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MECHANISTIC STUDY OF RISK FACTORS OF RHEUMATOID ARTHRITISAND ITS ASSOCIATION WITH ENDOTHELIAL DYSFUNTION, ATHEROSCLEROSIS AND INFLAMMATION - A REVIEW

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Abstract:

Rheumatoid arthritis (RA) is a chronic autoimmune disease that mainly affects the lining of the synovial joints, which are characterized by painful, swollen joints that can severely impair body function and quality of life. Risk factors of RA involve age, gender, genetics, and environmental exposure (smoking, air pollution etc.). RA, leads to the activation of endothelial cells (ECs). Leukocyte adhesion molecules are activated due to activation of ECs which induce atherosclerosis. Endothelial (ED) dysfunction is considered to be a failure of endothelial remodeling processes.

Atherosclerosis is a condition of inflammation which alters endothelial functioning and promotes response to injury, associated with increased exposure to adhesion molecules. Inflammatory cytokines such as IL-6, TNFa, are independent of predicting subsequent atherosclerosis. Endothelial dysfunction is an autoimmune diseases of RA involve body's immune response like macrophages and dendritic cells may be helpful in diagnosing atherosclerosis and endothelial dysfunction.

Symmetric (SDMA) and asymmetric (ADMA) dimethylarginines are biomarkers (CVD) in many areas of atherosclerosis.

Inflammatory cytokines such as IL-6, TNFa, are independent of predicting subsequent atherosclerosis. In the current review, a link between RA, Endothelial dysfunction and atherosclerosis will be discussed in emphasizing inflammation as a cause of disease.

Key words: Rheumatoid arthritis, endothelial dysfunction, atherosclerosis, inflammation.

Introduction:

Rheumatoid arthritis (RA) may be a chronic autoimmune disorder that happens more often in women when compared with men, most ordinarily seen in adults[1].Rheumatoid arthritis is autoimmune disease best referred to as synovitis[2]. the speed of increase reported in 2002 went from 0.5% to a quarter of the population and had regional variability. [1] RA strongly affects the liner of the synovial joints and may cause progressive paralysis, premature death, and social and economic burdens. Clinical manifestations of concomitant joint involvement include arthralgia, inflammation, redness, and reduced range of motion [3].The release of pro-inflammatory cytokines and other pro-inflammatory molecules results in joint degeneration [4,5]. Inflammatory cytokines, including tumor necrosis factor (TNF) -a, interleukin (IL) -1, IL-6, IL-17 and mediators produced by downstream pathways on the edges of the bones, forming cartilage and bone destruction[6] This includes other mediators like IL-1 (IL-33, IL-36, IL-37, IL-38) and IL-12 (IL-27, IL-35), also as other cytokines like IL-. 32, IL-34.

Inflammatory synovium, inflammatory cytokines, autoantibodies, are the most explanation for bone erosion and also the receptor activator of the RANK Ligand. The breakdown of tolerance leads to the activation of immune and non immune cells that increase the assembly of inflammatory mediators.[7] Compared with patients without RA, the patients with RA have increased cardiovascular morbidity and mortality. Cardiovascular mortality occurs within 8 years of the primary symptoms of RA, but a pathophysiological process that has shown endothelial dysfunction (ED) may begin earlier [8,9,10].The explanation for ED in RA could also be partly thanks to altered size or function of endothelial cortex cells, which are involved within the regulation of vasculogenesis and vascular repair [11]. The increased increase in CV mortality is especially the results of rapid atherogenesis which is that the second commonest endothelial dysfunction (ED) [12], a rare vascular disorder present in RA patients [13].

Proinflammatory cytokines involved within the pathogenesis of RA, like TNF, IL-1, and IL-6, also are involved within the formation and progression of atherosclerotic plaque. the primary step in plaque formation is to use endothelial cells and therefore the insertion of endothelial dysfunction (ED) by active cytokines. Proatherogenic

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and prothrombotic endothelium is characterized by regulation of adhesion molecules, increased vascular strength, cytokine and chemokine expression, and decreased production of vasodilatory molecules, like gas [14].Nitric oxide (NO) may be a major vasodilatory and antiproliferative compound, which inhibits the activity and adhesion of the vessel wall of leukocytes and platelets [15]. The ineffective ability of endothelial cells to supply NO may be a major ED driver. [16]

Inflammation and atherosclerosis in RA

They share many similarities, including T-cell, mastocyte activation, tumor-necrosis factor (TNF) production of anti-inflammatory cytokines such TNFa and interleukin (IL) -6, and increased expression of leukocyte synthesis molecules. [17]

Patients with RA have acute phase reactive C reactive protein (CRP) levels, a symbol of inflammation related to heart risk. additionally , CRP causes endothelial dysfunction by reducing endothelial gas synthesis, a potent anti-athogenic factor [18].

