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Avascular Osteonecrosis in Systemic Sclerosis Patient: Risk Factors and Role of Vasculopathy?

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ABSTRACT

Avascular Necrosis (AVN) or osteonecrosis refers to the death of osteocytes and osteoblasts. Sites such as the femoral head, the head of the humerus and the mandibular with restricted access to local blood supply are particularly vulnerable to osteonecrosis. Various traumatic and non-traumatic causes of AVN are known, including systemic autoimmune diseases. Among traumatic causes, physical trauma, decompression sickness or radiation may be cited. In the non-trauma cases, two theories are disputed: the first concerns the occurrence of an intravascular coagulation and the second one attributes the ischemia to extravascular compression. AVN has been well described in patients with autoimmune diseases such as systemic lupus erythematosus, but in systemic sclerosis (SSc) patients, there have been limited case reports and case series. We present a case of a 32-year old woman with systemic sclerosis on corticosteroid and avascular osteonecrosis and elaborating possible etiologies or mechanism of avascular osteonecrosis in SSc.

1. Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease in which inflammation and fibrosis play a crucial role and lead to severe damage and failure of multiple organs such as the skin, joints, tendons, gastrointestinal tract, lungs, heart and blood vessels. This disease makes B cell activation with characteristic autoantibodies. It primarily affects women (female : male ratio of 4 : 1 – 10 : 1, depending on age and ethnicity) and there are 2 clinical subsets according to the extent of skin involvement: diffuse cutaneous SSc (skin damage proximal to elbows and/or knees or that affects thorax and/or abdomen at any given time during the disease) and limited cutaneous SSc (skin damage distal to elbows and knees without involvement of either thorax or abdomen). This disease may lead to major disabilities due to vascular complications, cardiopulmonary involvement and musculoskeletal; likewise, it can cause malnutrition due to gastrointestinal tract involvement, and it can decrease quality of life as a consequence of the psychological and social impact.[1,2]

Avascular osteonecrosis of the femoral head may lead to progressive destruction of the hip joint and the femoral head. Although the etiology of osteonecrosis has not been definitely delineated, risk factors include corticosteroid use, alcohol consumption, trauma, and coagulation abnormalities. Size and location of the lesion are prognostic factors for disease progression and are

best assessed by MRI.[3] Avascular osteonecrosis is essentially a bone cell death from compromised micro-vascular circulation believed the result of mechanical vascular interruption, intravascular occlusion and extravascular compression. These processes can be the result of trauma, corticosteroids, alcohol use, blood dyscrasias, and miscellaneous factors.[4,5]

Corticosteroids have been the most commonly reported risk factor for avascular osteonecrosis. Autoimmune conditions have been reported to be commonly associated with or without the presence of steroid use. Up to one-third of patients with SLE may develop avascular osteonecrosis with only 9% of cases being symptomatic.[6] A review of 96 total cases of Multifocal avascular osteonecrosis by Sun et al. from 2005 to 2015 evaluated at one center revealed an association with an autoimmune rheumatic disease in the majority of cases. Forty of the cases were SLE patients, three cases with Sjogren's syndrome, and two cases with dermatomyositis.[7] Avascular osteonecrosis cases have also been described in other autoimmune rheumatic disorders such as Behcet's disease and juvenile dermatomyositis, to name a few.[8]

2. Case Ilustration

Female, 32 years old visited Rheumatology Outpatient Clinic Saiful Anwar Hospital with the chief complaint of radiated pain in right and left waist. Pain worsen with activity and did not relief with paracetamol 500 mg 3 times a day.

She had been diagnosed as SSc for 4 years with the history of difficult to hold any of the object. That time she only consumed herbal medicine because she thought that it might be only because of detergent contamination. Because of her problem worsen, she went to dermatovenereologist and consumed methylprednisolone 16 mg three times a day and the dose never been adjusted for 4 months. That time she started to feel swallow in face and pain in upper abdominal region.

