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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

RESEARCH ARTICLE

CORONARY ARTERY DISEASE IN RHEUMATOID ARTHRITIS – PREVALENCE,PATHOPHYSIOLOGY,RISK AND TREATMENT

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Manuscript Info	*Abstract*

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Coronary Artery Disease (CAD),is a significant contributor morbidity and mortality in Rheumatoid Arthritis (RA) .[1] Familiarity with the pathophysiology of coronary atherosclerosis will have important practical implications for patient care .Insights in to the mechanisms of thrombosis will give further insight into the concomitant therapy used during acute revascularization.[2]The purpose of this review is thorough understanding of the connection between atherosclerosis and RA and stress in accurate risk stratification in RA patients and timely intervention to improve outcomes .The review also highlights comprehensive collaboration between Rheumatologist and cardiologist to help in prevention of cardiovascular diseases in RA patients and improve patient care in a total spectrum.

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Introduction:-

Rheumatoid Arthritis (RA),is the most common autoimmune articular disease with systemic manifestations.It affects 2,1 million Americans and 1.5 million women .It is more common in females .The reduced life span of RA patients is possibly explained by the cardiovascular diseases.[3]

Coronary Artery Disease (CAD),is a significant contributor morbidity and mortality in RA .[4]Rheumatoid arthritis patients have increased risk of Myocardial Infarction .Hence aggressive interventional prevention strategies are implicated in RA patients with cardiovascular diseases.

There is adeep connection between CAD and RA .Thorough understanding of this connection will help in accurate risk stratification in RA patients and timely intervention will improve outcomes ,Comprehensive collaboration between Rheumatologist and cardiologist will help in prevention of cardiovascular diseases in RA patients and will improve patient care in a total spectrum.

Atherosclerosis has inflammatory origin.[5]Similarity has been observed between pathology mechanism underlying in the synovium of joints of RA patients and endothelium of arteries in atherosclerosis.In both atherosclerosis and RA, there is infiltration of inflammatory cells , dysfunctioning of endothelial cells and synovial cells,smooth cell proliferation .The hallmark mechanism underlying both diseases is Inflammation.[6]

Chief contributors of atherosclerosis in RA are-Endothelial dysfunction caused by immune complexes,antibodymediated,cytokinemediated,Autoantibodies,hypercoagulability,dyslipidemia.Other traditional

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risk factors of consideration are hypertension ,diabetes,raised body mass index ,hyperhomocystinemia.:There is also association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis.[7]

Previously,our understanding of atherosclerosis was different as it is today .Earlier it was considered a cholesterol storage disease ,but now our understanding about its pathophysiology has remarkably evolved and now its considered an inflammatory disease .CAD causes stenosis hence need of revascularization to relieve ischemia..Besides treatment of stenosis through revascularization ,aggressive management of modifiable risk factors is also important .Disrupted plaques are the stimulus for thrombosis .Its a solid state stimulus .Changes in levels of circulating prothrombotic or antifibrinolytic mediators in blood predispose to acute coronary syndrome .Widespread inflammation and multiple high risk plaques predispose to ACS ,ACS is no more a localized or segmental disease .The goal of treatment should be treating early lesions and stabilizing other plaques to prevent recurrent events in the future .Treatment of stenosis should include mechanical revascularization and further preventive interventions to prevent future events.[8-10]

Discussion:-
Pathophysiology of chronic cad:-
Atherogenesis is a complex interaction of risk factors ,cells of the arterial wall and inflammatory mediators and proinflammatory cytokines .Inflammation plays role in all stages of atherosclerosis1

Inflammation also plays role in blood vessel ,cardiac and systemic complications of atherosclerosis .

The chief key players involved in the pathomechanisms are circulating cytokines,tissue necrosis factor alpha.,INFgamma,interleukin 1 ,interleukin 6,hyperhomocysteinemia,ESR,CRP .