Elevated erythrocyte erythrocyte sedimentation rate (ESR) in patients with RA have higher rate of cardiac death. This inflammatory marker also increases with arteria carotis intima-media thickness in patients with RA and healthy controls [19].

The system plays a crucial role within the progression and development of atherosclerotic disease and related problems. Atherosclerosis is really now considered an autoimmune disorder [19,20,21]. The presence of inflammatory cells like macrophages and activated lymphocytes within the atherosclerotic plaque may be a strong indicator of system involvement. additionally , the inflammatory load in RA and other rheumatic diseases increases the oxidative process of LDL (oxy-LDL), which results in the formation and progression of atherosclerotic plaque [22]. Bull-LDL macrophages [20] enhance the inflammatory response by synthesis molecules by endothelial cells and by pro-inflammatory cytokines (TNF alpha, IL-1, IL-6). Mature dendritic cells (DCs) express CCL17, which favors T-lymphocyte uptake; Further enhances the presence of modified or localized LDL, inducing T-lymphocyte proliferation of co-stimulating molecules in DCs. Modified LDL are often introduced by DC to make new antigenic epitopes and convey into clonal proliferation of LDL-specific T-lymphocytes. In fact, approximately 10% of all T-lymphocytes found in human atherosclerotic plaques detect uniquely modified or local LDL. Notably, LDL-specific T-lymphocytes also are in circulation [23]. Elevated levels of pro-inflammatory cytokines can eliminate the systemic inflammatory condition resulting in atherosclerotic proliferation: cytokines, along side their role in regulating immune responses, mediate many metabolisms within the short-term, transgenic or infectious Systemic release of produced IL-1, IL-17, IL-6 and TNF-of, pro-atherogenic functions. Promotes liver, fat , striated muscle , and vascular endothelium count, including insulin resistance, dyslipidemia, endothelial activation, and prothrombotic and antifibrinolytic effects [21].

CRP and other factors released by leukocytes contribute endothelial damage. Immune abnormalities like auto-antibody production could also be involved in endothelial damage and therefore the progression and cleavage process of atherosclerotic plaque. autoantibody are often found in atheroma within the sort of atherocomplex and is related to endothelial dysfunction and increased mortality [24].

Cardiac abnormalities and atherosclerotic vascular involvement, anti-citrulinated peptide antibodies (ACPA) were higher in RA. [25] Citrulled proteins, including citrulled fibrinogen, are present within the atherosclerotic plaque and are co-localized with peptidylargininediminase type 4 (PAD-4). additionally , ACPA serum levels correlated with subclinical atherosclerosis indicators. These observations, support that epitopes in the region of atherosclerotic plaque could also be targeted by the RA-associated ACPase, forming immune complexes that enable local plaque inflammation and progression occurs [26].

Several studies have shown that endothelial dysfunction play serious role within the pathogenesis of atherosclerosis, promoting early atherosclerotic changes and predicting the event of cardiac events [27,28]. Patients with RA have higher arterial atherosclerotic plaques formation [29,30] and therefore the atherosclerotic plaques corresponding with disease duration[31].

Cardiovascular disturbances and deaths are often prevented by early detection of atherosclerosis in RA.

Importance of TNF as a pro-inflammatory cytokine in rheumatoid arthritis

Biological treatment plans were used to deal with acute RA when you consider that 1997 and are designed to goal particular elements of inflammatory pathways. Among them are anakinra, an IL-1 antagonist; Abatacept, which regulates T mobileular activation; Chimeric anticancer CD20 antibody which inhibits infliximab, adalimumab and etanercept, rituximab, B mobileular activation which inhibit TNF activity.[32] The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) offer steering on the right symptoms for starting up biological remedy for RA in spite of the conventional DMARDs for the remedy of disorder or excessive disorder activity, and chance elements are lively in sufferers with bad outcome on radiography and ACP Positivity and tuberculosis[33]

As referred to above, TNFα is an vital cytokine withinside the pathogenesis of synovial infection in RA, even though it has been proven to play an vital position withinside the combat towards contamination in animal

