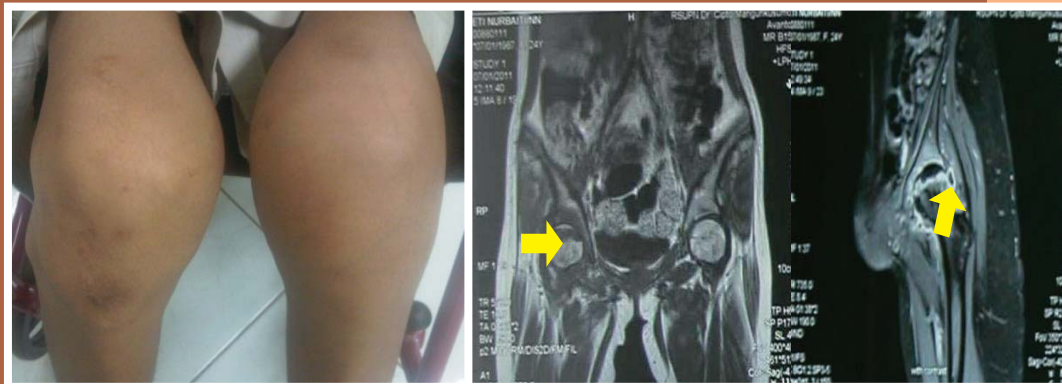


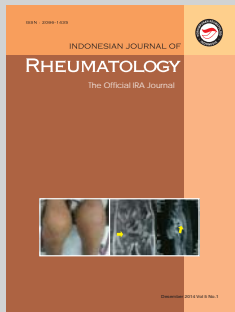
INDONESIAN JOURNAL OF

# RHEUMATOLOGY

The Official IRA Journal







Cover image: Physical examination revealed painful swelling of the left knee (see page 28) and Patient's MRI showed collapse of the right femoral head (yellow arrow) (see page 31).

**AIMS AND SCOPE**

*Indonesian Journal of Rheumatology* is self-focused on rheumatic diseases and connective tissue disorders in forms of original articles (extended or concise reports), review articles, editorial, letters, leaders, lesson from a memorable cases, book review, and matters arising. Both clinical and laboratory including animal studies are welcome.

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## Editor's note

YI Kasjmir

In this edition, the Indonesian Journal of Rheumatology emphasizes on aspects of physiology that serves as a reference in the treatment of diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), osteoarthritis (OA), osteomyelitis, and osteoarticular tuberculosis. RA is currently a devastating autoimmune disease. A review article by Pambudi et al studied the pathogenesis of atherosclerosis in RA and the role of intima media thickness (IMT) measurements in assessing the risk of cardiovascular disease. This review showed that common carotid IMT measurement on the arteries by B-mode ultrasound is a rapid non-invasive examination of the structural anatomy, is reproducible and has relatively low risks that are advantageous for assessing the risk of cardiovascular disease and monitoring disease progression. Another RA topic is an original article by Meriza et al which discusses the relationship between adiponectin and atherosclerosis in patients with rheumatoid arthritis. The result of the study showed that there was no statistically significant correlation between levels of adiponectin and markers of atherosclerosis in patients with rheumatoid arthritis.

There are two topics of SLE that discuss in this journal. SLE is a severe multisystem autoimmune disease, characterized by tissue deposition of antibodies, tissue damage, and heterogeneous clinical manifestations depending on which organs are affected. SLE is still a baffling disease because of its "clinical syndrome". Previous studies showed a significant role of vitamin D in modulating inflammation and immune abnormality in SLE. Neutrophil-Lymphocyte Count Ratio (NLCR) as an inflammation marker was significantly increased in the SLE patients. In the original article, Maslim et al evaluated the effect of vitamin D supplementation on disease activity and neutrophil-lymphocyte count ratio (NLCR) in SLE patients with hypovitaminosis

D. The other case report is by Sinaga et al which discusses about avascular necrosis of the right femoral head in a female patient with SLE. Avascular necrosis often involves multiple joints in SLE, in the which the femoral head is involved in most of these patients. Corticosteroid use is known as a major risk factor in the development of this complication. We report this case due to its common occurrence in SLE patients. The early recognition of avascular necrosis is essential to prevent morbidity.

Another original article presents a research about the correlation between the severity of knee osteoarthritis and serum levels of cartilage oligomeric matrix protein (COMP). OA is an ancient disease which to this day bears the aspect in the pathophysiology of inflammation and degeneration. Pain, inflammation, and joint stiffness due to osteoarthritis may cause physical disability. To prevent the increasing number of handicaps, an early diagnosis and accurate assessment of OA severity is needed. The sensitivity of radiographic examination in the diagnosis and severity assessment of knee osteoarthritis is still low. Kambayana et al evaluated the serum as a marker of cartilage damage indicator for the diagnosis and severity assessment of knee osteoarthritis.

