Journal of Research and Practice on the Musculoskeletal System JRPMS

Review Article

Bone Disease in Autoimmune Rheumatic Diseases Among Young Adults: A Comprehensive Review

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Abstract

Autoimmune rheumatic diseases (ARDs) encompass a diverse array of conditions with varied clinical manifestations affecting multiple body systems. Among young patients with ARD, the most common bone disorders are avascular necrosis (AVN) and osteoporosis. ARDs and glucocorticoid use pose major risk factors for AVN and osteoporosis in this population. Unexplained hip pain should raise suspicion of AVN, warranting further investigation, such as MRI. While traditionally associated with older individuals, osteoporosis should not be overlooked in young adults with ARDs. Assessing fracture risk and implementing appropriate management strategies are crucial. Early recognition and tailored treatment are essential for preserving quality of life. ARDs and glucocorticoid use increase osteoporosis risk. Premenopausal women with conditions like rheumatoid arthritis may experience a 17.1% decrease in femoral neck BMD. Similarly, patients with spondyloarthritis exhibit high osteoporosis rates. Diagnosing and managing osteoporosis in young adults remain challenging, highlighting the importance of fracture prevention. Guidelines offer recommendations for preventing, monitoring, and treating glucocorticoid-induced osteoporosis. Considering prevention, early recognition, and appropriate treatment are vital during the clinical evaluation of young adults. Addressing these aspects improves outcomes and mitigates skeletal comorbidity in ARDs.

Keywords: Avascular necrosis, Autoimmune rheumatic diseases, Osteoporosis, Glucocorticoids

Introduction

Autoimmune rheumatic diseases (ARDs) encompass a heterogeneous group of conditions, characterized by a diverse range of clinical manifestations affecting multiple systems. The severity of these diseases varies significantly, ranging from mild to extremely severe. Depending on the specific disease, different age groups may be affected, with certain disorders like Systemic Lupus Erythematosus (SLE) predominantly affecting young adults. It is important to recognize that many of these ARDs, including Rheumatoid Arthritis (RA) and SLE, carry an elevated risk of complications such as avascular necrosis (AVN) and osteoporosis. This heightened risk arises from both the inherent nature of the disease and the employed treatment regimens, such as the use of glucocorticoids (GCs) as part of the therapeutic approach[1,2].

The pathogenic mechanisms underlying rheumatic diseases and their impact on the musculoskeletal system are diverse and complex across all age groups. For instance, in rheumatoid and psoriatic arthritis, the RANKL/RANK (receptor activator of nuclear factor kappa-B ligand – RANKL/ receptor activator of nuclear factor kappa-B – RANK) signaling pathway appears to play a pivotal role in the development of these autoimmune conditions. Normally, this pathway is crucial for the proper differentiation of osteoclasts during the physiological process of bone remodeling[3].

The authors have no conflict of interest.

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Edited by: *George Lyritis*

Accepted *15 February 2024*

However, in the progression of several autoimmune diseases, it has been observed that the production of RANKL extends beyond the conventional bone-lining cells derived from the osteoblast lineage. Significantly, within the inflammatory lesions, a diverse array of cells including activated T-cells, synovial fibroblasts, and TRAP (tartrate-resistant acid phosphatase) – positive osteoclasts[1] are found to produce RANKL in addition to the normal bone-lining cells.

This aberrant production of RANKL by multiple cell types within the inflamed joint underscores the intricate interplay between immune and skeletal systems in autoimmune diseases. Further research is necessary to fully elucidate the precise mechanisms and interactions involved in these processes, offering potential therapeutic targets for the management of these conditions.

In the context of seronegative spondyloarthropathies, including reactive arthritis, ankylosing spondylitis, juvenile-onset ankylosing spondylitis, arthritis and spondylitis associated with inflammatory bowel disease or with psoriasis, and undifferentiated spondyloarthropathy, the inflammatory processes are characterized by distinct lesions occurring at the entheses. Entheses refer to the connective tissues that link ligaments or tendons to the bone. These lesions often result in new bone formation and have been associated with elevated levels of bone morphogenetic proteins-2 and -6 (BMP-2 and BMP-6) within the circulation[4].

Furthermore, one notable hallmark of the pathophysiology observed in almost all autoimmune diseases is the involvement of both the appendicular and axial skeleton, leading to significant bone loss. This intricate process involves various cytokines and molecular factors, including serum osteoprotegerin (OPG), RANKL, and tumor necrosis factor-α (TNF-α), which collectively influence the expression, differentiation, function, and survival of osteoclasts both *in vivo* and *in vitro*. However, the specific underlying mechanisms of these interactions have yet to be comprehensively elucidated[1].

