Pathogenesis of atherosclerosis in rheumatoid arthritis

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ABSTRACT

Increased morbidity and mortality in patients with rheumatoid arthritis (RA) is largely associated with cardiovascular disease. In this case, the factors that play a role is chronic inflammation. A chronic inflammatory associated with condition which accelerate atherosclerosis and increased cardiovascular morbidity and mortality. Inflammatory and atherogenic mediators have a role in pathogenesis of RA and atherosclerosis. Atherogenesis in RA start when cytokines from the inflamed synovial tissue are released into the systemic circulation. Circulating cytokines affects the function of other tissues such as adipose tissue, skeletal muscle, liver and vascular endothelium that would lead to proatherogenic transformation process such as insulin resistance, prothrombotic effects, pro-oxidative stress and endothelial dysfunction. Size, weight and duration of systemic inflammatory response in RA are the most important factor causing damage. IMT (Intima Media Thickness) measurement on common carotid arteries by B-mode ultrasound is a rapid non-invasive examination of the structural anatomy, reproducible and relatively low risks that are advantageous for assessing the risk of cardiovascular disease and monitoring disease progression.

Rheumatoid arthritis (RA) is an inflammatory disease - a chronic systemic autoimmune characterized by inflammatory polyarthritis and progressive joint destruction. In addition to an effect on quality of life, rheumatic diseases such as RA is also associated with increased morbidity and mortality.[1,2] Morbidity and mortality in RA is mostly associated with cardiovascular disease. Increased morbidity and mortality in patients with RA was not fully explained by traditional factors causes such as obesity, dyslipidemia, hypertension or smoking.[3-5] This paper reviews the pathogenesis of atherosclerosis and the role of IMT measurements in assessing the risk of cardiovascular disease and the factors that contribute to in RA patients.

Cardiovascular Morbidity and Mortality in Rheumatoid Arthritis

Population and cohort studies clearly explained that inflammatory diseases such as RA are associated with increased morbidity and mortality, mostly as a result of cardiovascular disease. The ratio of cardiovascular mortality is 50% higher in RA patients than controls which has reported by a population cohort study in Sweden between 1979 to 1994 that involved 606 patients with RA - positive RF.[6] Community study in the same place also reported that RA patients had a higher incidence of the myocardial infarction and the first cerebrovascular stroke than normal population.[7] Other data on UK General Practice Research Database (follow-up median of 5 years) showed all-cause mortality associated with myocardial infarction and vascular events of 1.5 to 1.6 times higher in patients with RA than in patients without RA.[8] The similar data were also obtained in the United States where there is an increase in all-cause mortality of patients with inflammatory polyarthritis RF positively with cardiovascular disease as the main cause.[9] Other studies with similar results obtain that RA is comparable to diabetes mellitus as an independent risk factor for cardiovascular disease events.[10]

In a cohort study in Rochester Minesota the United States found that the risk of cardiovascular disease in RA occurs earlier. Two years before the diagnosis according to the ACR criteria are met, the patient with RA 3 times more likely to experience a hospitalization due to myocardial infarction and nearly 6 times more likely to experience a myocardial infarction without symptoms. The pain of angina is more rarely reported and sudden death is more often experienced in patients with RA than without RA.[4]

Figures 30-days case-fatality rate is higher in patients with RA than patients without RA reported by Van Doornum[11] and Solomon et al.[12]

Increased cardiovascular morbidity and mortality in patients with RA is not able to be fully explained by traditional factors only as obesity, dyslipidemia, hypertension and smoking.[3-5,13] In a prospective study of the Nurses' Health Study (involving 114 342 women with 2.4 million patients follow-up-years), reported an increase of 2 times higher risk of myocardial infarction in women with RA than without RA.[3] Other studies, compared with the general population of patients RA is almost 4 times more at risk of new cardiovascular events even this risk remains three times higher despite already made adjustments to other traditional factors of cardiovascular risk.[5] Similar data from the UK General Practice Research Database also get a 1.47 times higher risk of incidence of acute myocardial infarction in patients with RA compared to without RA controls, which are independent of

other variables of the cardiovascular disease.[13]