Table 1. Laboratory Finding October 2016

Laboratory	Result	Normal value
Hb	12.2 g/dl	12.0 – 16.0
WBC	6200 /mm3	4500 – 11700
ESR	20 mm/hour	M < 15 F < 20
Hematocrit	37.0 %	M < 40 – 45, F < 38 – 47
Platelet count	314000 /mm3	150000 – 450000
Diff Count	-/-/-/61/32/7 %	1-4/ 0-1/ 3-5/ 50-70/ 15-40/2-8
MCV	74 um3	80-97
MCH	24.2 pg	26.5 – 33.5
Total cholesterol	165 mg/dl	< 200
Triglycerides	84 mg/dl	< 150
HDL	51 mg/dl	>> 55
LDL	97.2 mg/dl	< 150
Ureum	18.5 mg/dl	14 – 40
Creatinine	0.78 mg/dl	0.5 – 1.1
ALT	18 U/L	0 – 33
AST	20 U/L	0 – 33
Albumin	4.87 g/dl	3.5 – 5.5
PT	10.30 (10.90) s	9.4 – 11.3
APTT	29.20 (23.60) s	24.6 – 30.6
INR	0.99	< 1.5

She started to feel pain in right and left waist, so she went to the internist. The doctor adjusted the dose of methylprednisolone from 16 mg 3 times a day to 8 mg three times a day and gave her meloxicam but the pain did not become better. The patient was referred to a Rheumatologist and she had been diagnosed with osteonecrosis 7 months later. About the medication, the rheumatologist brought down the methylprednisolone and later discontinued it, and started her on methotrexate 10 mg/weeks. In January 2018, the methotrexate was discontinued and switched it to leflunomide. On June 2018, the medication was changed to chloroquine and she was given intravenous ibandronic acid every 3 months and subsequently switched to oral form due to financial constraints. She consumed ibandronic acid for a year, but there is no improvement, so she was referred to the orthopedic surgeon to undergo a Total Hip Replacement (THR), while the rheumatologist monitored the pain and also the activity disease of systemic sclerosis. In October 2019 she underwent total hip replacement and she still consumed azathioprine 1x50 mg.

These were some laboratories and radiological finding in this patient. In Table 1 showed that laboratory finding when she was diagnosed as a systemic sclerosis. Urinalysis showed no abnormalities. ANA test 71.3 unit (normal < 60), Anti ds DNA 116.8 IU/ml (normal < 92.6) and extractable nuclear antigen panel showed positive Anti Scl-70. Anticardiolipin was negative, β2-GP1 were not available, Lupus Anticoagulan was not ordered since APTT was normal. To evaluate other thrombosis rises, platelet aggregation test was ordered with results ADP was 85.8% (normal 70 – 100), collagen 86.3% (normal 70 – 100), and epinephrine 85.6% (70 – 100). For evaluation of cardiac function, echocardiography was done in August 2018 and the result within normal limit.

Pelvic X-ray showed stricture of the hip joint with irregular surface, sclerosis in subchondral bone, and shrinking of right and left femoral heads were consistent with avascular necrosis (Figure 1).