Systemic lupus erythematosus (SLE), one of the most prevalent autoimmune rheumatic diseases, exhibits a distinct characteristic of affecting the skeletal system in addition to other organs and systems. Among the skeletal complications observed in almost all SLE patients are osteoporosis, AVN, and terminal tuft resorption. The etiopathogenesis of these pathological conditions involves a combination of various factors, including chronic and systemic inflammation, nutritional factors, adverse effects of medications used for disease management, and reduced physical activity in patients[5].

Notably, young patients suffering from different autoimmune rheumatic diseases are particularly susceptible to two significant bone disorders: AVN and osteoporosis. This narrative literature review aims to present recent research findings on the pathogenetic mechanisms, progression, and treatment strategies for these two bone diseases specifically within this age group of patients affected by autoimmune rheumatic diseases. By examining the current evidence, we can gain insights into the complex interplay between these conditions and develop improved management approaches for these young individuals.

Avascular Necrosis

Avascular necrosis (AVN), is characterized by the death of bone tissue caused by insufficient blood supply or cytotoxic agents[6]. While it can occur at any age, it most commonly affects individuals between 30 and 65 years old[7]. Although any bone can be affected, AVN tends to occur primarily at the ends of long bones, such as the femur, particularly the femoral head, femoral condyles, and humeral head[8].

The clinical presentation of AVN can vary. The presence and severity of symptoms depend on factors such as the size of the affected area, its location, stage of progression, and any coexisting conditions. The primary symptom is pain, often accompanied by functional impairment of the joint in cases of more advanced disease. However, it is worth noting that avascular necrosis can sometimes remain asymptomatic, particularly in Ficat stages I and II[9].

In contemporary practice, magnetic resonance imaging (MRI) has become the preferred imaging modality for diagnosing AVN due to its superior sensitivity compared to plain radiography (X-ray), which often demonstrates lesions at a later stage[10]. It is advisable to include MRI in the evaluation of young patients experiencing hip pain without apparent causes and normal X-ray findings[10]. MRI provides distinct characteristics for each stage of FICAT disease, including the notable "double-line sign" observed in FICAT stage III. This sign manifests as a well-defined and homogeneous focal lesion, with a T1 sequence demonstrating a line that separates the healthy bone from the ischemic region, and a T2 sequence showing a high-density line[7]. Additional imaging modalities that can be employed include computed tomography (CT), which can aid in early detection of sclerosis at the center of the femoral head, and bone scintigraphy, particularly valuable in the initial stages of the disease and for lesion mapping[9]. For staging purposes, the Ficat and Arlet classification system is commonly utilized, incorporating clinical findings, radiographic observations, and MRI findings. This classification system encompasses five stages, ranging from stage 0 to stage 4[7] (Table 1).

AVN is a commonly observed complication in various rheumatic diseases, particularly in SLE and RA. Its occurrence may be linked to factors such as small vessel vasculitis, the presence of antiphospholipid antibodies, and the use of corticosteroids[1]. In patients with SLE, avascular necrosis is more frequently observed in women[7]. According to Tektonidou and Moutsopoulos (2004)[2], the reported prevalence of AVN in young adults with autoimmune rheumatic diseases, particularly systemic lupus erythematosus (SLE), ranges from 5% to 40%, with the majority of cases necessitating surgical intervention. While

Stages	Clinical Symptoms	X-rays	Scintigraphy	Pathological Findings	Histology
0	None	Normal	Decreased uptake		
I	None/Mild	Normal	Cold areas on the femoral head	Infarct of the weight-bearing surface of the femoral head	Abundance of dead bone marrow cells, osteoblasts
II	Mild	Change in femoral head density	Increased uptake	Automatic repair of the bone infarct areas	Deposition of new bone between necrotic trabeculae
IIA		Sclerosis or cysts, Normal articular line and contour of the femoral head	Increased uptake		
IIB		Flattening of the femoral head			
III	Mild to Moderate	Loss of the femoral head sphericity, Collapse	Increased uptake	Subchondral fracture, Collapse, contusion, necrotic fragmentation	Necrotic trabeculae and bone marrow cells on both sides of the fracture line
IV	Moderate to Severe	Medial Joint Space Narrowing, acetabular changes	Increased uptake	Osteoarthritic changes	Degenerative changes of the acetabular cartilage

Table 1. Ficat and Arlet classification system for avascular necrosis of the femoral head[7].

the exact primary causative factor for AVN in this population remains unclear, several factors have been implicated in its pathophysiology:

