corresponding to death and negative values representing health status worse than death **(Lingjia et al., 2024).**Others have criticized the EQ-5D for its limited score distribution, inability to distinguish between patients with modest morbidity, and discrepancies between patient and societal utility tariffs, despite the fact that some rheumatic illness users have found it to be valid and responsive **(Carr,2003).**

I.2.3.2.The axial spondyloarthritis–specific Assessment of Spondyloarthritis International Society utility index

The ASAS HI's17 health items were used in two consecutive preference experiments.Were performed among 3099 subjects without SpA to understand the relative importance of each of the 17 items, and rescale them on 0 to 1 utility scale **(Essers et al., 2019).** The societal conversion algorithm indicated a health utility of -0.24 for worst SpA, and 0.88 for best health. The mean utility among 199 patients

with SpA was 0.36 (standard deviation [SD], 0.30; range, -0.24 to 0.88) and discriminated well between patients having high or low BASDIA (BASDAI; ≥4, 0.18 [SD, 0.24] vs BASDAI <4, 0.51[SD, 0.27]; P<.01) **(Kiltz et al., 2020).**

I.3.Impact of Ankylosing Spondylitis on Health related quality of life

I.3.1.Physical effects

Inflammation in the sacroiliac joints and spine leads to chronic back pain, stiffness, reduced mobility, and fatigue significantly affecting daily activities such as personal care and housework **(Singh &Strand, 2009; Strand &Singh, 2017; Özdemir, 2011).** A study showed that AS patients with high disease activity engage in less exercise than those with lower activity **(Fongen et al., 2013).** Women report more negative impacts than men, with a higher proportion experiencing emotional distress related to household responsibilities **(Rsenbaum, 2010).** Additionally, sleep disorders are prevalent among AS patients, who suffer from conditions like insomnia, restless leg syndrome, and obstructive sleep apnea **(Tymms et al., 2022; Demirci et al., 2016; Jiang et al., 2018; Maatallah et al., 2022).** Studies report varying prevalence rates of sleep disorders, For instance, in Egypt, China, and Australia, the prevalence of sleep disorders was reported as 90%, 31%, and 19.2%, respectively, highlighting the need for further research in this area **(Tymms et al.,2022; Jiang et al.,2018; Abdulaziez& Asaad,2012).**

I.3.2.Psychological effects

Depression and anxiety are highly prevalent among ankylosing spondylitis patients. Studies report depression in 31% to 35% of AS patients **(Barlow et al., 1993; Zhang et al., 2019),** while anxiety affects 31.6% to 48 %**(Jiang et al.,2018;Nie et al.,2018).** Eren et al. (2007) further confirmed elevated levels of both conditions compared to controls using the Beck Anxiety and Depression Scale. Notably, Martindale et al. (2006) observed that anxiety scores fluctuate over time, highlighting the dynamic nature of psychological symptoms in AS. The frequent overlap of anxiety and depression in AS patients underscores the need for integrated care **(Sloan et al., 2002).**

A collaborative approach between rheumatology and psychiatry teams could

significantly improve depressive symptoms and enhance quality of life. Despite extensive research on psychological factors in other chronic illnesses, key aspects remain unexplored in AS, including personality traits, coping mechanisms, alexithymia, and illness perceptions. Investigating these areas is crucial, as patient-reported outcomes and illness representations play a vital role in managing chronic conditions.

I.3.3.Social effects

I.3.3.1.Impact on social interaction

The onset of AS typically occurs around age 26, a crucial period for career and family development **(Sieper et al., 2006).** The disease can severely impact health, well-being, and social interactions, leading to emotional consequences such as frustration, anger, and depression. Patients often face difficulties in relationships due to cancellations of social arrangements and a reluctance to discuss invisible fatigue, leading to feelings of disbelief from others **(McCabe et al., 2013).** Limited research has focused on social interaction challenges among AS patients, but surveys indicate that only a small percentage report concerns in this area **(Bakker et al., 1995)**.

