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RESEARCH ARTICLE

ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS-ROLE OF SYSTEMIC INFLAMMATION ,TRADITIONAL CVD RISK FACTORS IN ENDOTHELIAL DYSFUNCTION IN RHEUMATOID ARTHRITIS

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Abstract

Rheumatoid Arthritis (RA), is a inflammatory joint disease of chronic nature with predominant articular symptoms of pain ,swelling and stiffness.The most common extraarticular manifestation is cardiovascular disease which accounts for 50 % mortality in RA patients . Complex interplay between traditional CVD risk factors ,systemic inflammation and vascular function in RA are the reasons behind the scene worse outcome in RA patients .5

The MCC of mortality in Rheumatoid Arthritis patients is cardiovascular disease .1,2 Endothelial dysfunction is directly related to RA associated systemic inflammation

The aim of the review is to discuss Endothelium ,its morphology and normal physiology ,consider endothelial dysfunction (ED) in RA patients and relate endothelial dysfunction to systemic inflammation and traditional CVD risk factors and also consider the effect of drugs on vascular function.

Introduction:-

Rheumatoid Arthritis (RA), is a inflammatory joint disease of chronic nature with predominant articular symptoms of pain ,swelling and stiffness. 1RA patients have extra articular manifestations ,the most common is cardiovascular disease which accounts for 50 % mortality in RA patients .1,2RA patients have a worse outcome not from joint disease but due acute CVD events3,4.Complex interplay between traditional CVD risk factors ,systemic inflammation and vascular function in RA are the reasons behind the scene worse outcome in RA patients .5,6,7

The MCC of mortality in Rheumatoid Arthritis patients is cardiovascular disease .1,2 Endothelial dysfunction (ED) is directly related to RA associated systemic inflammation .8 RA patients ED in both microvasculature and microvasculature.9,10Anti inflammatory medications improve endothelial function 9,10

The aim of this review is -To discuss Endothelium ,its morphology and normal physiology ,consider endothelial dysfunction in RA patients and relate endothelial dysfunction (ED) to systemic inflammation and traditional CVD risk factors and also consider the effect of drugs on vascular function.

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Discussion:-

Endothelium and its role:-

Endothelium ,is a dynamic organ that lines the entire blood vessel system and acts as a barrier between blood and vessel wall .11 Endothelium responds to hormones ,neurotransmitters and vasoactive factors .It controls vascular functions like vasomotion,thrombosis,platelet aggregation and inflammation ,fibrinolysis ,coagulation,,vascular growth ,vasoregulation ,vasoprotection .Vasoactive factors balance is important for atheroprotection .Damaged endotheliun disrupts this balance .This imbalance causes endothelial dysfunction which is a precursor for atherosclerosis .12

Endothelial cells line the inner wall of the vessels and are located in the intima .Endothelial cells in arteries and veins are more thicker and continuous while in capillaries they are thinner and fenestrated to allow exchange of gases and metabolites.14 Endothelial cells responses are varied in different vascular beds and different sections of the same vascular bed .Endothelial dysfunction marks the start of atherosclerosis.

Blood vessels are the main link between the heart and tissues.The vascular wall has three layers-tunica intima ,media and externa .Intima is the inner layer made of endothelial cells and is responsive to hormones and vasoactive factors.The tunica media is a thick layer made of smooth muscle cells ,collagen ,elastic tissue .This layer is responsible for vasoconstriction and vasi dilation and gives vessel structural integrity .Tunica externa made up of loose connective tissue which adheres vessels to the surrounding organs .

Endothelium releases vasoactive factors .Vasodialators such as nitric oxide (NO) ,Prostacyclin (PGI2) and endothelium derived hyperpolarizing factor (EDHF) .Vasoconstrictors such as thromboxane (TXA2) and endothelin-1(ET-1) .

Vasodilator (NO) and underlying mechanism of vasodilation:-

Nitric Oxide (NO) is released by the endothelial cells and causes vasodilation of the smooth muscle cells of the tunica media .It was first identified by Furchgott and Zawadzki 15 .It also plays role in maintaining the basal vasodilator tone of the blood vessels 16 L arginine ,amino acid is converted to NO by the nitric oxide synthase (NOS).NOS exists in 3 isoforms –Neuronal isoform (n-NOS) acts as a neuronal messenger regulates synaptic neurotransmitter release .Inducible isoform only expressed in cells exposed to injurious stimuli .Endothelial NOS e-NOS produces nitric oxide in the vasculature..Blood vessel dialation is more dependent on e-NOS.InactiveNOS is located in small invaginations in the cell membrane called caveolae .The inactive form is bound to protein caveolin .17