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specimens[34]. TNFα is a kind II transmembrane protein that converts the enzyme (TACE) into TNF-through soluble form. It acts as a ligand for 2 receptors, TNFR1 and TNFR2, to transmit anti-apoptotic and pro-inflammatory signals. TNFα-mediated features include phagosome maturation, autophagy inhibition, and apoptosis after activation of Caspase eight through TNFR1.[35] By stopping those actions, anti-TNF remedy suppresses the immune system[36], and improves results to clinically suppress infection and function. However, TNF inhibitor remedy has been proven to result in neurological events[37]

Endothelial dysfunction

Endothelial dysfunction (ED) is a vital event within the method of atherosclerosis. In 2002, impotency was diagnosed in RA patients and is currently thought-about an important treatment for hardening of the arteries in RA patients.[38] Vasot endothelium is a full of life membrane, and it plays a vital role in regulation body processes similar to tube tone, inflammatory response, and blood clotting. epithelial tissue operate is impaired once exposed to mechanical and chemical stress. impotency ends up in a rise within the strength of inflammatory cells such as monocytes. On the opposite hand, this epithelial tissue disfunction is associated with the expression of synthesis molecules and inflammatory cytokines, permitting monocytes to enter the underlying endothelium. A mouse sample of RA showed a discount in acetylcholine-endothelium vasodilation.[39] On the opposite hand, the effectiveness of epithelial tissue depends on a balance between endothelin-like starch one and dilator substances similar to vasoconstrictor II (ANG II), thromboxane A2 (TXA2) and prostocycline (PGI2), element . Oxide. NO) and epithelial tissue hyper spinoff hyperproliferation issue (EDHFs)[40]. Animal species of RA are found to possess low NO detection. 2 blood vessel regulators created with TXA2 and PGI2 Cox (COX). COX a pair of will increase throughout inflammatory responses and inflated exposure to those enzymes is discovered in RA animal samples. In some ways, higher manifestations is seen within the production of nicotinamide purine dinucleotide phosphate (NADPH) oxidase, Lone-Star State syntheses, PGI2 syntheses and O2.7 (superoxide) .[41]

Flow Mediated vasodilation

Flow-mediated dilation (FMD) regulates the tone and structure of normal, healthy endothelium and enhances anti-platelet, anticoagulant and fibrinolytic properties . Preservation of the tone of blood vessels is achieved by the release of as many as nitric oxide (NO). Endothelial dysfunction occurs when any bioavailability availability is reduced [42,43,44,45,46].

FMD is most widely used endothelial function tests in vivo [47]

Factors of cardiovascular risk , such as smoking, poor posture, abnormal sugar or lipid dysbolism and high blood pressure, can alter endothelial function and interact with FMD dysfunction. In addition, FMD impairment increases the risk of future cardiac events and is a symptom of generalized atherosclerosis [48-51].

In RA patients, FMD was impaired without the presence of risk factors for classical atherosclerosis, compared with controls. RA patients showed a lower risk of FMD compared to with diabetic patient as RA is a risk factor for atherosclerosis. Endothelial stress in these patients is relates the disease activity (DAS28), duration of disease, HLA-DRB1 shared epithelium, and indicative of inflammation [52]. In addition, the magnitude of endothelial stress in RA patients is assessed by DAS28, ESR and CRP[53]. FMD also does not work well in patients with pre-existing disease, indicating that the atherosclerotic process begins early [54]. Other studies show nitroglycerin (NTG) for vasodilation loss in RA patients.

Intima-media thickness

High-resolution B-mode ultrasound is used to determine the carotid atherosclerosis by measuring the normal density of carotid intima-media (IMT). Increased IMT is associated with the onset of CVS events and is associated with atherosclerosis risk factors, such as smoke, hypertension, diabetes, hypercholesterolemia and esophagitis [55]. Numerous studies have reported an increase in IMT in patients with arthritis, particularly in patients with psoriatic arthritis, ankylosing spondylitis and systemic lupus erythematosus indicating an increase in control IMT [56,57]. The increase in IMT was observed with respect to age and similar controls for sex in RA and patients: a meta-analysis from 22 studies in 2011 have said that seventeen of the 22 studies reported statistically significant IMT in RA patients with controls. The mean IMT was 0.62 mm in the control group and 0.71 mm in patients with RA apart from other cardiac risk factors [58,59]. IMT in RA patients is associated with duration and severity of the disease. In addition, increased IMT and the presence of carotid plaques predict the risk of heart disease in RA patients [60,61]