Epidemiological studies above show that RA patients have a higher cardiovascular risk than patients without RA. This led to the perception of other factors that play a role. Another factor is chronic inflammation. Associated with a chronic inflammatory state that accelerates atherosclerosis and increasing the cardiovascular morbidity and mortality. Chronic and systemic inflammatory and immune dysfunction that occurs in the RA is considered to play a role in the acceleration of atherosclerosis and contribute to all stages of atherosclerosis (atherosclerosis, progression of atheroma and thrombosis).[4,14-16]

Pharmacological therapy that reduces inflammation, it can be shown to inhibit the progression of RA. Treatment with MTX reduces markers of inflammation in RA and lower cardiovascular mortality. Cardiovascular morbidity and mortality by all causes lower obtained in patients receiving MTX therapy was reported by Choi et al .[17]

Cohort study by Krishnan et al [18] in RA patients followed from 1980 - 1997 also get a drop in the number of deaths associated with atherosclerosis. Factors that lead to improved cardiovascular risk in these patients is the reduced use of NSAIDs, the improvement in functional status, physical activity and potent suppression of the inflammatory process.[17,19] Overall these things reinforce the view that inflammation plays an important role in cardiovascular events in RA.

Aterosklerosis and Rheumatoid Artritis

Atherosclerosis is a multifactorial process that has been started in childhood, but new clinical manifestations will emerge later in the elderly.[20] Atherosclerosis is cause of the main pathological process of cardiovascular diseases, including myocardial infarction and stroke.

The immune system plays a role in the pathogenesis of atherosclerosis.[21] Atherosclerosis is a process of immune-mediated that occurs in vascular system. The discovery of activated macrophages and lymphocytes in atherosclerotic plaques supports the concept of atherosclerosis as an inflammatory process of immune - mediated.[22] Tissue studies show many inflammatory cells at the edge of the atherosclerotic plaque that can lead to plaque rupture and the occurrence of cardiovascular events.[22,23] Studies of patients aortic specimens undergoing the coronary artery bypass grafting found the number of inflammatory infiltrates in the tunica media and adventitia were greater in patients with inflammatory rheumatic disease (including RA, SLE and vasculitis) than other patients.[24]

Increased risk of cardiovascular disease in patients with RA is a consequence of the presence of atherosclerosis. RA and atherosclerosis are both considered as an inflammatory disease. Both have similarities in several pathogenic mechanisms.[20,22,25,26] The RA through the resulting inflammation is an independent risk factor for accelerated atherosclerosis and cardiovascular disease. Traditional Framingham risk factors such as smoking, lipid profile and other factors clearly involved in improving mortality of cardiovascular disease. However, since the majority of cardiovascular deaths occurred in the group of RA patients with high inflammatory activity, RA autoimmune inflammatory factors can not be ignored and proved to have an important role.[3,4,8,25,27]

Table 1. Factors Play a Role in The Pathogenesis of Rheumatoid Arthritis and Atherosclerosis[25]

1.	Tradisional	Age
		Smoking
		Lipid Profile
		Hypertension
		Type-2 Diabetes Melitus
		Immobilization
		Sedentery Lifestyle
2.	Inflammation	Acute Phase Proteins (CRP, Fibrinogen)
		Autoantibodies (anti-CCP, RF, anti-OxLDL)
		Proarterogenik Cytokines (Th0/Th1 type)
		Chemokine
		Angiogenic *Growth Factor*
		Matrix-degrading Metalloproteinase
		Increased expression of adhesion molecules
		Hyperhomocysteinemia
		Impaired apoptosis
3.	Iatrogenic	Methotrexate – bimodal
		Corticosteroids – bimodal