- Vasculitis, particularly in the context of SLE.
- The use of corticosteroids is significant determinant of AVN occurrence and severity. Several crucial factors come into play, including the dosage and duration of GC therapy, the cumulative amount administered to the patient, the application of intra-arterial injections, and the intricate genetic variations present within pivotal genes such as vascular endothelial growth factor (VEGF), glucocorticoid receptors (GR), 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), collagen type 2 (COL2A1), plasminogen activator inhibitor-1 (PAI-1), and P-glycoprotein. Furthermore, the presence of certain comorbidities such as inflammatory bowel disease and Human Immunodeficiency Virus (HIV), as well as the use of dexamethasone (in comparison to prednisone), contribute to the increased risk of AVN[11].
- Hyperlipidemia.
- Fat embolism.
- Leucopenia.
- Raynaud's syndrome.
- Antiphospholipid antibodies and antiphospholipid syndrome: Antiphospholipid antibodies often coexist with rheumatic diseases, including SLE. These antibodies have been associated with thrombosis in vessels of various organs, independent of vessel size[12]. In the case of AVN, their pathogenic role is attributed to thrombotic microvasculopathy affecting the terminal bone arteries. Asymptomatic AVN has been observed in up to 20% of individuals with antiphospholipid syndrome[13]. Notably, the incidence of AVN is higher in younger patients, as well as in those presenting with livedo reticularis, a common skin manifestation in antiphospholipid syndrome, resulting from reduced blood flow in arterioles and concurrent dilatation of capillaries and venules. These various factors collectively contribute to the complex pathogenesis of AVN in young adults with ARDs, including SLE. Understanding the interplay of these factors can aid in early detection, risk assessment, and appropriate management strategies for individuals at risk of AVN.

In a recent retrospective case-control study conducted by Wei et al. (2022)[12], the investigation focused on identifying potential risk factors for AVN of the femoral head in 22 patients with rheumatoid arthritis. The study yielded significant findings, highlighting the following risk factors associated with the development of AVN: 1) Hyperlipidemia, 2) Simplified Disease Activity Index (SDAI) at disease onset, 3) Clinical Disease Activity Index (CDAI) at disease onset, and 4) Concentration of anti-cardiolipin antibody (ACL-IgG).

The treatment approach for AVN is determined based on the stage and location of the necrotic lesions. Non-surgical interventions aim to alleviate symptoms and halt disease progression. These include joint unloading techniques, administration of vasodilators, bisphosphonates,

Table 2. Summary of recent studies assessing therapeutic interventions for avascular necrosis of the hip joint (Pt: patients, mo: months, yr: years).

Author	Therapy	No. of pt	Mean Age (yr)	Stage of disease	Mean Follow-up	Survival (%) (no radiographic progression or need for surgery)	Comments
Gianakos et al., (2016)[15]	Bisphosphonate	29 (40 hips)	43±12.1	Ficat stage I or II	25.3±11.5 mo	47.5%	Hip AN
Lai et al., (2005)[16]	Bisphosphonate (alendronate 70mg per os / week) vs conservative	40 (20/20)	42.6/42.4	Steinberg stage-II or III	24-28 mo	93.3%	Results: Bisphosphonate> conservative Hip AN
Chen et al., (2012)[17]	Bisphosphonate (alendronate 70mg per os / week) vs conservative	52 (26/26)	48.4 ±11.4 / 44.2 ±9.2	Stage IIC or IIIC according to University of Pensylvania system	2 years		Results: Bisphosphonate= conservative Hip AN
Lee et al., (2015)[18]	Bisphosphonates (zoledronate 5mg iv per year)	110 (55 zoledronate / 55 placebo)	43.8 ± 11.8/ 45.2 ± 11.6	Steinberg stage-I or II	2 years	47.3%	Results: Bisphosphonate= conservative Hip AN
Koren et al., (2015)[19]	Hyperbaric oxygen therapy	68	43.3 ± 11.7	Steinberg stage I and II	11.1±5.1 years	93%	Hip AN
Albers et al., (2015)[20]	Acetylsalicylic acid	10	52.9 ± 5.3	Ficat stage II	44.4 ± 21.6mo	91.7%	Hip AN
Xie et al., (2018)[21]	Extracorporeal shock wave therapy	31 (44 hips)	41.2	Stage I, II and III according to the ARCO classification	130.6mo	81%	Hip AN clinical success: 87.5% in ARCO stage I, 71.4% in ARCO stage II, 75.0% in ARCO stage III
Wang et al., (2009)[22]	Extracorporeal shock wave therapy	39 (15 SLE pt / 24 control)	32.33 ± 8.97 / 36.47 ± 8.95	Stage I, II and III according to the ARCO classification	minimum of 24-month	88% (SLE pt)	Results: SLE pt = control Hip AN
Nazal et al., (2019)[23]	Core decompression (CD)	8 (11 hips)	36.4±9.2	Ficat stage 0, I, IIa, and IIB	7 years ±1.48	54.5%	Hip AN
Kang et al., (2018)[24]	Core decompression+ mesenchymal stem cell (MSC) implantation (BMMSC) vs CD	100 (106 hips)	46.7	ARCO stage I-IV	4.28 years	71.7%/ 51%	Hip AN
Yildiz et al., (2018)[25]	Non-vascularized bone grafting	21 (28 hips)	33.2	Steinberg stage I-IV	5 years		Results: no radiological progression identified in 71% Hip AN Lightbulb technique used
Woo et al., (2014)[26]	Total Hip Arthroplasty (THA)	13 with SLE (19 hips / 19 non-SLE	41.3 ± 12.5 / 58.1 ± 10.4	Ficat stage III or IV	97.8 mo		Results: SLE = non-SLE, THA is an acceptable treatment for SLE patients Hip AN