ADMA and endothelial dysfunctioning in RA pathophysiology

An assortment of techniques can cause ADMA levels to ascend in RA patients. Induble (NOS) is an isoform installed in different cell types under the state of irritation; INOS assumes a significant part in the intracellular recognition of microbes and vasodilation of incendiary tissues [62]. Nonetheless, expanded creation of NO by INOS, particularly by incendiary cytokines, prompts S-nitrolysis of dynamic cysteine in DDAH, prompting ADMA catabolism, in this manner expanding its levels and forestalling three isoforms of NOS [63]. In vitro concentrates on endothelial cells have shown that TNF, a cytokine that assumes a critical part in pathogenesis of RA, inhibitorily affects DDAH prompting degenerative ADMA inadequacy. [64] In RA patients, openness to free extremists and nitrocytosine delivered by rheumatoid synovia and DDAH catalysts in the hypoxic district of fiery

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synovia adds to DDAH inhibitors and builds levels of plasmatic ADMA [65,66,67]. Another clarification for the undeniable degrees of ADMA is its item development through PRMT work: Begger et al. Expanded creation of ADMA in endothelial cells communicated in nearby and oxidized LDL (oxyLDL) has been accounted for because of some improvement in PRMT quality articulation [68]. Oxidation rate is higher in solid subjects than in patients with RA because of provocative conditions because of oxidative pressure [69,70]. Likewise, other LDL interpretation changes are additionally included [71]. In rheumatoid synovia, endothelial cells go through morphological changes because of expanded action, angiogenesis and apoptosis [72]. Expanded cell multiplication related with expanded endothelial cell recovery and angiogenetic micronization of developed joints might be a wellspring of methylarginine. Because of the advantages of methylated protein, the creation of ADMA in endothelial cells and maturing increments: [73]

Homocysteine (Hcy) is a sulfide-containing amino corrosive that is basically created from the fundamental amino corrosive methionine. HC levels are influenced by various components, including age, sexual orientation, way of life factors (espresso utilization, smoking propensities, active work and liquor), hereditary variations of proteins engaged with high catabolism, and medications and sicknesses that meddle with its digestion. R, and particularly bunch nutrients. (Folic corrosive, pyridoxine and cobalt) [۸.]. Hyperhomocysteinemia (HHcy) is a notable danger factor for CVD in everyone and in patients with RA [74,75]. A few creators have proposed a connection between expanded HHcy and ADMA levels; truth be told, Hcy represses DDAH movement and improves endoplasmic reticulum stress reaction proteolysis in broken endothelium, in this manner expanding ADMA levels [76,77]. In RA patients, a few elements add to the increment in Hcy serum levels. Constant aggravation expands the turnover of safe cells, builds the requirement for folate, and the utilization of methotrexate adds to folate insufficiency by hindering the compound dehydrofolate reductase [78,79]. The low bioavailability of methylenetrohydrofolate reductase, the primary surface of methylenetrohydroflate, confines the change of hess methionine, prompting HHCE [80]. The connection between NO digestion and HHcy isn't completely clear, as Hcy-decreasing specialists don't essentially influence ADMA levels [81].

The typical endothelium is liable for a significant number of the real capacities needed to keep up vascular uprightness, for example, guideline of vascular tone and anticoagulant and calming activities [82]. NO is the fundamental go between for some elements of the sound and useful endothelium, and thus, the capacity to deliver NO is a sign of ED [83]. The epithelial layer that prompts the early and subclinical phases of atherosclerosis incorporates cytokine and chemokin creation, articulation of combination atoms, platelet initiation, strange fibrinolytic movement, lipoprotein affidavit and safe cell relocation. To serious issues [84,85,86,81].

Methyllarginins influence endothelial capacity in an assortment of ways. Topsy-turvy methylarginins hinder the three isoforms of NOS, diminishing NO creation [87]. Likewise, ADMA and MMA contend with arginine for transmembrane transport by means of CAT, lessening surface accessibility for NO amalgamation [88]. Notwithstanding meddling with arginine-based NO creation, ADMA decides "NOS unplugging", an adjustment in NOS enzymatic movement from reductase to oxidase [89]. At the point when its surface is missing, NOS moves electrons to the particle.