NO Agonists like bradykinin ,acetylcholine ,ATP ,ADP Acetylcholine ,substance P ,thrombin,18 .NO agonists release Ca^{2+} from the endoplasmic reticulum .When intracellular levels of Ca^{2+}increase ,eNOS detaches from caveolin and is activated .Once intracellular calcium is depleted , a signal sent to membrane receptors open Ca^{2+} channels allowing extracellular calcium into the cell .This process is called capacitative Ca^{2+} entry.Ca^{2+} attaches to protein calmodulin in the cytoplasm of the cell ,it undergoes structural changes and bind to eNOS and then eNOS convert L arginine to NO.Hence its well evident that NO production is dependent on intracellular Ca 2+ sores and extracellular calcium..When Ca 2+ levels decrease it causes calcium –calmodulin complex to dissociate from eNOS ,which in turn binds with caveolin and becomes inactivated again .Release of NO relies on intracellular Ca 2+.

Shear stress ,by the action of protein kinases causes eNOS phosphorylation and increases NO production .Shear stress allow transfer of blood borne agonists to attach to endothelial cell receptors and stimulate them and increase intracellular Ca^{2+} .Shear stress also activates specialized Ca^{2+} activated K^+ channels on the endothelial cell surface causing K^+ efflux and Ca^{2+} influx into the cells .Duration of shear stress determines the proportion of contribution from Ca^{2+} and eNOS phosphorylation to NO production.NO production in short duration shear stress depends on intracellular Ca^{2+} and in long duration shear stress ,it depends on eNOS phosphorylation .

Once NO is synthesized in the endothelial cells ,it diffuses across the endothelial cell into the adjacent smooth muscle cells and bind to the enzyme soluble guanylyl cyclase .This activated enzyme convert GTP to CGMP.This decreases smooth muscle contraction and also CGMP reduces Ca2+ release from sarcoplasmic reticulum .Both these actions reduce smooth muscle contraction .NO is responsible for resting vasodilator tone.

Other functions of NO are –prevent platelet activation,leukocyte activation and also prevent adhesion to the vessel wall ..Endothelial damage initiates inflammatory cascade .It begins with recruitment of leukocytes at the damaged site .

Role of PGI-2 and TXA_2 in regulation of vascular function:-

PGI-2 and TXA_2 regulate vascular function .They are produced by COX enzymes .COX-1 is expressed in endothelial cells and COX -2 is expressed when endothelium gets damaged and is exposed to inflammatory cytokines.

Arachidonic acid is converted to PGH_2 by COX-2 ,which is converted to $PGI_2$by prostacyclin synthase .PGI_2 binds to prostacyclin receptors located on platelets and vascular smooth muscle cells .286Activation of platelet IP receptors lead to inhibition of platelet aggregation . PGI_2 binds to prostacyclin receptors on vascular smooth muscle cells activate adenylate cyclase and induce synthesis of cAMP.cAMP then activates protein kinase A and causes smooth muscle relaxation .Thus both NO and PGI_2 are responsible for dilation of blood vessel.

TXA2 is responsible for platelet aggregation and vasoconstriction .Arachidonic acid is converted to PGH_2 by COX-1 ,after which TXA2 is formed by thromboxane synthase . ,TXA2 acts on thromboxane –prostanoid receptors located on platelets and cause their activation and cause platelet aggregation .TXA2 acts on thromboxane –prostanoid receptors located on vascular smooth muscle cells,activate phospholipase C .This causes increase in intracellular Ca 2+ levels in the smooth muscle cells causing vasocontriction.Balance in levels of PGI2 and TXA2 maintain homeostasis in the healthy vessel .

Endothelial dysfunction (ED) marks the initial stage in atherosclerosis .Its a good prognostic marker of future cardiac events in patients with CVD .Drugs used in CVD diseases such as anti hypertensives and statins have beneficial effect on endothelial function by decreasing oxidative stress and lipid accumulation .

Endothelium is atheroprotective and ED leads to atherosclerotic lesion formation and subsequently to cardiac events..

Techniques to assess endothelial function:-

Endothelial function are most commonly assessed in the peripheral circulation and it helps in assessing the endothelial function in the coronary arteries .Patients who have established CVD or at risk of CVD assessment of endothelial function is a good predictor of future cardiac events .Assessment involves measurement of dilation in response to stimulus ..Impaired vasodilation is indicative of poor endothelial function . Assessments of microvascular endothelial function can be done with LDI with iontophoresis,and assessments of macrovascular endothelial function using FMD with Doppler Ultrasound19,20-22].

Iontophoresis-The assessment of NO bioavailability in the microvasculature is conducted using Iontophoresis.

Forearm blood flow and venous occlusion Plethysmography –Assesses Endothelial function of the forearm resistance vessels

Nailfoldcapillaroscopy- helps to assess capillary morphology .It helps to diagnose changes in size of capillaries ,changes in numbers and also structural impairments.