Inflammatory and atherogenic mediators play a role in the pathogenesis of RA and atherosclerosis (see Table 1). The concept that inflammation causes and aggravate the atherosclerosis is proven by the discovery of inflammatory molecules and immune cells, especially on the shoulders of atherosclerotic plaques. The inflammatory cells in plaque facilitate erosion and rupture the collagen layer that separates the atheromatous material with blood. The situation like this is similar to the inflammation that occurs in the synovium in patients with RA. Atherosclerotic plaque immunologically similar to the synovitis in RA, characterized by the accumulation of inflammatory cells, especially monocytes / macrophages and T-cells.[28,29]

Inflammatory responses that occurs in atherosclerosis similar to the inflammation in RA which is cellular immune response (Th 1 immune response) dominated, characterized by large involvement of CD4+ T-cells. Lesions or infiltrates containing T-cells are always found in atherosclerotic lesions. Infiltrates that dominated by CD4+ T-cells recognize antigens of protein presented as fragments bound by class II major-histocompatibility complex (MHC). If the antigen receptor on T-cells binds to antigen, there will be an activation of cascade that causes the expression of cytokines, surface molecules and enzymes that are proinflammatory in nature. The macrophages are activated and initiate an inflammatory response that similar to delayed-type hypersensitivity which is a function of defense against intracellular pathogens.[23] The inflammatory cells in atherosclerosis and RA produce proinflammatory cytokines, chemokines, and metalloproteinase enzymes that will degrade the matrix. TNF-α and IL-6 are the major cytokine that plays an important role in the incidence of atherosclerosis and joints destruction in RA.[21,22,30]

In RA the key site of the inflammation is the synovium tissue. Sinovium cytokines will be released into the systemic circulation. Levels of TNF-α, IL-1β and IL-6 plasma are higher in untreated RA patients. Circulating cytokines can affect the function of tissues other than synovium, including adipose tissue, skeletal muscle, liver and vascular endothelium, that lead to a series of processes proarterogenik changes such as insulin resistance, prothrombotic effects, pro-oxidative stress and endothelial dysfunction. Each of these processes and the pathological pathways are interrelated, ends on the acceleration of atherogenesis (see Figure 1). Severity and duration of systemic inflammatory response in RA are the most important factors causing damage. Although the RA in a state of "silent", cytokines in the systemic circulation and regulator components often remain in a state of dysregulation than individuals without RA and continue to cause vascular damage.[30,31]

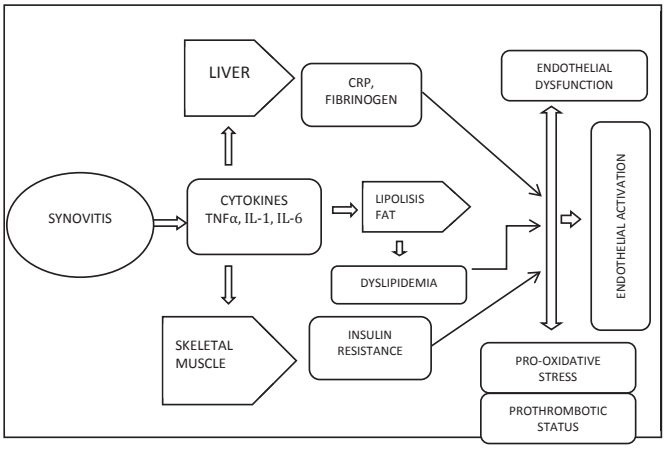

Figure 1. Mechanisms of Atherogenesis in RA
In RA, the main point is the inflammation is of the synovium tissue. From the site, cytokines are released into the systemic circulation. The circulation cytokines can effect the function of other tissues including fat tissue, skeletal muscle, liver and vascular endothelium; which resulted emergence a number of changes proaterogenik such as insulin resistance, dyslipidemia, pro-oxidatitive effect, dysfunction and endothelial damage (Modification by Sattar N, McInnes IB, 2008)1.