ADMA is also associated with subtle symptoms of subclinical atherosclerosis, such as flow-mediated dilation (FMD) and intima-media thickness (IMT). The Brachial FMD artery is an ineffective method of measuring the response of a flow stream to non-invasive motions. FMD is a useful indicator of the risk of CVD because it is related with a higher rate of ED, an increased risk of heart attack, and coronary artery vasodilatory function [90]. In healthy studies, increased ADMA levels are correlated with lower FMD, indicating that ADMA is an ED biomarker [91,92]. In RA patients, endothelium-derived macrophages are identified during a year of the disease; Some authors associate the function of disease, while others have not confirmed it and have been associated with serology [93,94].

Ultrasonographic examination of carotid IMT is a reliable indicator of cardiac outcomes associated with traditional risk factors and the incidence of cardiac clinical events [95,96]. A meta-analysis of the literature published in 2015 reported an increase in carotid IMT with a higher prevalence of carotid plaque in RA patients compared with control subjects [97]. A meta-analysis showed that more than 6,000 patients had a positive association between carotid IMT and ADMA, suggesting the role to serological biomarker of cardiac risk [98]. In the case of RA, the literature data appears no confirmation in association between carotid levels IMT and ADMA [99,100,101,102]. One recent study, in 197 patients showed a strong association between ADMA levels and IMT by investigating biomarkers of micro- and macrovascular function , in those patients showing high disease activity: the authors showed a positive association between levels in ADMA and CIMT and between body mass index and ADMA / SDMA ratio, mainly in patients with high levels of inflammatory markers [103].

The current study demonstrated that changes of the endothelial phenotype occur at the first clinical signs of arthritis. However, some clinical studies have shown that CV risk increases RA onset [104,105]. In our study, at the preclinical stage of vascular dysfuctioning the depressed to NE without any changes in response to KCl contraction. Since this exploration is obtained in endothelial-dend rings, the problem is based on VSMCs and not on endothelial cells. Our results obtained in AIA mice echoed the recent discovery of Reynolds et al. [106] that

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mCIA shows a weaker contractile response to serotonin in the starting stages of development, which is associated with endothelial function as in our study. We added new information that this rheumatic disease is unstable only during arthritis. It is difficult to back down on the underlying policy right now. The role of pro-inflammatory cytokines can be ruled out as TNF-α and IL-1β levels are not elevated during this time of arthritis. From a clinical point of view, our data argue for the early diagnosis of vascular stress in RA to focus on vascular contractile response, for example "low-flow mediated contraction" (L-FMC), for which new technology has been introduced. Draining the arterial obstructive response to reduced human flow [107].

In conclusion, the current study in AIA mice provided new insights into the mechanism of ED in RA and showed that the pathology of vasodilator and vasoconstrictor responses occurs with a different time course in RA progression. From a clinical perspective, they identified plasma IL-1 TN, TNF-α and MIP-1α as biomarkers of ED in RA. From a therapeutic point of view, they emphasized the role of sperm in cross talk between NOS and COX-2 in RA-ED, a new antidote to NO-releasing NSAIDs to reduce the risk of CV in RA [108].

Conclusion:

Rheumatoid arthritis is an autoimmune inflammatory disease pathologically characterized primarily by synovitis. Joint destruction, which is associated with prolonged arthritis. Early diagnosis and intervention are essential for the prevention of serious damage and loss of essential bodily functions. The duration and severity of inflammation in RA is associated with a production of pro-inflammatory cytokines and a deregulation of anti-inflammatory cytokines. In recent years, the pro- and anti-inflammatory cytokines has expanded rapidly as the some of the new members identified that there is involvement of these mediators the pathogenesis of RA.

we demonstrated that microvascular functioning, IMT and arterial stiffness are associated with circulating ADMA and SDMA levels in RA patients with high inflammatory mediators, high systemic inflammatory load exerts its deleterious effects on vascular wall by inhibiting the production of NO as there is an interaction between dimethylarginines and endothelial cells. Therefore dimethylarginines, considered as an important mediators of endothelial dysfunction

Patients suffering from autoimmune disorders, such as RA, may suffer from accelerated atherosclerosis, due to the intense systemic inflammation. Our study confirms the study of endothelial function using the brachial artery method (FMD%) in clinical practice for detection of atherosclerosis. This review has highlighted on the role of systemic inflammation, proinflammatory cytokines, expression of adhesion molecules, immune dysregulation in the pathogenesis of atherosclerosis.

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