Flow Mediated Dilatation (FMD) –FMD ,checks NO bioavailability, it quantifies dilation .

Strain gauge plethysmography-Another method to quantify dilation .

Pulse wave analysis and Pulse wave velocity –evaluate coronary microvascular endothelial function .It also assesses arterial stiffness from the peripheral circulation ..PWA is the single measurement of radial artery pressure waveforms.

Carotid intima –media thickness -Carotid intima –media thickness is assessed by B mode ultrasound .It detects thickening of the medial layer of the vascular wall .It helps to predict cardiac events in patients of early atherosclerosis and also restenosis in patients who undergone PCI .

Overall IMT is increased in RA patients as compared to the healthy controls . Longitudinal assessment of ESR and CRP revealed CRP was related to IMT ,but not to ESR .Hence more research is needed to determine why CRP is related to IMT and not ESR.

Endothelial dysfunction in ra:-

Endothelium plays vital role in homeostasis and prevention of atherosclerosis .Turbulence leads to ED and if left untreated leads to atherosclerosis and cardiac sequale.

There is substantial evidence to support the fact that there is ED in RA ,a precursor to cause atherosclerosis as a sequale. 23,24Therefore assessment of ED in RA patients with traditional risk factors is vital to identify vascular abnormalities and plan strategies to improvise endothelial function and lower CVD risk 61

*Cardiovascular diseases contribute a major cause of mortality in Rheumatoid Arthritis patients.*1,2.Inflammation and severity of RA are the major determinants of ED in RA patients. 27 There is also evidence that high grade inflammation associated with RA induces accelerated atherosclerosis 28,30

.As compared to healthy control group ,RA patients have poorer endothelial function in both the microvasculature and the microvasculature 31-35.Antiinflammatory agents improve endothelial function in different vascular beds 32, highlighting the role of inflammation on the vasculature in RA .

The pathogenesis mechanisms behind articular inflammatory process in RA andthe inflammatory process in blood vessels of atherosclerotic CVD are similar.Also raised levels of inflammatory mediators (CRP,IL-6,TNF –ALPHA) are seen in both the conditions ,so it has been speculated that RA disease related inflammation might contribute to accelerated atherosclerosis.28These proinflammatory molecules promote endothelial dysfunction (ED). In Ra both microvascular and macrovascular endothelial functions are affected Adequate control of disease activity and inflammation in RA patients can lead to improvements of CVD outcomes in RA patients.36.Non invasive assessments of vascular function and structure in RA patients will help in screening these patients at and an earlier stage and plan a management .

.Inflammation is evaluated by measuring CRP ,ESR . CRP is directly linked to arterial stiffness and vascular dysfunction .37,38 The acute phase response is attributed to TNF-ALPHA and IL-6.

There is a noted trend for an association between microvascular endothelial-dependent function and CRP. Continuous long-term high levels of inflammation play vital role in ED in RA.CRP duration is a better predictor of ED in RA than current CRP and ESR levels .ESR/CRP duration affect arterial stiffness39-40 and so is for cIMT41-43

Disease activity and x ray scores are used to assess disease state and response to treatment .Hingori et al 44proved direct proportionality between high levels of disease-relatedinflammation at the time of the assessments may have contributed to theimpairments in endothelial function. acute inflammation can result intransient impairments in endothelial function 44.Disease duration has a lesser influence on endothelial function than current disease-related inflammation.45,46.The link between inflammation and vascular function was demonstrated in RA patients without established CVD disease ,47.Vascular function is progressively affected in course of RA .Patients with long disease duration of RA have significantly impaired endothelial function .Long term inflammatory burden associated with vascular function 49 In the context of RA, various disease related parameters may exert differential effects in different sized vessels .In RA ,systemic inflammation has significant impact on the vasculature and is a significant contributor of atherosclerosis.

Both of RA disease duration and greater frequency of inflammatory fluctuations which could impact on endothelial function. It is possible that cyclical fluctuations of high and low disease activity which could acutely impact on the vasculature 50 could be more critical than disease duration on impacting endothelial function.

However, cIMT has been reported to be associated with disease duration 52 and represents a later stage of atherosclerosis .There is evidence that structural defects in the vessel as determined by carotid intima-media thickness are present in patients newly diagnosed with RA 51

Radiographic damage using sharp score is a marker of inflammatory activity in the joints was found related to arterial stiffness.They provide better reflection of burden of RA

CVD risk factors such as ageing ,smoking,hypertension ,dyslipidemia cause arterial stiffness CVD risk factors are known to impair endothelial function in the general population 12 their contribution to impairments in endothelial function in RA is worth exploration . global CVD risk was greater in the RA patients. Role of traditional risk factors in the context of systemic inflammation as key players of impairing endothelial function in RA requires further exploration. inflammation has been reported to independently contribute to CVD 13.
Stiffening is caused due to a reduction in NO production from endothelial cells ,loss of smooth muscle tone ,degeneration of elastin fibres,increased collagen deposition in the vascular wall.Morphological changes in the vasculature cause arterial stiffness and affects the function of the blood vessels.