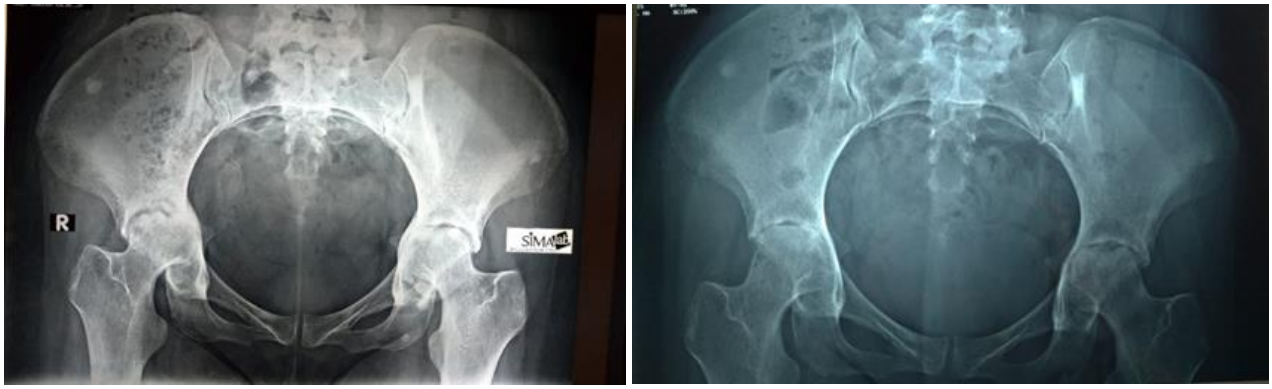


Figure 1. Pelvic X-Ray

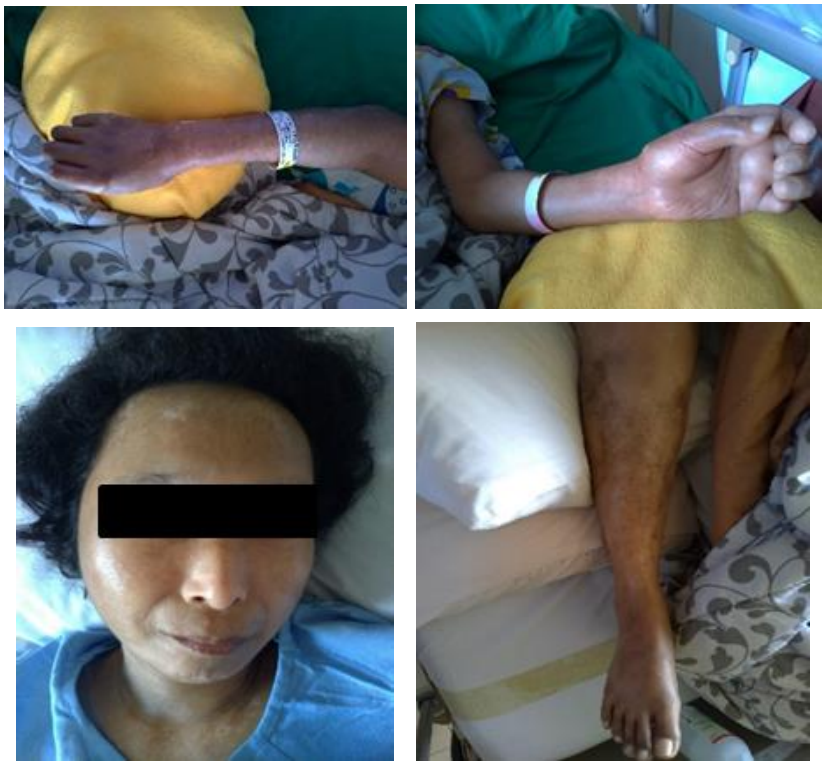


Figure 2. Pursed lips, sclerodactyly. Moderately severe flexion contractures of the fingers were present. Areas of hypopigmentation, called salt-and-pepper appearance, surrounded skin hyperpigmentation of the lower legs.

3. Discussion

Avascular osteonecrosis of the femoral head commonly affects patients in the third to fifth decades of life. In the United States, it is estimated that 20,000 to 30,000 new patients are diagnosed with osteonecrosis annually, and 5% to 12% of total hip arthroplasties (THAs) are performed based on this diagnosis. Although several risk factors have been identified, the pathogenesis of avascular osteonecrosis has not been elucidated. The disease typically follows a progressive course leading to femoral head collapse and hip joint destruction.[9,10]

Most theories point towards an alteration in the intravascular blood flow as the potential mechanism of avascular osteonecrosis initiation. These alterations may occur either from a traumatic or a non-traumatic cause or be a consequence of some well-accepted risk factors (Figure 3). Regarding the traumatic cause, it is important to notice that the majority of the blood supplied originates from the retinacula arteries supplying the superolateral weight-bearing portion of the femoral head. These retinacular vessels originate from the lateral epiphyseal artery, which is a branch of the medial circumflex arteries. Among traumatic causes, physical trauma, decompression sickness or radiation may be cited. In the non-trauma cases, two theories are disputed: the first concerns the occurrence of an intravascular coagulation and the second one attributes the ischemia to extravascular compression.[11,12]