acetylsalicylic acid, statins, anticoagulants and hyperbaric oxygen therapy Surgical treatment options are contingent upon the stage of necrosis. For cases in Ficat stages up to 2, where there is no subsidence of the articular surface, joint preservation techniques can be employed. This may entail decompressing the area of AVN through drilling and the potential use of a bone autograft, such as a vascularized pin or tantalum screw. Another viable option is the Mont Trap Door technique, which involves placing a bone graft subchondrally to promote healing and restore joint integrity[14]. In more advanced stages characterized by subsidence of the articular surface and osteochondral fractures, arthroplasty emerges as the most suitable solution, offering the potential for functional improvement and pain relief through joint replacement. Table 2 summarizes recently published original clinical studies on the effectiveness of various types of therapeutic interventions (both conservative and surgical) for the treatment of AVN of the hip joint.

In conclusion, AVN represents a serious and prevalent issue among patients with rheumatic diseases, particularly those in younger age groups, with reported incidence rates of up to 40%. Despite substantial scientific research conducted in recent years, the precise pathophysiological causes of AVN have not yet been fully elucidated. Multiple factors have been implicated, including long-term corticosteroid use in the treatment of autoimmune rheumatic diseases, disturbances in intravascular blood flow leading to increased coagulation and local vascular damage, hyperlipidemia, atherosclerosis, and the presence of antiphospholipid antibodies. It is speculated that the pathogenesis of AVN involves a complex interplay of various factors rather than a single causative agent.

Therefore, early identification of potential risk factors for disease development and the diagnosis of patients in the early asymptomatic stage of AVN are of paramount importance. Additionally, it is worth noting that there are currently no specific guidelines for the treatment of AVN in young patients with ARD. The treatment approach primarily depends on the site and stage of the disease's progression. Further research is needed to advance our understanding of the pathophysiological mechanisms and optimize treatment strategies for this specific patient population.

Osteoporosis

Osteoporosis is a systemic, chronic disease characterized by reduced bone strength and a susceptibility to low-energy fractures. The risk of developing osteoporosis rises with age and primarily affects postmenopausal women and older men. However, it can rarely manifest in young adults, specifically premenopausal women and men up to 49 years of age[27,28]. In these cases, osteoporosis typically arises within the context of chronic diseases or the use of certain drugs that affect bone metabolism. Examples of such drugs include those employed in the treatment of ARDs and GCs[28].

ARDs pose a significant risk for the development of osteoporosis, primarily due to the inflammatory processes and immobilization associated with these conditions. Additionally, treatment with GCs can lead to a specific form of osteoporosis known as glucocorticoid-induced osteoporosis (GIOP)[29].

Premenopausal women with RA exhibit lower bone mineral density (BMD) as compared to healthy women. A study conducted by A. Fassio et al., (2016), demonstrated that premenopausal women with RA had an 8.3% reduction in BMD in the spine and 17.1% reduction in the femoral neck, as compared to the control group[30]. Factors associated with low BMD in this population include lower body mass index (BMI), disease activity and duration, GC use (both dose and duration), reduced mobility, and the underlying disease itself[29,30]. The influence of these factors seems to be cumulative, as evident from statistical adjustments made for glucocorticoid use, body mass index (BMI), and health assessment questionnaire (HAQ) scores. Following these corrections, the observed differences in bone mineral density (BMD) diminished in the femoral head and became negligible in the lumbar spine. However, the sustained lower BMD values in the femoral head support the notion that the disease itself is associated with osteoporosis, particularly in premenopausal women. This finding suggests that rheumatic disease has an independent impact on bone health, contributing to osteoporosis development in this specific subgroup of patients.

Osteoporosis is also a common comorbidity in patients with spondyloarthritis (SpA), such as ankylosing spondylitis. Despite the less frequent use of GCs in these patients, a study by Moltó A. et al., (2016)[31], reported a high prevalence of osteoporosis, up to 13.4%, making it the most frequent comorbidity in this population. It is noteworthy that the prevalence rates of osteoporosis-related fractures in young adults with rheumatic diseases are substantially higher compared to those in healthy young adult men (5%). However, it is important to highlight that the occurrence of proximal hip and vertebral fractures remains relatively low, with rates of 0.2% and 2%, respectively. These findings indicate that while the overall prevalence of osteoporotic fractures is elevated in this population, the absolute risk for fractures in the proximal hip and vertebral regions is relatively uncommon. The presence of osteoporosis in SpA is attributed to both the disease itself and the resultant immobilization.