Major histocompatibility complex (MHC) class II of HLA-DR,-DQ and-DP subtypes are a regulator of immune responses in T-cell. Expression aberant/abnormal of antigen tissues in the endothelia is well known in an autoimmune disease such as RA and SLE.[32] The increase expression MHC class II in the endothelial plays an important role in activation and migration of T-cells and monocyte into the vascular wall. There is evidence of an association between abnormal endothelial expression with diffuse endotelial dysfunction. [33]

In chronic inflammatory conditions, there is a population of T-cells that express a particular phenotype such as absence of co-stimulatory molecules CD28. The number of T cells (CD4 + CD28-) is increased in the peripheral blood of chronic inflammatory diseases such as RA, especially in severe RA with systemic involvement and in patients with unstable angina. These T-Cell produce more INF-gamma, are cytotoxic and express natural killer cells markers includes CD56 and killer immunoglobulin -like receptors.[34-36] This pro-inflammatory subset of CD4+/ CD28- T cells cause tissue damage and lead to plaque instability. Besides found in culprit unstable coronary artery plaques, T cells with this phenotype is well known associated with thickening of the intima media tunica and endothelial dysfunction in RA.[37-38]

The Factors Associated with Cardiovascular Events in Rheumatoid Arthritis

1. The Severity of Disease

The severity of the disease is associated with increased risk of cardiovascular disease in RA. Disability as measured using the Health Assessment Questionnaire (HAQ), is a predictor of all-cause mortality and cardiovascular events[39,40] and associated with increased atherosclerosis.[41]

2. Genetic

The major genes that are known to cause someone more vulnerable to suffer from RA and inflammatory polyarthritis in Northern Europe is the HLA-DRB1 and PTPN22. HLA-DRB1 gene is associated with more severe disease in inflammatory of polyarthritis and RA.[42-44] An HLA-DRB1 allele groups that have the homology of amino acid in hypervariable region 3 in the chain of DR beta, which is known as the shared epitope (SE), is a genetic marker associated with RA poor outcomes such as disability and erosive disease.[44.45] Farragher TM et al.[46] found that the SE mainly the heterozygous alleles, relates to the all-causes mortality and cardiovascular disease, does not depend on anti-CCP and RF (Rheumatoid Factor) autoantibodies status.

3. Smoking

Smoking increased mortality and is a risk factor for the presence of atherosclerosis which is dose-dependent. Silman et al.[47] studied twins and found that smoking is an environment risk factor for RA. Population study by Goodson et al[48] found smoking increases the risk of cardiovascular disease before the onset of seropositive inflammatory polyarthritis. Hutchinson et al.[49] discovered a strong relationship between the amount of smoking (pack-years smoked) with severity of RA. Smoking is an important pathogenic factor in the disease course of RA. Smoking is also known initiate an increase protein formation and production of synovial citrulinasi anticyclic citrullinated peptide antibodies (anti-CCP) in RA patients who have HLA-DR antigen share epitope.[50]

4. Age and Duration of Illness

Atherosclerosis is an ongoing process that began at a young age and increases throughout life. Age of a person is one of the main factors that determine the extent of aterosklerosis.[51] Patients who have long suffered RA have more severe atherosclerosis than RA patients of the same age with an earlier onset. Del Rincon discovered IMT thickening rapidity per age unit increased proportionally to the length of suffering from RA, starts 0.154mm / 10 years in patients with

RA 7 years or less, up to 0.295mm / 10 years on patients 20 years or more. Atherogenesis accelerates after the onset of the RA. The length of suffered RA aggravate the effects of age on atherosclerosis. [52]

5. Extra-Articular Manifestation

The presence of extra-articular manifestations in patients with severe RA increases the risk of developing coronary and perifer artery disease.[53] Turesson et al found an increased risk of first cardiovascular events and coronary artery disease in patients with RA with extra-articular manifestations (pericarditis, pleuritis, Felty's syndrome, polyneuropathy, mononeuropathy, scleritis, episcleritis, glomerulonephritis, vasculitis major in the skin, vasculitis in other organs) compared with no extra-articular manifestations. This increase has nothing to do with age, gender, smoking, RF and erosive joint damage. [14]