Table 2. Pathogenic mechanism of osteonecrosis

Ischemia	Direct Cellular Toxicity	Altered differentiation of mesenchymal stem cells
Vascular Disruption Femoral head fracture Hip dislocation Surgery **Vascular compression or constriction** Increased intraosseous pressure due to marrow fatty infiltration ➢ Corticosteroids, alcohol Vasoconstriction of arteries perfusing femoral head ➢ Corticosteroids, eNOS polymorphism **Intravascular occlusion** Thrombosis ➢ Thrombophilia: • Protein C and S deficiency • Activated protein C resistance, factor V mutation • Hyperhomocysteine • eNOS polymorphisms ➢ Hypofibrinolysis • High PAI activity, PAI-1 polymorphisms • High lipoprotein(a) Embolization Fat, air Sickle cell occlusion	• Pharmacologic agents • Irradiation • Oxidative stress	• Increased adipogenesis and decreased osteogenesis • Corticosteroids, alcohol

Intravascular coagulation can occur as the end result of local vascular impairment. Vascular occlusion occurs because of thrombus formation due to abnormally shaped red blood cells as seen in sickle cells anemia or embolism of fat and nitrogen.[12,13]

Extravascular compression may arise secondary to damaged femoral head vessels that permit the accumulation of fat and blood in the extravascular space which leads to alterations in blood flow through local compression.

Most studies have attributed the disease process to the combined effects of genetic predisposition, metabolic factors, and local factors affecting blood supply such as vascular damage, increased intraosseous pressure, and mechanical stress. This results in bone ischemia and infarction leading to bone death. The precipitating mechanism which leads to this pathway is variable though. Ischemia can result from external or internal vascular insult typically caused by direct trauma, vascular occlusion, direct cellular toxicity or altered mesenchymal stem cell differentiation.[13]

There are several risk factors that lead patient to avascular osteonecrosis (table 3). The direct risk factor can be excluded to this case but some of the indirect risk factor may give an effect. In this case report, patient had consumed prednisone 60 mg/day for 3 months continues with 30 mg/day for 7 months. High doses of corticosteroid prevalent in systemic as well as excessive alcohol intake have been associated with alterations in circulating lipids with resultant microemboli in the arteries supplying the bone.[13] Corticosteroid administration induces a vasoconstriction and leads to an increase of a procoagulant factor production. It also increases

adipogenesis, decreases osteogenesis and downregulates osseous repair and remodeling through fatty emboli production.[13,14] A meta-analysis by Mont et al 2015 found a statistically significant association between high-dose corticosteroid use (>20 mg prednisone-equivalents per day) and avascular osteonecrosis, but cases have been reported from long-term and short-term doses and after oral, intravenous, topical, and intraarticular application.[15, 21,22] Some case reports also show the low dose corticosteroid impact to create avascular osteonecrosis. A case report by Dharmsaku et al 2016 showed a patient with hypopituitarism on prednisone 5 mg for 2 years without any history of high dose corticosteroid had avascular necrosis.[30] The multiple-hit theory revealed that corticosteroid alters bone homeostasis, injure bone cells, impair blood flow, and suppress bone cell precursors in susceptible patients. In support of the multiple-hit theory, Wang et al 2000 found increased differentiation of pluripotent stem cells into adipocytes and reduced expression of type I collagen and osteocalcin messenger RNA in an animal model. Corticosteroids inhibit angiogenesis and promote a hypercoagulable state, which could contribute to the formation of intravascular thrombosis leading to avascular osteonecrosis. Also, studies have investigated whether there is a genetic susceptibility to corticosteroid-induced avascular osteonecrosis (Figure 6).[20-24]