I.3.3.2.Impact on work productivity

Ankylosing spondylitis typically affects individuals during their most productive years, leading to physical impairment and decreased health-related quality of life **(Sieper et al., 2015).**Compared to the general population, AS patients experience worse HRQoL and greater work productivity loss, characterized by absenteeism and presenteeism **(Boonen&Van derLinden, 2006; Tran‐Duy et al., 2015).** In various countries, yearly sick leave for AS patients ranges from 12 to 46 days, significantly higher than the 7 to 16 days for the general workforce **(Boonen et al., 2001; Boonen et al., 2002).** Withdrawal from work is notably more common among AS patients, increasing from 5% in the first year post-diagnosis to over 30% by the two-decade mark (**Sieper et al., 2002; Boonen et al., 2001).** One-third of hospital attenders with AS give up work before retirement age and others modify or reduce their work **(Barlow et al., 2001).**

I.3.4.Financial effects

The financial burden of living with AS is significant, categorized into direct and indirect costs **(Bakker et al., 1994).** Direct medical costs average €266,295 per patient annually, including €107,218 for systemic medications, €1,369 for local treatments, €3,648 for osmic acid synovectomy therapy, €18,811 for physical therapy, €13,661 for surgery, and costs for inpatient (€80.28) and outpatient (€18.75) care, alongside €23,906 for radiographs. Indirect costs amount to approximately €279,625 per year, averaging €1,165.50 for patients on sick leave and €411.375 for those working **(Pall et al., 2012).** The societal impact is also notable, with a potential loss of up to one-third of AS patients from the workforce **(Boonen et al., 2002).** A large study in the Netherlands indicated that labor force participation was 15.4% lower for male patients and 5.2% lower for female patients compared to the general population. This economic burden is substantial, particularly as the disease typically manifests during peak working years **(Boonen et al., 2010).**

I.3.5.Treatment‑related side effects

a).Adalimumab

Adalimumab (Humira®) is a human monoclonal TNF-α antibody that inhibits the effects of TNF-α and is administered via subcutaneous injection. It is approved for treating rheumatoid arthritis in the EU and US, either alone or in combination with methotrexate. Compared to traditional systemic treatments, its side effect profile is favorable and does not require laboratory monitoring.The most common side effects include injection site reactions, while there is an increased risk of rare serious infections, with a two-fold risk reported in the Premier trial. Adalimumab should not be used during active infections, particularly due to the risk of reactivating tuberculosis. Tuberculosis screening should follow country standards, potentially including purified protein derivative tests or chest X-rays.Other serious infections, including deep fungal infections, may also occur. Additionally, adalimumab has been rarely associated with skin rashes, worsening of congestive heart failure, lupus-like syndrome, lymphoma promotion, significant cytopenias, and neurological diseases like multiple sclerosis. There have been reports of pancytopenia and elevated

transaminases, suggesting that intermittent monitoring of blood counts and liver function may be beneficial. Its use should be carefully considered in patients with these conditions. Overall, adalimumab can be a useful medication when its side effects are acknowledged **(Scheinfield, 2005).**

b). Tofacitinib

Tofacitinib was the first JAK inhibitor approved for rheumatoid arthritis treatment in 2012**(Taylor et al., 2017; Fleischmann et al., 2019).** Following its approval, the FDA required a post-marketing surveillance study to assess safety, including malignancy risks. In the ORAL Surveillance trial, an open-label RCT comparing tofacitinib with TNF inhibitors in adults over 50 years with RA, non-inferiority criteria for malignancies and major adverse cardiovascular events were not met **(Ytterberg et al., 2022).**