6. Hypertension

Diastolic blood pressure was higher in a population study in patients with RA compared to control.[31] The same result was also found in a cohort study by Del Rincon et al in patients with RA match with normal population.[5] Adhesion molecule-1 (soluble ICAM-1) and IL -6 found by Chae et al significantly associated with blood pressure.[54] It seems that inflammation can cause the onset of hypertension, and contribute to the incidence of accelerated atherosclerosis. TGF-β genetic polymorphisms 689T / C and endothelin-1 found associated with increased blood pressure, independent of other hypertension risk factors and treatment.[55]

7. Dyslipidemia

Proarterogenik lipid profile has been found in blood donors 10 years before the onset of RA symptoms. Low HDL cholesterol levels, increased levels of oxidized LDL, and high levels of small dense LDL cholesterol are the description of the risk of atherosclerosis.[56] Inflammation caused by RA led to a situation that promotes structural changes in lipoproteins, causing changes in lipid profile proarteriogenik and increase cardiovascular risk in patients RA.[57,58] Proinflammatory cytokines such as IL-6 and TNF-α causes fatty tissue increasing free fatty acid synthesis. At the liver these cytokines also increase the formation of free fatty acids and triglycerides; and inhibit vascular endothelial lipoprotein lipase activity which is the main catabolic enzyme of lipid-rich trigliserida.[30,59]

8. Insulin Resistance

Glucose intolerance has been known to be found in patients with RA and other chronic inflammatory diseases. There is a positive correlation between the severity of impaired glucose tolerance with inflammation. Impaired insulin sensitivity (insulin resistance) in peripheral tissues associated with severe inflammation. Insulin resistance is found in several chronic inflammatory diseases and occurs more severe, especially in the muscle tissue rather than the liver. [59] Proinflammatory cytokines play a role in glucose intolerance and insulin resistance. Increasing TNF-α levels generating a state of chronic hyperglycemia. TNF-α that aggravate insulin sensitivity plays a role in chronic complications of diabetes.[60] These proinflammatory cytokines cause insulin resistance through its ability to reduce the activity of the insulin receptor tyrosine kinase. TNF-α also directly inhibit insulin dependent-glucose uptake on muscle tissue framework.[61]

9. Erythrocyte Sedimentation Rate

Improved Erythrocyte Sedimentation Rate can predict cardiovascular disease mortality in patients with RA. In RA population studies in Rochester United States revealed a higher risk of cardiovascular mortality in patients with ESR ≥ 60mm / h, vasculitis and pulmonary disease RA.[4]

10. C-Reactive Protein

CRP concentration, both in the general population and in cardiovascular disease populations, has a strong relationship with the incidence of coronary heart disease. CRP is an acute phase protein produced by the liver in response to an increase in systemic levels of IL-6. There was an evidence show that CRP has a direct effect on the walls of blood vessel resulting in the onset of atherosclerosis. These effects include stimulate cellular adhesion molecules formation, support adhesion and migration of monocytes pass through the blood vessel wall, help LDL-cholesterol macrophages uptake, and start complements activation.[14,62,63]

Biological markers of inflammation high-sensitivity C-reactive protein (hs-CRP) can predict cardiovascular events in general population. High hs-CRP levels indicate poor prognosis in acute coronary syndromes.[64] Baseline CRP is a predictor of cardiovascular mortality in patients with polyarthritis. In a cohort study for 10 years, Goodson et al[65] found CRP levels ≥ 5 mg / L was an important cardiovascular disease mortality predictor factor in newly inflammatory polyarthritis diagnosed patients, and was independent of other indicators (age, sex, smoking, HAQ score, RF and number of inflamed joints).