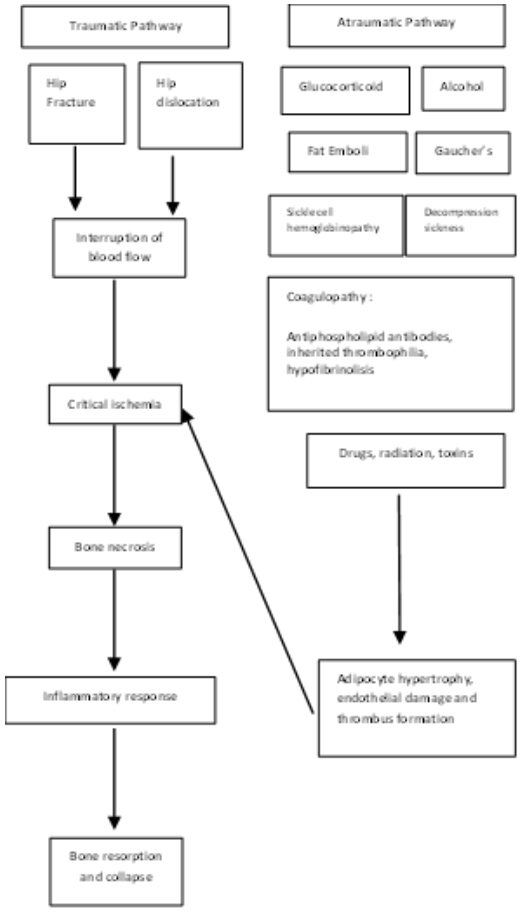


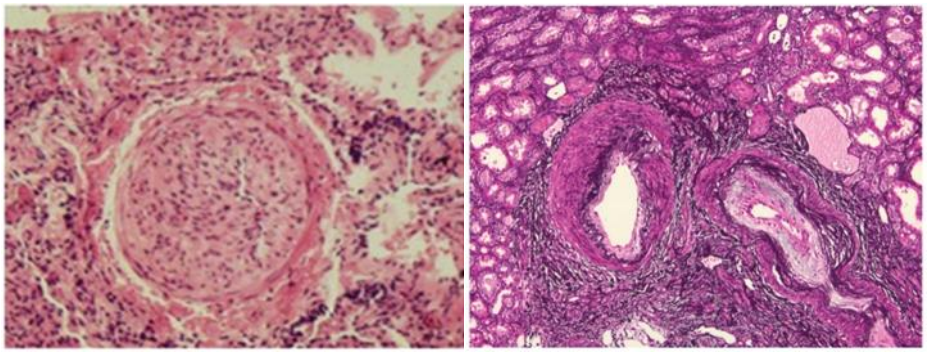
Figure 3. Mechanism of osteonecrosis

Table 3. Risk factors for osteonecrosis of the femoral head

Direct	Indirect
Femoral head/ neck fracture	Chronic corticosteroid use
Hip dislocation	Excessive alcohol consumption
Slipped capital femoral epiphysis	Coagulation disorders
Radiation	Hemoglobinopathies
Sickle cell disease	Dysbaric phenomena
Caisson disease	Autoimmune disease
Myeloproliferative disorders	Smoking
	Hyperlipidemia

In SSc patients there is vasculopathy of small artery and capillary which is affected by endhothelial cell injury, adhesion and activation of platelet, prostaglandine F, thromboxane A2 release, vasoconstriction & growth of endothelial cell and fibroblast, narrowing or obliteration and increased permeability. Vascular injury is proposed to be a seminal event in SSc pathogenesis (Figure 5). Initial studies revealed that SSc patients with early disease have a unique capillaroscopic pattern that shows dilated, giant, and malformed capillaries.[31] This is due in part to endothelial cell injury and subsequent vascular remodeling. Furthermore, as the disease progresses, affected areas become increasingly avascular. [30,31] Dysregulation of endothelial cell (EC) function within the vascular wall plays an important role in vascular remodeling associated with the fibroproliferative vasculopathy observed in SSc. Endothelial cell injury is proposed as a crucial initiating event leading to vascular remodeling with intimal proliferation of arterioles and capillary breakdown and finally, blood vessel occlusion.[32]

On the other hand, this patient has been suggested that the underlying vasculopathy may be causative in the development of AVN. There were 2 cases reported by Fossaluzza et al and Wilde et al where surgical intervention was undertaken in patient with SSc without any corticosteroid therapy. It reported interstitial fibrosis with absence of any vasculitic lesions on tissue pathology and some fibrinoid necrosis of the vessel wall (Figure 4).[25] Thus, avascular osteonecrosis may be effect of vasculopathy on SSc itself without any other risk factor through endhotelial injury (Figure 5).[30]



(A) (B)

Figure 4. Vasculopathy in SSc. (A) Fibroproliferative vasculopathy pulmonary arteriole. (B) Prominent arterial adventitial fibrosis in a patient with scleroderma renal crisis.