In SLE, elevated levels of cytokines contribute to the activation of bone resorption, leading to decreased bone density. SLE patients have double the risk of fractures, with younger age and the presence of nephritis being identified as risk factors. The presence of lupus nephritis in individuals with SLE exacerbates the impact on bone health, significantly increasing the risk of fractures by threefold compared to the general population. Furthermore, when considering age-related changes, younger patients with SLE face a 2.3-fold higher likelihood of experiencing fractures, while older

Race
Sex
Familial history of hip fractures
History of previous fractures
Significant weight loss or low body mass index (< 19 kg/m^2)
Smoking
Excessive alcohol consumption (≥ 3 units/day)
Malnutrition
Sedentary lifestyle or immobility
Medical Conditions that affect bone health (e.g. hypogonadism, secondary hyperparathyroidism, thyroid disease)

Table 3. Risk factors for osteoporosis.

patients have a 1.7-fold increased risk. These findings emphasize the importance of recognizing the additional vulnerability of SLE patients, particularly those with lupus nephritis, and the need for proactive measures to mitigate the heightened fracture risk in both younger and older age groups[32].

Patients with ARDs often require treatment with GCs, which can lead to the development of GIOP as a side effect. The risk of GIOP is dependent on the dosage and duration of GC therapy[33]. According to the guidelines provided by the European Alliance of Associations for Rheumatology (EULAR), young adults who receive a daily prednisolone dose greater than 15 mg and those with a history of fractures are at an increased risk of developing GIOP. The American College of Rheumatology (ACR) categorizes patients into low, moderate, and high-risk groups based on various factors. The low-risk group comprises individuals with no additional risk factors (Table 3), the moderate-risk group includes patients who are currently receiving or anticipated to receive a dose of ≥ 7.5 mg for ≥ 6 months and have a BMD Z-score <-3.0 at the hip or spine or a ≥ 10% loss of bone mass at these sites within the past year. Lastly, the high-risk group consists of individuals with a history of osteoporotic fractures, or receiving dose of 30mg/day or cumulative dosage of ≥5 g/year[33-35].

In contrast to the clear diagnostic criteria for osteoporosis in postmenopausal women and older men, the guidelines for diagnosing osteoporosis in young adults are less well-defined. The International Society for Clinical Densitometry (ISCD) defines a bone mineral density (BMD) threshold with a Z-score < -2, indicating lower BMD compared to the reference population[36]. On the other hand, the International Osteoporosis Foundation (IOF) defines osteoporosis as the presence of a known chronic disease affecting bone metabolism and a T-score < -2.5 in the spine or hip. In the absence of a secondary cause, a low T-score combined with a fragility fracture may suggest genetic etiology or idiopathic osteoporosis[37].

Dual-energy X-ray absorptiometry (DXA) is the gold standard for diagnosing osteoporosis. However, DXA has certain limitations in patients with ARDs. These individuals may experience fragility fractures despite having normal areal bone mineral density (aBMD) as measured by DXA[28,38]. Furthermore, diseases affecting the spine can result in falsely normal bone density measurements due to degenerative arthritis lesions or spinal arthropathies with spinal column involvement. Therefore, it is essential to also evaluate bone density in the hip[28,38].

Other imaging techniques, such as High Resolution Peripheral Quantitative Computed Tomography (HRpQCT) and heel ultrasound, have been explored for assessing osteoporosis. However, these modalities currently have limited research evidence and have not yet been widely established in routine clinical practice[28].

In young adults, clinical laboratory testing and DXA should be considered in individuals who have experienced a fragility fracture, have a chronic disease that may contribute to fracture risk, or are taking medications that increase the risk of fractures[28]. According to the guidelines provided by the ACR, individuals aged 40 years or younger who initiate GC therapy should undergo evaluation for fracture risk factors. Those who have either identified risk factors or a history of osteoporotic fractures should undergo bone density testing by DXA within 6 months of starting GC therapy. For individuals older than 40 years, the fracture risk can also be assessed using FRAX[34]. The FRAX, a fracture risk assessment tool developed by the World Health Organization, serves as a valuable resource for evaluating fracture risk. This tool utilizes individual patient models that integrate risks associated with clinical risk factors and bone mineral density of the femoral neck. By incorporating these important factors, the FRAX provides a comprehensive assessment of fracture risk, aiding in the identification and management of individuals

Table 4. Summary of recent studies assessing therapeutic interventions for osteoporosis in young adults.