11. Body Mass Index

In contrast to the normal population, a low BMI - not obesity - is associated with increased cardiovascular disease in patients with RA. RA patients with low BMI (<20 kg / m ^{2}) had a risk of death was significantly higher cardiovascular compared to non-RA patients with a normal BMI.[66] BMI had an paradox effect on RA patient mortality. Patients with a high BMI have a lower mortality than patients who are thinner. Patients with BMI ≥ 30 had the lowest mortality, 1.7 deaths per 100 person years. Mortality increased in each BMI category decline. There was 15.0 deaths per 100 person years in BMI < 20.[67]

12. Anti-CCP Antibodies

Antibodies to citrullinated proteins and cyclic citrullinated peptides (anti-CCPs) are a highly specific marker for RA. These autoantibodies may predict poor outcomes and is associated with radiological damage and plays essential role in the pathogenesis of RA.[68,69] Lopez-Longo FJ et al[70] discovered anti-CCP antibodies are independently associated with the incidence of ischemic heart disease and was not associated with

anti-CCP antibody titers. There was no association between anti-CCP antibodies with other cardiovascular risk factors such as smoking, hypertension, dyslipidemia, overweight, or diabetes mellitus. Patients with anti-CCP positive (> 25 units / ml) had ischemic heart disease more frequent (6.5% versus 2.6%) and had a higher mortality than anti-CCP negative patients (11.2% versus 6, 8%). [70]

13. Antibodies Anti-Oxidized LDL

Oxidized LDL (ox-LDL) is a type of LDL cholesterol uptake by macrophages and had transformed into foam cells which is a typical sign of aterosclerosis.[71,72] Elevated levels of antibodies against ox-LDL is found in patients with premature peripheral vascular disease, severe carotid atherosclerosis and coronary heart patients who performed angiography. Antibodies against ox-LDL can also be found in patients with atherosclerosis, autoimmune rheumatic disease and healthy individuals. Autoantibodies against ox-LDL has been studied in several autoimmune rheumatic diseases such as systemic sclerosis, systemic vasculitis, SLE and RA.[72,73]

14. Thrombotic Factors Change

Some thrombotic markers of cardiovascular risk factors such as fibrinogen, von Willebrand factor, fibrin D-dimer and tissue plasminogen activator antigen increased in RA.[31] Thrombocytosis, which is one factor contributing to hipercoagulabel state, often found in RA patients. Proinflammatory cytokines (IL-6, IL-1, and TNF-α) is known as the cause of increased tissue factor and endothelial cell changes from state of anti-thrombotic to procoagulant and promoting clot. IL-6 also increases levels of fibrinogen.[59,74]

Intima Media Thickness (IMT) Carotid As Surrogate Markers of Cardiovascular Disease in Rheumatoid Arthritis

Measurement IMT (Intima Media Thickness) on carotid artery by B-mode ultrasound is a non-invasive examination of structural anatomy rapid, reproducible and relatively without risk useful for assessing the risk of cardiovascular disease and monitor disease progression. Case-control studies have shown that increased IMT measured using this method is a good indicator the presence of generalized atherosclerosis and coronary artery disease. Many epidemiological studies have proved that carotid IMT can provide preliminary information of early-stage or subclinical atherosclerosis at-risk individuals. The use of IMT carotid as a surrogate or a predictor of cardiovascular disease has been widely used. Increased IMT consistently associated with increased cardiovascular risk, and is not related to other traditional vascular risk factors. Increased IMT may occur several years prior to a cardiovascular event.[75-77]

IMT, a vascular layer of the tunica intima and media contains endothelium, smooth muscle and connective tissue, is the location of lipid deposition and plaque formation.[78,79] In a healthy middle-aged adult common carotid artery IMT varied from 0.6-0.7 mm. In the carotid bulb, IMT generally thicker. The thickness varies depending on age, gender and ethnicity. The thickness increases with age and is generally thicker in women. The IMT normal value is difficult to determined because of the differences in risk factors, location of measurement (segments, wall near / far wall), ultrasound devices and reading system used (manual or automatic). These things can lead IMT different values between studies. [76,80]

Common carotid artery thickness (CIMT) ≥ 0.60 mm is generally considered a sign of atherosclerosis and carotid plaques finding indicates of progress atherosclerosis. IMT acquired carotid > 0.90 mm and the discovery of atherosclerotic plaque can be considered as a sign of subclinical organ damage and effect cardiovascular prognosis.[79,81-83]