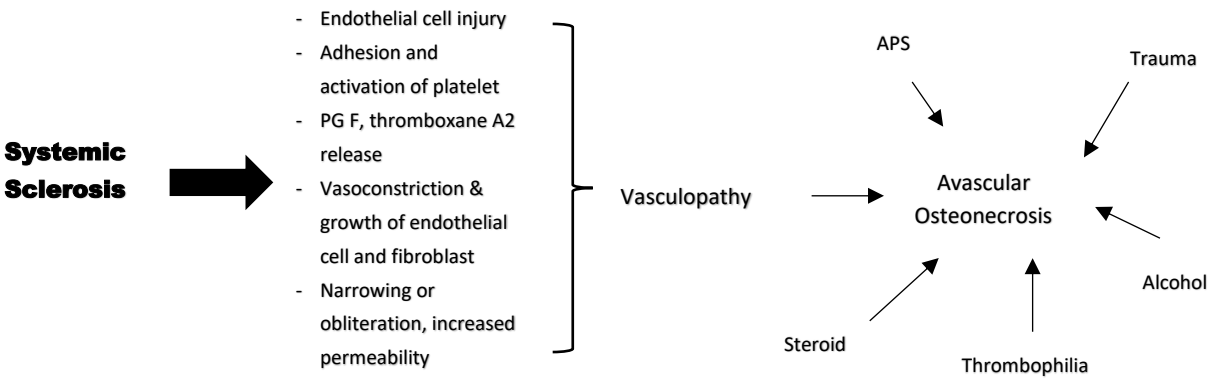


Figure 5. Vasculopathy in SSc may affect Avascular osteonecrosis directly.[27,28]

Some patient with SSc had antibodies against cardiolipin (aCL) and β2-glycoprotein I (β2-GPI) which associated with various adverse events including arterial and venous thromboembolism and recurrent miscarriage. Endothelial cell injury in SSc patients is accompanied by an elevation in the level of von Willebrand factor.[26] Assous, et al 2005 revealed that there was significant correlation between the IgG aCL titer and the amount of von Willebrand antigen produced. They also found an association between patients having pulmonary arterial hypertension (PAH) and the amount of von Willebrand factor produced. This suggests that aCL positivity is associated with endothelial injury and PAH.[26] The coagulation disorders can lead endothelial injury which also may cause AVN. Our elaboration to this case results probability of APS in this patient.

We found normal limit of hemoglobin, WBC, lipid profile and also there was no history of consumed alcohol and smoking so we can exclude the risk factor of those to AVN in this case but one of the direct risk factor was fracture.

Initial workup usually involves multiple views with plain radiograph which may show changes in bone density which at later stages progress to sclerotic or cystic changes. However, plain radiographs have low sensitivity and may appear normal in many cases, especially at early stages. In advanced cases, joint space narrowing or collapse of a joint may be visible on imaging which can progress showing severe destructive lesions consistent with avascular osteonecrosis.[17]

There are 4 most commonly used systems of classification in Avascular Osteonecrosis to provide information on prognosis and assist with treatment decisions: Ficat and Arlet, University of Pennsylvania/Steinberg, Association Research Circulation Osseous (ARCO), and the Japanese Orthopedic Association, but in Internal Medicine usually use Ficat and Arlet or University of Pennsylvania/Steinberg.[16,17]

Almost all of the cases of avascular osteonecrosis reported in the literature had been diagnosed with an MRI, except for cases where presumably MRI were not available at the time MRI remains the gold standard in detecting precollapse lesions and allows differentiating avascular osteonecrosis femoral head (ONFH) from other diagnosis such as a transitioned osteopenia of the femoral head or bone bruises. MRI has a sensitivity and specificity of about 99%.[14] Many of the SSc patients who were asymptomatic when AVN was discovered were followed up with MRI scans to evaluate progression.[14,18] About the workup, this patient

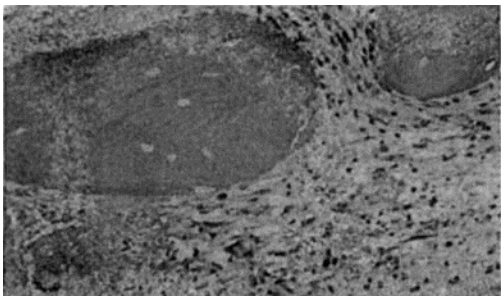
used plan X-Ray before she referred to an orthopedist and did MRI examination.