During a median follow-up of 4 years, a higher incidence of adjudicated malignancies (excluding non-melanomatous skin cancers) was found with tofacitinib (4.2% of patients) compared to TNFi (2.9%; HR 1.48; 95% CI 1.04 to 2.09). Non-melanomatous skin cancer incidence was also higher with tofacitinib (2.2% vs 1.1% for TNFi). The most common cancers reported were lung cancer for tofacitinib and breast cancer for TNFi. However, it remains uncertain whether the ORAL Surveillance trial results can be generalized to other JAK inhibitors, diseases, or populations, particularly those under 50 years without additional cardiovascular risk factors; where malignancy frequency is lower **(Curtis et al., 2023).**

II. Sexual quality of life

II.1.Definitions

II.1.1.Sexuality

Sexuality is a person's ability to experience or express sexual feelings. It is unique to every person and does not exist alone: it is a part of the bio psychosocial perspective. Moreover, it is a broad term that affects a person in many ways and is affected by biological, physical, social, erotic, and spiritual dimensions **(Graugaard et al., 2019).** The motive for sexual activity is both complex and unpredictable. Sexuality is part of human life and has different purposes, such as reproduction,

feelings of love, relief of tensions, intimacy, relations between people, and respect of people's own and other boundaries. Sexuality can also be used as a component of rehabilitation, recreation, and relaxation **(Graugaard et al., 2019; Greenberg et al., 2016).** Every person is a sexual being, but sexuality in terms of how it affects the body and intimacy has varied over time and has been influenced and affected by cultural and value systems. One of the key points in maintaining QOL, as defined by the World Health Organization, is sexuality, defined as:

'… A central aspect of being human throughout life encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships. While sexuality can include all these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, legal, historical, religious and spiritual factors' **(WHO, 2006b).**

Human sexuality encompasses a network of feelings that is unique for every person. This unique feeling is built by a person's individual experience and inherent properties. Sexuality is affected by biological, psychological, socio-cultural, moral, spiritual, and ethical and legal factors. How this network is composed on the individual level is unknown **(Almås & Benestad, 2010; Graugaard et al., 2019; Greenberg et al., 2016).**

II.1.2.Sexual health

Sexual health is an important part of overall health, consisting of psychological, physiological, moral, and cultural aspects **(Greenberg et al., 2016).** Because all individuals are sexual beings and sexuality is part of the individual identity, sexual health concerns everyone **(Greenberg et al., 2017; Greenberg et al., 2016).** A definition of sexual health was given in 2006 by the WHO **(WHO, 2006a).**

'… A state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual

relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination, and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled.'

Sexual health is a relatively new concept and was first taken into the International Statistical Classification of Disease and Related Health Problems in 2019 **(Epstein, 2021).**Helland et al. (2013) found that health personnel accepted sexual health as an important issue for patients and relevant for health care in the field of rheumatology. At the same time, they identified some barriers to addressing sexual health, such as the feeling of being uncomfortable with the topic and lack of knowledge and education on how to address sexual health issues**.**

II.1.3.Sexual activity

Sexual activity is considered to be an important part of sexual health, health, HRQOL and SQOL. Sexual activity is influenced by personal characteristics, interpersonal relationships, family circumstances, socio-cultural conditions, environment, physical and mental health and hormonal status **(IsHak, 2017).**Furthermore, physical difficulties **(Fu et al., 2019; Yao et al., 2016),** fatigue, and sleep disturbance **(Rostom et al., 2013),** can influence sexual activity negatively. The frequencies of sexual activity and level of intimacy might change in different phases of life, decreasing with ager. Moreover, sexual activity might be affected by a person's view of their body, having a partner, culture and society **(Sexologi, 2019).**