Endothelial dysfunction first marks the   first step of atherosclerosis.[11]It is the earliest event that signals the beginning of atherosclerosis.Exposure of arterial endothelium to proinflammatory cytokines derived from excess adipose tissue ,products of glycoxidation associated with hyperglycemia ,vasoconstrictor hormones in hypertension,dyslipidemia and bacterial products ,leads to expression of adhesion molecules .[12]These adhesion molecules allow blood leukocytes to stick to the inner surface of the arterial wall .Next step is the transmigration of the adherent leukocytes .The leukocytes reside in the intima and communicate with the endothelial cells and smooth muscle cells .[12]Mediators of inflammation that are involved in this process are prostanoids ,leukotrienes ,histamine cytokines,protein mediators and complement components .[14,16]As a next sequel ,SMC s migrate from the tunica media to the intima .These secrete extracellular matrix .,SMC ,endothelial cells and monocytes secrete MMP in response to hemodynamic stresses .MMP s play vital role in regulating functions of vascular cells ,angiogenesis,healing ,destruction of extracellular matrix of arteries.Proteoglycans of extracellular matrix binds to lipoproteins ,prolong their residence in the intima ,render them susceptible to glycation and oxidative modifications .Lipoprotein modification gives products such as oxidized phospholipids and advanced glycation end products .They propagate inflammatory response .Next step of progression is the calcification and the bone formation .[15]There is both proliferation and death of lipid laden macrophages .The extracellular lipid coalesce in the intima and form lipid rich necrotic core of atherosclerotic plaque .

The atherosclerotic lesion grows outward rather than inward .Thus stenosis is the last stage of atherosclerosis .By the time stenosis is diagnosed and treated ,atherosclerosis already had a widespread and diffuse distribution .Thus the prevalence of atherosclerosis is still underscored and underdiagnosed specially in adolescent and young adult Americans .[17]

Complications in plaques like disruption of plaque, superficial erosion ,intraplaque hemorrhage and erosion of calcified nodule account for all acute coronary thromboses.Disrupted plaques lead to thrombosis .When the plaque disrupts ,collagen is exposed and this exposed collagen in the extracellular matrix triggers platelet activation .Smooth muscle cells and macrophages secrete TF and it activates the coagulation cascade .Thus disrupted plaque is a stimulus to both thrombosis and coagulation .Thrombin amplifies platelet activation .Fibrinogen is converted to fibrin .Activated platelets release vWF.vWF helps in the formation of white arterial thrombus which is a dense mesh of fibrin network in which platelets are entrapped.This is the solid state of the disrupted plaque .In addition to this we have the fluid phase also which predisposes to coronary thrombosis .Raised levels of plasminogen activator

inhibitor -1,specially in diabetes,obesity and hypertensive patients is responsible for fluid phase changes .Disrupted plaque plaque secrete particulate TF which increase thrombogenicity of blood .[18-19]

Plaques with thin fibrous cap and a large lipid core with numerous inflammatory cells and few SMCs are prone for rupture.These are high risk plaques.Patients with high risk plaques and wide spread inflammation are prone to acute coronary syndrome .Plaques with outward remodeling lead to hidden lesions that lack angiographic detection but harbor a substantial burden of atherosclerosis .They donotcause symptoms nor do they cause ischemia.Myeloperoxidase is a marker of inflammation and is raised in ischemia.Diffuse arterial inflammation is responsible for focal lesions and clinical presentations

Signs and symptoms:-
The key clinical manifestations of CAD are stable angina pectoris ,unstable angina pectoris ,MI.Chest discomfort is the first symptomatic episode.[20]Sometimes the first coronary artey diagnostic presentation is acute plaque rupture or acute myocardial infarction .Cardiac dysrhythmias represent underlying electrical instability.Angina pectoris is a cardinal symptom developed due to inadequate oxygen supply to the myocardium.Cardinal angina symptoms are discomfort in arm ,throat ,jaw,exertional fatigue ,shortness of breath,heartburn.Angina Pectoris is said to be stable when its pattern of duration ,intensity ,frequency are not changed over time .Administration of sublingual nitroglycerin can help to differentiate stable and accelerating pattern.

Accelerating Angina shows a change in pattern of stable Angina.Easyprovocation,more prolonged episodes,more intensity ,longer recovery and more often use of nitroglycerin.Its a transitioning stage from stable to unstable angina.Transition from Stable Angina to accelerating pattern warrants medical attention.

Unstable Angina ,pattern of chest discomfort changes abruptly .Chest pain at rest ,increase in frequency ,discomfort with minimal activity .Unstable Angina occurs when there is sudden rupture of atherosclerotic plaqueor abnormal occlusion of coronary artery .MI follows as asequale of unstable angina.Immediate medical attention is warranted.