A case report by Kawai, et al 1985 presented patient with progressive SSc and carpal scaphoid AVN. The necrotic lesion of carpal scaphoid was consistent with the area of the carpal scaphoid supplied by the dorsal ridge vessels. The pathophysiologic mechanism behind the avascular necrosis of the carpal scaphoid in this particular case was presumed to be the combination of vascular changes in progressive systemic sclerosis, large doses of a corticosteroid and recurrent minimal fractures while working (Figure 6). Biopsy specimen of hip after THR may important to look for histopathological of AVN in SSc patient.[33]

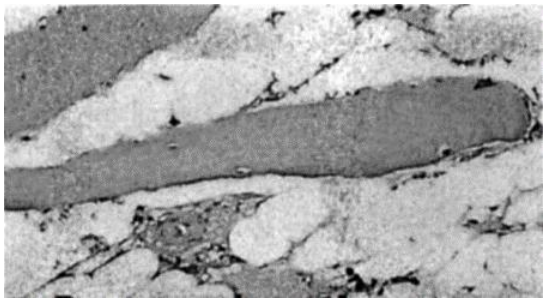
The management of SSc-AVN is aimed at symptom control as well as prevention of complications to preserve skeletal support and joint function. Most of the cases we reviewed were managed conservatively with symptom management, physiotherapy, and follow-up MRIs to monitor progression. Treatment options employed in some patients included calcium, vitamin D supplements, and bisphosphonates as well as hyperbaric oxygen.[19]

Bisphosphonates significantly reduce the incidence of collapse of the femoral head in osteonecrosis hips by reducing osteoclast activity. Alendronate has been shown to prevent early collapse of the femoral head in Steinberg stages II and III non-traumatic AVN at 24-28 months follow up and has been reported to diminish the amount of pain at one year follow up compared with placebo treatment. Alendronate has been used as an adjunctive therapy with surgical procedures and has been found to reduce pain and the risk of collapse in early stages of ONFH.[11]

(A)



(B)



(C)

Figure 6. (A) Necrotic bone tissue with empty lacunae and dead marrow tissue. (B) Proliferating granulation tissue is remarkable in the marginal area between the dead and normal marrow tissue. (C) Normal bone tissue. [33]

Table 4. Some studies of avascular osteonecrosis in systemic sclerosis patients

Author	Case	Treatment	Notes	Reference
Taccari et al. (1989)	Woman 50 yo Risk factors: - Steroid - Thrombophilia	NSAID and THR	Steroid for 9 mo, micro-vasculitis	27
	Woman 25 yo Risk factors : - Steroid - Osteopenia - Thrombophilia	NSAID	Steroid for 30 mo, destruction femoral head, micro-vasculitis	
Sahrain et al. (2011)	Woman 25 yo Risk factor: - Secondary thrombophilia	Hip joint surgery	Steroid only 10 days and switched to Interferon beta 1a (Cinnovex) once weekly for 15 mo	28
	Woman 22 yo Risk factors: - Steroid - Secondary thrombophilia - Stress oxidative (smoking)	Referred surgeon Hip joint surgery	Smoking for 2 years, used methylprednisolone pulse 1 g/day for 5 days, interferon beta 1a. Symptom of AVN existed 3 months after methylprednisolone pulse	
	Woman Risk factors: - Steroid - Secondary thrombophilia	Surgery	Methylprednisolone pulse 1 g/day for 5 days, interferon beta 1a once every month. Symptom of AVN existed a year after methylprednisolone pulse	
	Man 36 yo Risk factor: - Steroid	Surgery	Methylprednisolone 1 g/day for 5 days with a short course of oral prednisone. Symptom of AVN existed 8 months after pulse	
	Woman 22 yo Risk factor: - Steroid - Thrombophilia		Methylprednisolone pulse 1 g/day for 5 days, interferon beta 1a. Symptom of AVN existed 6 months after methylprednisolone pulse	
Pinar et al. (2006)	28 patient with SSc and AVN	No data	Total 60 patients, 27 patients didn't received pulse steroid and 33 had it.	29
Baysal et al. (2020)	30 patient with SSc and AVN from research of literature	11 patient treated with surgical 18 patient with pharmacological	6 patients exposed pulse steroid or long-term use. 4 patients exposed intermittent high dose steroid. 13 patients exposed low dose steroid. 1 patient in alternate dose.	18