II.1.4.Sexual quality of life

Sexual QOL is defined as the status that describes the individual's subjective evaluation of the positive and negative aspects of one's sexual relationship, and his/her subsequent affective response to this evaluation **(Koh & Sewell, 2015).** It includes both sexual health and sexuality involving communication, culture, ethical, and global areas **(Graugaard et al., 2019; Greenberg et al., 2016).** To have a fulfilling sex life is important for sexual QOL at all ages. Forbes et al. found that being older was a negative factor for sexual QOL, but learned strategies—also called sexual wisdom—together with a positive relationship with a partner was positive for

sexual QOL **(Forbes et al.,2017).** Therefore, measuring sexual QOL is an important issue for assessing short- and long-term outcomes of disease, especially when having a disease that can cause sexual problems **(Hwang et al., 2021; Symonds et al., 2005).** To have good sexual QOL and satisfactory HRQOL, it is important to focus on both subjective and objective perspectives associated with axSpA, such as demographic and clinical variables, functional status, damage, comorbidity, the disease impact on sexual activity and sexual QOL**(Spilker, 1996).**However, better disease control and a treat to target approach of the patients might imply less pain and better physical function and thereby influence HRQOL, SQOL and sexual activity positively **(Dagfinrud et al., 2004)**

II.2.Measures of sexual quality of life

II.2.1.15D questionnaire

Item 15 in the 15D questionnaire was used to study the effects of health status on sexual activity .Item 15 addresses the effects of health on sexual activity with the following response options **(Rohde et al., 2025).**My state of health:

1. … has no adverse effect on my sexual activity;

2. … has a slight effect on my sexual activity;

3. … has a considerable effect on my sexual activity;

4. … makes sexual activity almost impossible;

5. … makes sexual activity impossible.

II.2.2.Sexual quality of life-Female questionnaire (SQOL-F)

In 2005, Symonds, Boolell, and Quirk developed the SQOL-F, based on the work of Abraham and co-workers, which again was based on Spitzer's QOL measure. The SQOL-F is a generic self-reporting questionnaire for assessing the relationship between female sexual dysfunction and QOL**.**The questionnaire can also be used for partners and male partners with minor modifications**.**It comprises 18 positive and negative items, rated on a 6-point response: completely agree, moderately agree,

slightly agree, slightly disagree, moderately disagree, and completely disagree. The response categories are scored 1–6, giving a total score range of 18–108. A higher score indicates better sexual QOL **(Symonds et al., 2005)** except for sexual and relationship satisfaction, for which a low score indicates better SQOL **(Berg et al., 2019).**The questionnaire has shown good psychometric properties according to convergent validity, discriminant validity, and test–retest validity **(Symonds et al., 2012; Symonds et al., 2005).** To our knowledge, no other studies has used SQOL-F in patients with axSpA but used other questionnaire on SQOL **(Donget al., 2015).**

Maasoumi et al. (2013) translated SQOL-F into Persian and identified four categories: psychosexual feelings (range 7–42), sexual and relationship satisfaction (range 5–30), self-worthlessness (range 3–18), and sexual repression (range 3–18). These reflect various aspects or dimensions of sexual QOL and showed good psychometric properties in the Iranian population.

II.3.Impact of Ankylosing Spondylitis on Sexual quality of life

Ankylosing spondylitis significantly affects patients' sexual quality of life, with long-term effects often linked to perceptions of health status **(Rohde et al., 2025).** Sexual activity plays a vital role in human relationships, serving purposes such as pleasure, bonding, affection, and reproduction **(Graugaard et al., 2019).** While few studies have specifically examined the impact of health status on sexual activity in individuals with axSpA, it has been reported to have a negative effect **(Fu et al., 2018; Gallinaro et al., 2012; Rostom et al., 2013; Yao et al., 2016).**In a study of axSpA patients with a mean age of 46 years (33% women), approximately 18% indicated that their health status significantly impacted their sexual activity **(Hansen Berg, 2022).** The use of NSAIDs to manage disease activity, including pain, stiffness, and fatigue, may create physical challenges during sexual activity **(Rostom et al., 2013; Fu et al., 2019; Yao et al., 2016).** These findings highlight the importance of addressing sexual health in managing ax-SpA, as sexual activity and sexual quality of life are closely related to physical, mental, and social health factors. A comprehensive treatment approach that considers these aspects may improve the sexual quality of life for patients with ankylosing spondylitis **(Rohde et al., 2025).**