In the general population, the carotid IMT was a powerful predictor of future cardiovascular events was found in the meta analysis by Lorenz MW, et al.[77] In the meta analyst, involving 37.197 subjects who followed for 5.5 years (including the study of Kuopio Ischemic Heart Disease, Rotterdam study, Atherosclerosis risk in Communities study study, study the Cardiovascular Health Study), each absolute difference intima media thickness of 0.1 mm, the risk of myocardial infarction and stroke increased 10-15% and 13-18% respectively. So more than 20 cohort studies in subjects with / without cardiovascular disease and in subjects with / without previous cardiovascular risk factors, have consistently demonstrated that increased carotid IMT was associated with increased cardiovascular risk, not related to existing cardiovascular risk factors.[76]

In patients with RA, the increase in IMT and the presence of carotid atherosclerotic plaque was found both in patients with and without cardiovascular risk factors. Research Park YB et al[84] in Korea found RA postmenopausal women have an ultrasound marker of early atherosclerosis. Average IMT of carotid arteries RA patients without history of atherosclerosis and its complications found thicker than controls (0.77mm vs. 0.68). Early RA (<1 year) was associated with a thinner IMT than the late (> 1 year) RA (0.72mm vs. 0.78).

Kumeda Y et al[41] examined 138 patients and 94 controls RA of similar age, sex, and major risk factors for atherosclerosis. IMT carotid and femoral arteries found thicker than controls. IMT positively associated with carotid artery disease duration, Larsen scores and scores on the metacarpal joints and M-HAQ score.

The study by Roman et al[85] in 98 RA patients and 98 control patients similar for age, sex and ethnicity discovered carotid atherosclerotic plaques were more common in RA patients than in controls (44% vs. 15%,). The association between the RA and the presence of carotid atherosclerotic plaque remained significant after adjustment the traditional risk factors (age, hypertension, cholesterol, smoking).

Gonzales-Juanatey et al[86,87] disclosed an increase in IMT (0.779 mm vs 0.699) and atherosclerotic plaque (34% vs 15%,) in patients with RA (n = 47) without a history of atherosclerosis or previous cardiovascular risk (diabetes mellitus, renal insufficiency, hypertension, cardiovascular disease and cerebrovasular and smoking) compared to control. After five years, RA patients who have had a cardiovascular event have thicker IMT (1.01) compare to patients without cardiovascular events (0.74). IMT categorized into quartiles additionally associated with cardiovascular events. No cardiovascular events found in patients with carotid IMT

less than 0.77 mm, while 6 of 10 patients with IMT > 0.91 mm suffered cardiovascular events. This study shows that IMT carotid artery has a high predictive value for the onset of a cardiovascular event in next five years for patients with RA. RA patients with carotid IMT > 0,91mm have a risk of a cardiovascular event in the next 5 years. The finding of subclinical atherosclerosis manifested as an increase of IMT in RA patients without cardiovascular disease, is an explanation why the incidence of asymptomatic ischemic heart disease and the rate of sudden cardiac death in RA patients are high. [4]

Evans et al[88] discoverd the role of carotid plaque as a predictor of cardiovascular events in patients with RA. They revealed a 2.5 times increased risk of complications of cardiovascular events in patients with unilateral plaque, and 4.3 times if plaque was bilateral.

Del Rincon found thickening of IMT per unit age increased proportionally in line with the duration of RA.[52] IMT thickening ranging from 0,154 mm / 10 years in patients with 7 years or less RA up to 0.295 mm / 10 years in patients with 20 years or more RA. Patients who had been suffering prolonged RA are more often have atherosclerosis than patients with new onset. These results support the statement that atherosclerosis accelerated after the onset of RA.

CONCLUSIONS

Atherosclerosis and cardiovascular disease is an important cause of morbidity and mortality increase in RA patients than the normal population. Systemic inflammation caused by inflammation of the synovium in patients with RA resulted in a number of atherogenic changes, endothelial dysfunction and damage that initiate and aggravate systemic atherosclerosis in patients with RA. IMT carotid ultrasound examination using USG can identify subclinical atherosclerosis in RA patients who are high risk of experiencing cardiovascular events.

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