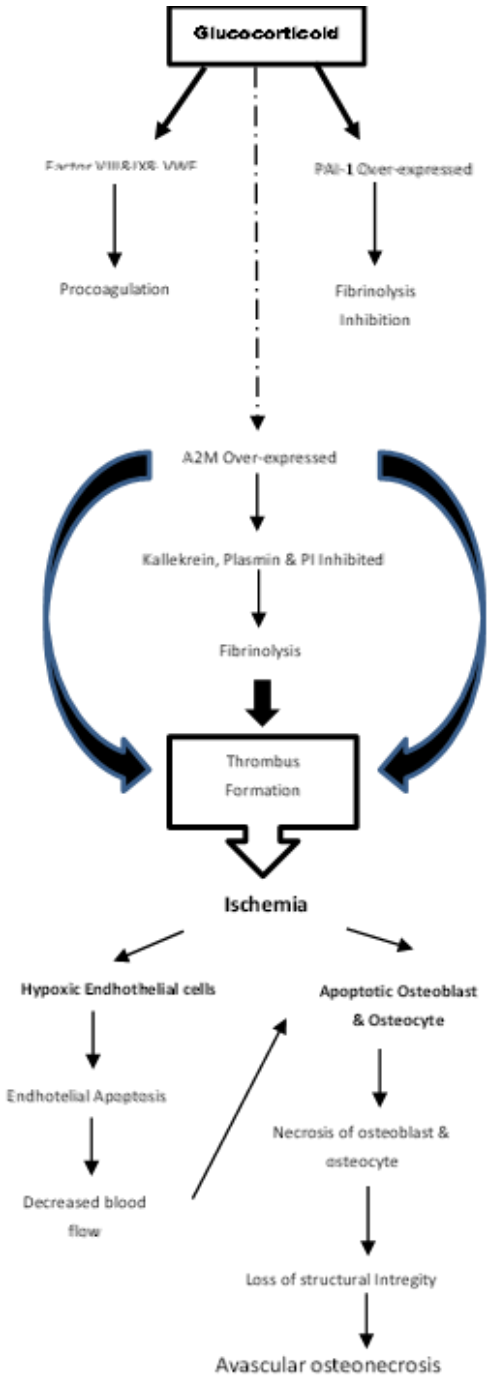


Figure 7. Different Mechanisms of Glucocorticoid effect on ANFH.

Surgical management remains integral in cases, especially in advanced cases of complications or when symptoms are refractory to conservative treatment. Based on reported cases, it is difficult to predict complications and the rate of progression and to recognize patients who would benefit from surgical intervention. The decision to refer for surgical intervention should be a shared decision between providers and patients and should be individualized. [15,18] For later-stage avascular necrosis or patients

who have had unsuccessful non operative treatment, the next step is consideration of operative management. The most common operative interventions are discussed, including core decompression, bone grafting, and THA, with a brief mention of procedures that were more common historically.[20]

4. Conclusion

There have only a few case reports of avascular osteonecrosis reported in systemic sclerosis patients in the literature. Several risk factors of AVN are corticosteroid use, alcohol, hemoglobinopathies, trauma, smoking, hyperlipidemia, autoimmune disease. In our case the possible mechanism include corticosteroid use and vasculopathy from SSc itself. We suggest histopathological evaluation should be done in all SSc-AVN after total hip replacement.

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