II.4.Reproductive health in women with ankylosing spondylitis

II.4.1.Contraception in women with ankylosing spondylitis

Effective contraception in women with rheumatic disorders is critical to prevent unintended pregnancies that may worsen disease activity and lead to unfavorable outcomes, such as pregnancy loss and severe preterm **(Sammaritano et al., 2020).** To reduce flare-ups, the illness must be in remission for a minimum of six months prior to trying to conceive **(Tedeschi et al., 2015).** Estrogens and inflammation in rheumatic disorders have a complicated interaction. Estrogen has the ability to reduce inflammation, but its metabolites might do the exact opposite. In diseases such as rheumatoid arthritis and systemic lupus erythematosus, elevated estrogen metabolites have been found in synovial tissue, suggesting a connection to disease activity. Oral contraceptive tablets are considered safe for women with ankylosing spondylitis , and they have no discernible effect on the onset or severity of AS **(Mahendira et al.,2014).**In addition to providing contraception, combined estrogen-progestin pills also affect bone density, which is important considering that osteoporosis and fractures are very common in AS (34.4% and 24.6%, respectively) **(Ramírez et al.,2018).** Examining the patient's personal and family medical history is crucial before prescribing estrogen-progestin medication. This includes taking into account diseases including thrombophilia, cardiovascular problems, hormone-sensitive malignancies, and other pertinent conditions **(FSRH,2019).**Alternative forms of contraception, like intrauterine devices, may be suggested if difficulties are evident, and the advantages and disadvantages of systemic estrogen-progestin hormone therapy should be evaluated**(Figure15).**