Author	No	Disease	Exam	Intervention	Follow-up	Endpoint	Comment
Okomura et al., (2022)[47]	86	Young females after oophorectomy	DXA	Minodronic acid		Efficacy of minodronic acid for prevention of osteoporosis	Effective treatment after cessation of hormone therapy (HT) or in cases where HT is contra-indicated
Comninos et al., (2022)[48]	26	Healthy young males	Total and carboxylated osteocalcin levels	Kisspeptin		Kisspeptin acutely increases the bone formation marker osteocalcin but not resorption markers in healthy men	The first human evidence - both in vitro and in vivo study.
Matsumoto et al., (2020)[49]	360	Patients with glucocorticoid-induced osteoporosis (GIO)	DXA	Eldecalcitol vs Alfacalcidol	24 months	Eldecalcitol is more effective than Alfacalcidol	Eldecalcitol is a good candidate for primary prevention of GIO
Soen et al., (2020)[50]	152	Patients with GIO	DXA	Minodronate plus alfacalcidol vs alfacalcidol	24 months	Minodronate plus alfacalcidol more effective than alfacalcidol alone	Minadronate is a good candidate for primary treatment of GIO
Kyvernitakis et al., (2018)[51]	70	Premenopausal women with breast cancer	DXA	Zoledronic acid vs placebo	60 months	Zolendronic acid superior to placebo	Zoledronic acid prevents cancer treatment induced bone loss in premenopausal women
Aryaeian et al., (2016)[52]	52	Young patients with rheumatoid arthritis	Telopeptides C, osteocalcin, MMP3, PGE_2, ALK-P of bone	Conjugated linoleic acid (CLA) vs placebo	12 weeks	Statistical significant differences in telopeptides C, osteocalcin and IGF 1	CLA could benefit the bone health of young patients with ARDs
Matsuno, (2016)[53]	427	Females with rheumatoid arthritis	DXA	Denosumab vs bisphosphonates	102 weeks	Denosumab is superior to bisphosphonates	The onset of the increase of BMD after treatment with denosumab is slower in patients with RA
Mok et al., (2015)[54]	42	Females with chronic glucocorticoid use	DXA	Denosumab vs bisphosphonates	12 months	Denosumab is superior to bisphosphonates	
Cohen et al., (2015)[55]	21	Premenopausal women with idiopathic osteoporosis	DXA	Teriparatide	24 months	Substantial increase of BMD in lumbar spine, femoral neck and total hip	May require further antiresorptive treatment after the end of the treatment with teriparatide
Nisiyama et al., (2014)[56]	20	Premenopausal women with idiopathic osteoporosis	High-resolution peripheral quantitative computed tomography (HR-pQCT)	Teriparatide	18 months	Increase in trabecular volumetric BMD	Improved bone microarchitecture
Jensen et al., (2014)[57]	106	Early, active RA	DXA	Alendronate	12 months	Alendronate prevented bone loss	Alendronate did not affect the radiologic progression

who may be at higher risk for fractures[39].

In a large retrospective study conducted by Lai et al. (2019)[40], which included a large cohort of 802 patients with chronic autoimmune diseases such as SLE, RA, and primary Sjogren syndrome, the aim was to evaluate the predictive ability of the FRAX tool in this specific population. The study findings indicated that the FRAX tool accurately predicted the probability of fracture occurrence in patients with RA. However, it was observed that the tool underestimated the fracture risk in patients with SLE and primary Sjogren syndrome, even after appropriate statistical adjustments were made considering glucocorticoid treatment and patient age.

Moreover, it is important to highlight that a significant limitation in the diagnostic capability of healthcare providers is that up to 30% of patients with chronic diseases, particularly ARDs, may experience osteoporotic fractures despite having normal BMD levels. This limitation needs to be addressed in the future[33]. In a cross-sectional prospective study conducted by Li et al. (2009)[41] involving 152 Chinese women with SLE, it was found that 20.4% of the participants had asymptomatic osteoporotic vertebral fractures, despite 30% of them having normal BMD values. The authors recommended the inclusion of additional assessment methods, such as vertebral morphometry, to evaluate fracture risk in this patient population. Early initiation of therapeutic interventions is crucial to prevent the occurrence of osteoporotic fractures.