Arterial stiffness is increased in RA compared to control group.Inflammatoryburden ,ESR ,joint assessment and physician global assessment are predictive of arterial stiffness,39Further, ESR was only found to associate with cIMT in the presence of classical CVD risk factors.

Further analysis revealed that age was the main contributor for these associations, andmost likely accounted for the higher FRS and TC SCORE in RA patients relative to healthy controls.A limitation of global CVD risk is that they only incorporate classical CVD risk factors .It should include inflammation as a factor also. 13. It has also been suggested that incorporating coronary artery calcification into the FRS algorithm would increase the accuracy of estimating future risk of CVD, as high FRS score independently associates with coronary artery calcification in RA53.

Microvessels because of their widespread area and large proportion have greater exposure to injurious stimuli 55Small changes in global CVD risk could have a greater effect on microvascular endothelial-dependent function.Microvascular dysfunction is common in diabetes and hypertension and may even contribute to the development of macrovascular disease 54 Hence assessments which examine both vascular beds may provide more meaningful clinical information on vascular risk in RA.

High disease-related inflammation and inflammatory fluctuations both have significant affect on on microvascular and macrovascular endothelial function in patients with RA.ED is also dependent on FRS, metabolic syndrome, parameters of insulin resistance, SBP,presence of high cholesterol and hypertension as well as the total number of CVD risk factors..CVD risk factors may differentially affect endothelial cell and smooth muscle function.56,57and cause smooth muscle dysfunction.74,75

In RA patients which reported that components of the metabolic syndrome such as insulin resistance, were strongly associated with cIMT.These metabolic parameters cause ED and lead to carotid atherosclerosis subsequently Carotis atherosclerosis is caliberated by measurement of cIMT.

Besides disease-related inflammation and individual classical CVD risk factors, other RA specific factors such as physical inactivity 58, rheumatoid cachexia 59 and genes 60 that may also affect endothelial function in RA.Hence further research is needed to identify other RA specific factors

Targeting Different Inflammatory Pathways:-
Treatment of RA with i disease-modifying anti-rheumatic agents (DMARDs) such as methotrexate.exert beneficial effects both in terms of RA disease progression as well as CVD risk factors, endothelial function and eventual CVD outcome 61,62

However, in patients who are DMARDs non responders , biologic agents suchas the anti-TNF-α, anti-IL6 receptor, anti-CD20 and selective co-stimulation modulators are often used. These agents target different pathways of inflammation, and hence improvements are seen in RA symptoms and endothelial .63-65These medications by affecting inflammatory pathways ,thus effect the CVD outcomes in RA patients.

Conclusion:-

Rheumatoid Arthritis patients have impaired vascular function and structure.A correlation between RA and accelerated atherosclerosis has been well established24

A number of studies have reported impaired microvascular endothelial function in the coronary circulation of RA patients 66-68 which can be reversed with anti-inflammatory therapy 66,67

In RA patients, both RA disease-related inflammation and classical CVD risk factors have a greater impact than on the vasculature. High grade inflammation in RA is the cause of accelerated atherosclerosis 30 .This fact become more evident with a number of studies that have reported impaired microvascular endothelial function in the coronary circulation of RA patients67,68, which can be reversed with anti-inflammatory therapy 66,67
There is differential impact onmicrovascular and macrovascular endothelial function. Several studies in patients suspected of CVD and those with established CVD report that poor microvascular and macrovascular endothelial function at baseline are good predictors of atherosclerotic progression and future cardiac events 70,71

Assessment of endothelial dysfunction in Rheumatoid Arthritis patients with CVD risk patients will help to identify vascular abnormalities and help to plan a management with strategies and interventions that can improve endothelial function and cut down CVD risk .

More research is needed needed to confirm whether CVD risk factors affect vascular function and to determine parameters to predict long-term CV outcomes in RA.

Future Research:-
Few studies have analyzed the effect of traditional CVD risk factors on endothelial function in RA 72,73.More research is is required to explore the interplay of traditional risk factors and endothelial function in RA patients .We have ample evidence for ED in RA patients but its correlation to disease activity and synergist role of traditional CVD risk factors still has to be explored further.

Longitudinal studies are required to examine the concept of accelerated atherosclerosis .Studies are needed to assess the effect of fluctuations in disease activity on vascular changes over time . High levels of IMT are predictive of cardiac events in RA .Vascular functions are predictive for cardiovascular events but detailed longitudinal studies are further required .Once the causes of ED are clear ,interventions can be developed to improve vascular function and structure in RA

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