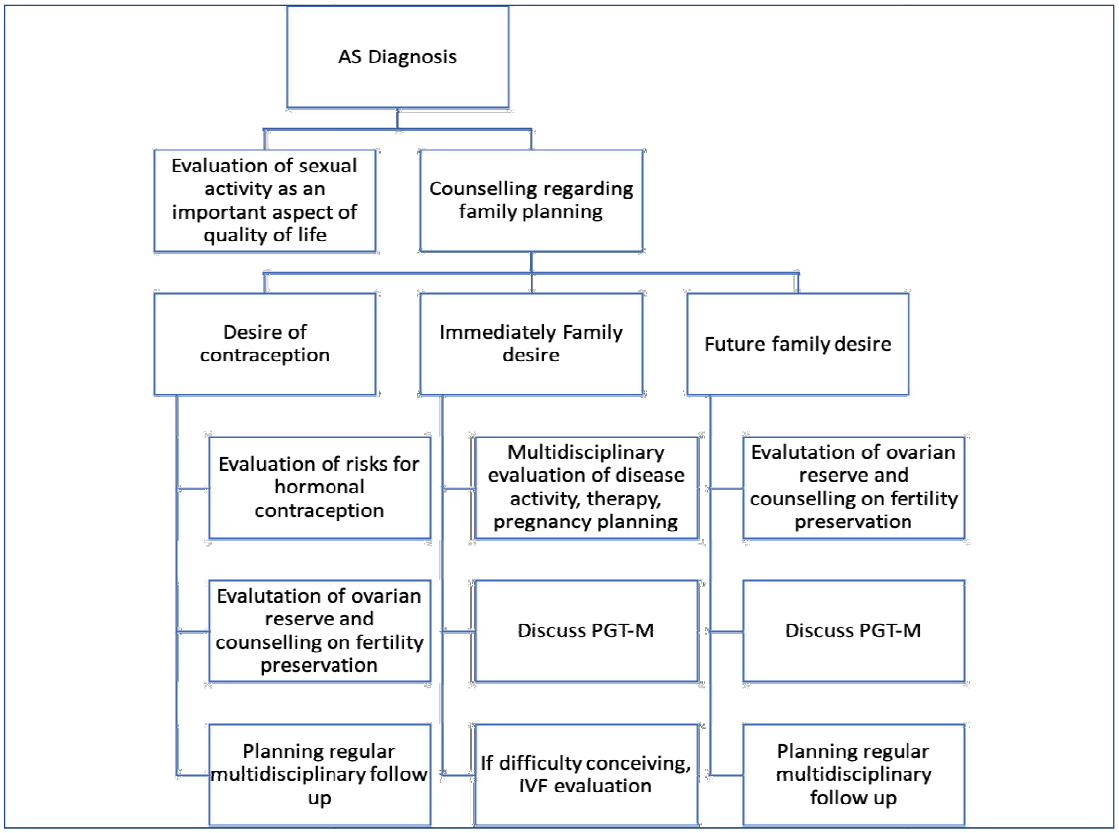

Figure 15: Flowchart of reproductive health management in women with ankylosing Spondylitis.AS, ankylosing spondylitis; PGT-M, preimplantation Genetic testing for Monogenic defect; IVF, in vitro fertilization **(Marin& Andrisani, 2024).**

II.4.2.Fertility in women with ankylosing spondylitis

There is a dearth of research on the relationship between AS and fertility; the little information that is available is of low quality and comes from studies that have limitations **(Ostensen& Ostensen, 1998; Ciurea&Finckh, 2013),** despite the fact that nulliparity is much higher in these women. Using a questionnaire administered in 13 countries, Ostensen et al. examined fertility in women with AS in 1998. They found no evidence of decreased fertility, but there was a lack of a healthy control group **(Ostensen& Ostensen, 1998)**. Since then, there have been significant changes in the diagnostic capabilities and proposed treatments for AS.A number of research **(Ostensen& Ostensen, 1998; Wallenius et al., 2011)** have not consistently examined factors that impact fertility, including partner characteristics, ovarian reserve, smoking, body mass index, and associated disorders. Compared to birth-year-matched references, a greater percentage of women with AS were childless; however, the

enrolled women were not questioned about their desire for a child **(El Hasbani et al.,2024).**Pregnancy chances may be impacted by an illness that reduces sexual activity.A lady with AS who developed early ovarian insufficiency was reported in a 2008 case study **(Aslanidis et al.,2008).**Pregnancy may be hampered by AS treatment; non-steroidal anti-inflammatory drug use is common in women with high disease activity, and this might have an adverse effect on ovulation and implantation **(Ying et al.,2022;Sammaritano&Bermas,2018).**Infertility caused by luteinized unruptured follicle syndrome has been linked to the usage of COX-2 inhibitors **(Gaytán et al.,2006).** Given the well-established risk of miscarriage associated with NSAID usage, women with AS may want to wait for remission before attempting to conceive **(Ying et al.,2022;Sammaritano&Bermas,2018).**The urge to conceive may also be limited by worries that the sickness may be passed on to the offspring.Following genetic counseling, preimplantation genetic testing for monogenic disorders, including HLA-B27, and the potential for assisted reproductive procedures should be explored **(Verlinsky et al.,2004;De Rycke et al.,2020).** The time between pregnancies increases when AS is diagnosed after the first birth since there is sometimes a delay in getting pregnant again **(El Hasbaniet al., 2024).** The pathology's severity, the type of treatment, the stabilization period, and the interval between diagnosis and pregnancy should all be taken into account during family planning conversations. Shorter menstrual cycles, rapid follicular depletion, and an earlier menopausal age are all consequences of smoking's dose-dependent detrimental effects on fertility **(Practice Committee of the American Society for Reproductive Medicine, 2018; de Angelis et al., 2020).**