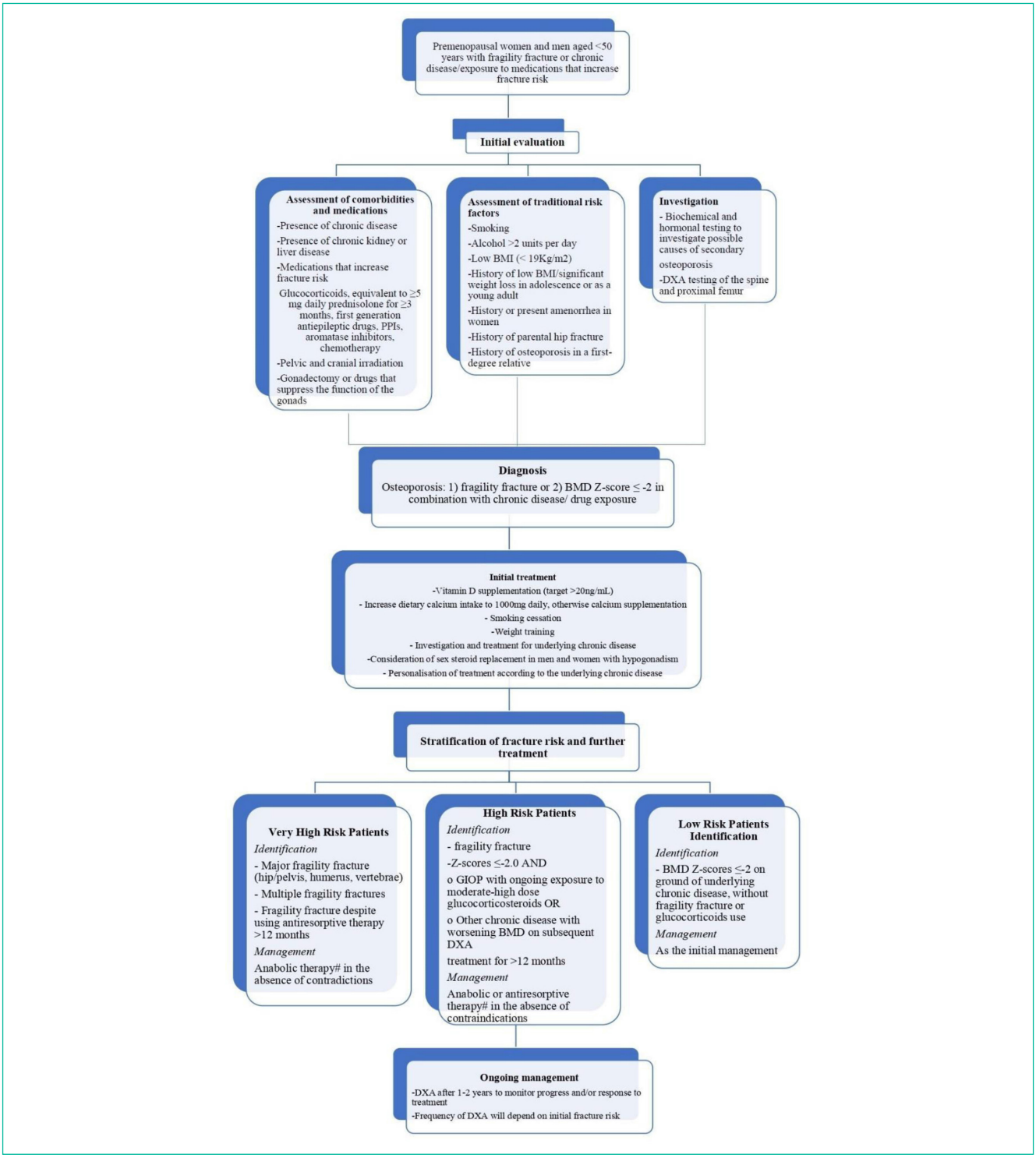
Managing osteoporosis in young adults poses a unique challenge. For all patients with fragility fractures, it is important to provide vitamin D supplements, implement lifestyle modifications such as smoking cessation, exercise, and a calcium-rich diet or calcium supplementation, and consider treatment with osteoanabolic or antiresorptive drugs. Follow-up DXA testing should be performed after 1-2 years to assess the response to osteoporosis therapy and adjust the management strategy accordingly[28].

Additionally, all patients receiving GCs should be prescribed calcium and vitamin D supplements. Those at moderate or high risk of osteoporosis anti-osteoporotic treatment should be initiated. Bisphosphonates are considered the first-line treatment, while in premenopausal women, teriparatide may be considered as a second-line option. Studies have demonstrated the superior efficacy of teriparatide compared to alendronate and risedronate for GIOP[33,34]. Alendronate or risedronate are the preferred options, supported by clinical trial evidence showcasing their effectiveness in both men and women with GIO. In cases where patients face challenges tolerating oral bisphosphonates or struggle with dosing requirements and adherence, intravenous zoledronic acid serves as a viable alternative. Oral bisphosphonates, which are relatively safe, available as generic and cost-effective options, have been the focus of comparative effectiveness trials. Notably, zoledronate has exhibited superiority over risedronate in increasing lumbar spine BMD[42]. Furthermore, evidence derived from meta-analyses supports the conclusion that both alendronate and risedronate reduce the incidence of vertebral fractures[43,44]. Moreover, moderate-quality evidence from meta-analyses[43] and real-world observational data suggests that oral bisphosphonates also contribute to the reduction of non-vertebral fractures[45,46]. However, it is important to note that in the pivotal non-inferiority study comparing zoledronate to risedronate, the fracture rate was too low to definitively establish the anti-fracture effectiveness of these treatments[42]. The ACR also recommends initiating an anti-osteoporotic treatment for patients aged 30 or older who receive an initial dose of prednisolone ≥ 30 mg and a total cumulative dose of ≥ 5 g within a one-year period. In cases where fractures occur despite the initiation of the antiresorptive treatment and the individual continues to use prednisolone at a dose ≥ 7.5 mg, a switch to an osteoanabolic drug may be considered[33].