Clinical symptoms pertaining to metabolic syndrome should also be evaluated and be a part of work up plan .[21]

Diagnosis:-
Key diagnostic approach is detail patient history,through physical examination,EKG,laboratory blood tests ,stress test and cardiac catheterization. Imaging methods help to assess the regional myocardial perfusion and function. New imaging technologies that provide risk of progression and further cardiovascular events are optical coherence tomography,thermography,Infrared spectroscopy ,electron beam computed tomography,MRI.[22]

Treatment:-
The aim of treatment is to reduce myocardial oxygen requirements and increase the myocardial blood flow .Medications that reduce oxygen requirements are nitroglycerin ,nitrates ,Beta blockers and calcium channel blockers .Revascularization procedures thrive on the concept of restoring forward coronary artery blood flow .New procedures of revascularization include arteriogenesis stimulation by cells,protein and gene.Besides treatment of flow limiting lesions ,non obstructive plaques should also be addressed.Angiography helps to assess the severity of lesions .Ischemia is the end result of dynamic obstruction superimposed on fixed stenosis .Sudden rapid progression of the lesion leads to poor prognosis .Fixed stenosis progress in sudden spurts [23]There is discontinuous progression of plaques .Sudden increase in the severity of the obstruction is due to episodes plaque disruption ,thrombosis and healing .Revascularization procedures relieve ischemia but donot protect against future acute thrombotic events .Modification of risk factors delay disease progression .Thus for atherosclerotic patients combination of treatment strategies are used ,revascularization procedures,lifestyle modifications and pharmacological measures .Modification of risk factors include –reduction in blood pressure ,reduction in LDL ,smoking cessation .Diabetes Mellitus ,Metabolic syndrome lead to adverse lipid profile and dyslipidemia leading to CVD events.[24]

Primary prevention of cardiovascular disease is lifestyle modification .The hear protection study promotes the use of statins in individuals with total cholesterol >135 mg/dl and with traditional risk factors .The physician's health study ,showed aspirin significantly reduces MI in men aged 40-80 yrs 20 .EUROPA study showed that ACE inhibitor significantly reduce CVS events .Besides pharmacological therapies ,lifestyle modification carry equal importance .Biomarkers linked to inflammation have been studied and it was found that they predict coronary events better than traditional risk factors.24These markers include acute phase reactants,cytokines ,MMPs.Patients with elevated CRP

at baseline are benefited most by aspirin and statin therapy in primary prevention trials .They reduce CRP and other markers of inflammation .This supports the beneficial use of anti-inflammatory in atherosclerosis.[25]

Bypass surgery and percutaneous revascularization treat localized segmental disease .The goal of treatment should be to restrict thrombosis and embolism both ,maintain perfusion and limit loss of cardiomyocytes..Severe ischemia leads to ST-T segment abnormalities and release of troponin T or I .These are signs of poor prognosis .Aggressive management should include platelet inhibition ,inhibition of thrombin generation revascularization of culprit lesions .This approach will improve outcome in high risk patients.Best combination recommended for high risk patients is oral aspirin ,clopidogrel and intravenous glycoproteinIIb/IIIa during angioplasty during angioplasty .[26]

Through understanding of pathophysiology of ACS will help to reduce plaque atherogenicity ,achieve rapid control of disease process,prevent future recurrences.Use of statins helps to prevent recurrences of ACS in the future by reducing cholesterol levels and by anti-inflammatory actions.COX-2 inhibitors also retard atherosclerosis

Management of ACS should aim to stabilize lesions .Stabilization of lesions reduce recurrent events .Systemic factors that cause plaque disruption should be adequately controlled ..Statins by affecting the biology of the plaque reduce recurrent coronary events.55.Inflammation underlies the mechanism of plaque formation hence anti inflammatory will have beneficial effects 56.Statins reduce CRP levels ,hence improve outcomes in ACS .

Prime aim of treatment should be to stabilize lesions and control all systemic factors adequately that leads thrombotic complications of atherosclerosis .Both size of the plaque and composition of the plaque decides future complications .Larger plaques cause stenosis and ischemia .Smaller plaques could grow oblong towards the outer wall and can be silent killers and cannot be detected on the angiogram. Sturdier extracellular matrix skeleton are less likely to rupture and less likely to trigger clot formation .

Conclusions:-
Our understanding about CAD has significantly changes in the last few decades .Now atherosclerosis is not merely just a cholesterol storage disease but its more of an inflammatory disease .Familiarity with the pathophysiology of coronary atherosclerosis will have important practical implications for patient care .Insights in to the mechanisms of thrombosis will give further insight into the concomitant therapy used during acute revascularization .Therapies should be individualized based on patient's specific characteristics..Preventive therapy should be emphasized in more efficient and cost effective manner.LDL should be targetized to reduce risk of atherosclerotic complications.Lifestyle modifications with drug treatments should be used patients with obesity,metabolic syndrome and diabetes.

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