II.4.3.Fertility preservation in women with ankylosing spondylitis

Counseling for possible conception problems is necessary at diagnosis for women with ankylosing spondylitis, as they may have a diminished ovarian reserve **(Alexander et al.,2021;Aslanidis et al., 2008).**It is best to schedule a pregnancy while the illness is in remission **(Chimenti et al.,2021; Somers,2020;Sammaritano& Bermas,2018).** Prolonged treatment for remission may exacerbate low ovarian reserve **(Barbieri et al., 2023; Park et al., 2021).** For postpubescent women, cryopreservation of oocytes and embryos is a proven fertility preservation technique. The selection of preservation methods, which also rely on

individual and cultural preferences, may be influenced by legal constraints**.** Oocyte cryopreservation is frequently more appropriate because of the possibility of relationship instability, especially since many women with AS are diagnosed in their 30s **(Marin et al., 2022).**Since December 2019, the American Society of Reproductive Medicine has acknowledged ovarian tissue cryopreservation and transplanting as a non-experimental method of fertility preservation **(Practice Committee of the American Society for Reproductive Medicine, 2018; de Angelis et al., 2020).** Systemic rheumatic disorders can cause primary ovarian insufficiency (POI), and ovarian tissue transplantation may help you regain your fertility and endocrine function **(Oktay et al., 2022).**The effectiveness of this procedure hinges on developments in cryopreservation and transplantation techniques. The freezing-thawing procedure and post-reimplantation ischemia usually cause approximately two-thirds of the follicles to be lost **(Oktay et al., 2022; Marin et al., 2020).**Women with AS should seek fertility preservation at specialized centers with a multidisciplinary approach. Cooperation between rheumatologists and gynecologists with experience in reproductive medicine is essential for optimizing fertility preservation strategies and minimizing patient risk. One important question is whether the removal of an ovary affects reproductive lifespan equal to the duration of endocrine function after autotransplantation **(Oktay et al., 2021).**

III.Strategies and interventions to improve the HRQOL and SQOL

III.1.Health related quality of life

a).Education programs

Patient education is a vital component in the management of rheumatic and musculoskeletal illnesses. It can be defined as “any set of planned educational activities designed to improve patients’ health behaviors, and through this, their health status and ultimately long-term outcomes” **(Hill, 1997).** Patient outcomes, such as disease activity, functional ability, and quality of life, may be improved by education programs that give patients the tools they need to manage their rheumatic condition **(Ramos-Remus et al.,2000;Nikiphorou et al.,2021).**In recent years; European Alliance of Associations for Rheumatology has provided guidelines to help healthcare professionals integrate education into patients’ management**(Nikiphorou et al.,2021;Zangi et al.,2015).**When a patient is diagnosed, when pharmacological

treatment is started or modified, and whenever the patient's physical or mental health demands it, patient education should be given**(Zangi et al.,2015).**To maximize effectiveness, education should include information about the disease process (diagnosis, symptoms, and prognosis), its management (risks and benefits of each treatment option, self-management, comorbidities) and function-social aspects (daily activities, ergonomic advice, community involvement, lifestyle changes)**(Nikiphorou et al.,2021;Ritschl et al.,2021;H&C,2017;Passalent& SO,2016).**Education can be delivered through written materials, multimedia formats, or spoken communication (in person, online, or over the phone)(**Ritschl et al.,2021**; **Zangi et al.,2015).**A multidisciplinary team, HPs, or trained patients are examples of providers offering education**(Zangi et al.,2015).**Crucially, education needs to be customized for every patient. The usefulness of patient education has been documented in a number of trials, mostly involving patients with rheumatoid arthritis (**Carnes et al., 2012**; **Riemsma et al., 2003**).However, the evidence is still conflicting. Programs for education that are conducted in groups seem to be more successful than those that are conducted alone. Shorter courses (defined as < 8 weeks) and those led by HPs also exhibit greater results **(Carnes et al., 2012).**However; there is currently no evidence of long term advantages **(Riemsma et al., 2003).** Additionally, there is a lack of knowledge about axial spondyloarthritis patients' education. A recent comprehensive review of the literature on the safety and effectiveness of non-pharmacological and non-biological pharmacological treatments showed that non-pharmacological interventions **(Regel et al.,2017)**were beneficial, especially when administered by health professionals utilizing printed materials like pamphlets**(Brites et al.,2024).**