Women of reproductive age constitute a specific subgroup. When considering the initiation of antiosteoporotic treatment in premenopausal women, it is important to consider family planning due to the contraindication of antiosteoporotic drugs during pregnancy and lactation. Therefore, treatment should be limited to women who do not plan to conceive during the treatment period or who are utilizing effective contraceptive measures. Discontinuation of bisphosphonates should be recommended at least 1 year before attempting conception[28,34]. Among oral bisphosphonates, risedronate is preferred due to its shorter skeletal residence time in comparison to alendronate and IV bisphosphonates[28]. As for denosumab, it is contraindicated during pregnancy as it can pass through the placenta. Discontinuation of denosumab triggers a rebound in osteoclast activity, resulting in the rapid loss of accrued bone mineral density and the subsequent loss of therapeutic effectiveness. Table 4 provides an overview of recent literature on the effectiveness of various therapeutic approaches in the treatment of osteoporosis in young adults of both sexes.

In summary, individuals of both sexes who suffer from ARDs are at an elevated risk of developing osteoporosis and experiencing osteoporotic fractures. Several factors contribute to this increased risk, including alterations in bone tissue structure resulting from the underlying disease, heightened exposure to inflammatory cytokines, and the chronic use of medications that promote bone loss. Premenopausal women with SLE are particularly susceptible to the development of both osteopenia and osteoporosis. It is important to acknowledge that chronic glucocorticoid administration poses a significant concern for both younger and older patients, warranting systematic screening and the implementation of preventive and therapeutic measures based on specialized protocols that have been developed in recent years.

Figure 1. Management of osteoporosis in premenopausal women and men aged under the age of 50 (Adapted from "Dilemmas in the Management of Osteoporosis in Younger Adults" by Herath M, Cohen A, Ebeling PR, Milat F. JBMR Plus. 2022 Jan 19;6(1):e10594. doi: 10.1002/jbm4.10594 [28], published under https://creativecommons.org/licenses/). *PPIs: proton pump inhibitors, DXA: dual-energy X-ray absorptiometry. - Treatment is recommended for premenopausal women who are not pregnant or breastfeeding. # It is essential to notify patients of the current approval status of these agents for young men and women in their specific country, as this varies. These recommendations are based on available efficacy data from small studies in young adults, clinical expertise, and well-established safety and efficacy data in the treatment of postmenopausal osteoporosis. § In cases where there is insufficient data to support a safe transition or discontinuation of denosumab without the risk of spontaneous vertebral fractures, especially in young individuals, bisphosphonates may be considered as a preferable option. ^ All women of reproductive age starting treatment should receive counseling regarding the potential theoretical teratogenicity of these drugs, the benefits for the woman's bone health, and the proper use of effective contraception. If conception is planned within 12 months, treatment should be postponed. Additionally, a thorough discussion of the known effects of pregnancy and breastfeeding on bone health is warranted.*



Conclusions

ARDs and the administration of GCs for their treatment pose significant risk factors for AVN and osteoporosis in young adults. In the presence of unexplained hip pain, AVN should be considered as the most frequent manifestation and necessitates further investigation, typically through MRI. Early identification of possible risk factors for the development of AVN is crucial, as well as diagnosing patients in the incipient asymptomatic stage of the disease.

Although osteoporosis has predominantly been associated with older individuals, it should not be overlooked in young adults with ARDs. Therefore, a comprehensive evaluation of fracture risk and appropriate management strategies should be implemented. Despite the considerable scientific research conducted in recent years, treating osteoporosis in premenopausal women and men under the age of 50 remains a significant challenge for physicians. Successful management of the disease, particularly in young patients with ARDs, should involve accurately identifying the secondary causes of osteoporosis, promoting a healthy lifestyle with emphasis on regular exercise and physical activity, and ensuring regular intake of calcium and vitamin D. Drug administration should be individualized, taking into consideration the severity of osteoporosis and the rheumatic disease, evidence regarding the anti-fracture effect of the drugs, and potential adverse effects, especially in young women planning pregnancy. Several aspects still require clarification, such as the exact pathophysiology of osteoporosis, the significance of isolated low bone BMD values, and the development of reliable diagnostic and monitoring tools for osteoporosis in these patient populations. These tools should consider the age, type of chronic disease, gender, and ethnicity of the patients.

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