b).Social media

The internet has become a vital source of health information, particularly for patients with rheumatic diseases like ankylosing spondylitis .With the growing use of online resources, many individuals turn to the internet to better understand their chronic conditions **(Simoncic et al., 2014).** Social media platforms have emerged as significant tools for increasing disease awareness and facilitating patient support. A study by Shen et al. (2016) highlights those patients with AS are eager to utilize online resources for this purpose**.** Furthermore, social networks provide valuable support for health-related coping and social interactions **(Onen et al., 2008).**A 2024 cross-sectional study involving 155 Turkish AS patients found that most participants

owned at least one internet-connected device and regularly used social media platforms, particularly Facebook and WhatsApp. Many utilized these platforms for health-related inquiries, which positively influenced their mental health by alleviating depression symptoms **(Uslu et al., 2024).**

III.2.Sexual quality of life

Addressing sexual concerns is important to sexual QOL. One useful method is to implement a model for communication such as the Permission, Limited Information, Specific Suggestions, and Intensive Therapy model (PLISSIT). When asking patients to participate in a study of sexual activity and sexual QOL, HPs need to give patients the permission to talk about such topics. Giving permission is the first step in the PLISSIT model **(Annon, 1976; de Almeida et al., 2019).** However, by inviting patients to participate in a study, HPs acknowledge that sexual activity and sexual QOL are important subjects to address. Giving patients the opportunity to express their concerns about and thoughts on their sexual activity and sexual QOL is part of the recognition of the patient as a whole person and not just a person with a disease. As seen in a Norwegian study, HPs in rheumatology with more knowledge and education about sexuality addressed sexual issues more frequently **(Helland et al., 2013).** The PLISSIT is a good tool for structuring patient–HP conversations and may render HPs more confident in discussing sexual activity and sexual QOL, which may be a sensitive area for both people.

The goal for medical treatment for patients with axSpA is to reduce disease activity, obtain remission, and improve and maintain flexibility in the spine to produce a normal posture and reduce functional limitations **(Strand & Singh, 2017).** Combining treatment strategies, implementing management programmes, and including patients in the decision-making may help to reduce disability and improve HRQOL **(Smolen et al., 2018; van der Heijde et al., 2017).** Maintaining the ability to work and reducing other complications related to the disease, such as comorbidities, are also important **(Nikiphorou & Ramiro, 2020).** These factors all influence the overarching goal of supporting QOL, including HRQOL and sexual QOL.

Conclusion

Conclusion

In conclusion, ankylosing spondylitis (AS) is a complex and multifaceted autoimmune disease that poses significant challenges for patients and healthcare providers alike. Through this dissertation, we have explored the various causes and risk factors associated with AS, highlighting the intricate interplay between genetic predispositions, environmental influences, and immune system dysfunction. Understanding these factors is crucial for improving early diagnosis, developing effective intervention strategies, and ultimately enhancing patient outcomes.

With the observation of World Ankylosing Spondylitis Day on May 3rd, it is imperative to raise awareness about this often-overlooked condition. This day serves as a platform to educate the public, healthcare professionals, and policymakers about the prevalence and impact of AS. It emphasizes the importance of recognizing the symptoms early and seeking appropriate care to manage the disease effectively.This year's theme, **"Lace Up for axSpA",** encourages both awareness and action.

The imagery of lacing up symbolises the active effort needed to understand what it's like to live with axSpA illustrating the daily challenges faced by those living with axSpA. Even a seemingly simple task like tying shoelaces can become a significant hurdle for individuals experiencing the pain and limited mobility associated with this condition.Where,even a seemingly simple task like tying shoelaces can become a significant hurdle for individuals experiencing the pain and limited mobility associated with this condition.

As we continue our research and advocacy efforts, we must focus on promoting a greater understanding of AS and its associated factors. By doing so, we can foster a supportive environment for individuals living with AS and contribute to the global movement aimed at enhancing their quality of life. Together, we can make significant strides in addressing the challenges posed by ankylosing spondylitis and work towards a future where effective treatments and preventive measures are readily available for all those affected.

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