And finally, there are two case reports in this issue on infection. This interesting case report by Singh et al is about osteoarticular manifestation of tuberculosis infection affecting the left knee in a man presenting with a history of tuberculosis pleural effusion. The diagnosis of tubercular arthritis can be challenging, particularly in the presence of confounding factors such as preexisting arthritis. The second case report presented by Utari et al is about the unusual case of chronic osteomyelitis of the wrist joint. This case became more complicated because of the patient's immunodeficient condition.

# 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.<sup>1,2</sup> 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.<sup>3-5</sup> 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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> Other studies with similar results obtain that RA is comparable to diabetes mellitus as an independent risk factor for cardiovascular disease events.<sup>10</sup>

In a cohort study in Rochester Minnesota 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.<sup>4</sup>

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

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.<sup>3-5,13</sup> 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.<sup>3</sup> 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.<sup>5</sup> 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.<sup>13</sup>

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).<sup>4,14-16</sup>

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.<sup>17</sup>

Cohort study by Krishnan et al.<sup>18</sup> 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.<sup>17,19</sup> Overall these things reinforce the view that inflammation plays an important role in cardiovascular events in RA.

### Atherosclerosis and Rheumatoid Arthritis

Atherosclerosis is a multifactorial process that has been started in childhood, but new clinical manifestations will emerge later in the elderly.<sup>20</sup> 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.<sup>21</sup> 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.<sup>22</sup> 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.<sup>22,23</sup> 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.<sup>24</sup>

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.<sup>20,22,25,26</sup> 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.<sup>3,4,8,25,27</sup>

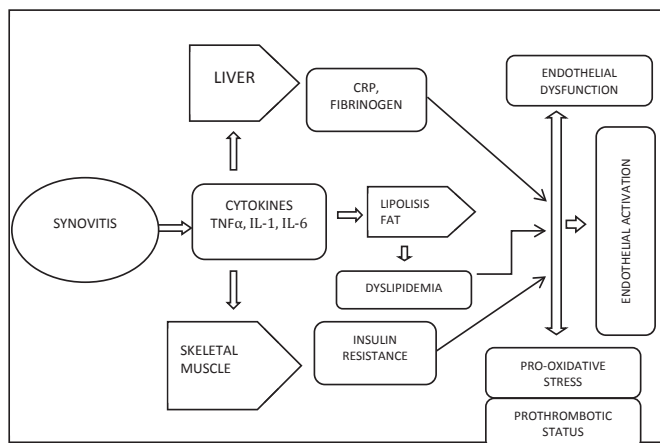
**Table 1. Factors Play a Role in The Pathogenesis of Rheumatoid Arthritis and Atherosclerosis<sup>25</sup>**

1. Tradisional	Age Smoking Lipid Profile Hypertension Type-2 Diabetes Melitus Immobilization Sedentary Lifestyle
2. Inflammation	Acute Phase Proteins (CRP, Fibrinogen) Autoantibodies (anti-CCP, RF, anti-OxLDL) Proarterogenic Cytokines (Th0/Th1 type) Chemokine Angiogenic <i>Growth Factor</i> 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.<sup>28,29</sup>

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.<sup>23</sup> The inflammatory cells in atherosclerosis and RA produce proinflammatory cytokines, chemokines, and metalloproteinase enzymes that will degrade the matrix. TNF- $\alpha$  and IL-6 are the major cytokine that plays an important role in the incidence of atherosclerosis and joints destruction in RA.<sup>21,22,30</sup>

In RA the key site of the inflammation is the synovium tissue. Synovium cytokines will be released into the systemic circulation. Levels of TNF- $\alpha$ , IL-1 $\beta$  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 proarterogenic 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 atherosclerosis (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.<sup>30,31</sup>



**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 proarterogenic such as insulin resistance, dyslipidemia, pro-oxidative effect, dysfunction and endothelial damage (Modification by Sattar N, McInnes IB, 2008)<sup>1</sup>.

Major histocompatibility complex (MHC) class II of HLA-DR,-DQ and-DP subtypes are a regulator of immune responses in T-cell. Expression aberrant/abnormal of antigen tissues in the endothelia is well known in an autoimmune disease such as RA and SLE.<sup>32</sup> 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 endothelial dysfunction.<sup>33</sup>

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.<sup>34-36</sup> 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.<sup>37-38</sup>

## 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<sup>39,40</sup> and associated with increased atherosclerosis.<sup>41</sup>

### 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.<sup>42-44</sup> 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.<sup>44,45</sup> Farragher TM et al.<sup>46</sup> 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.<sup>47</sup> studied twins and found that smoking is an environment risk factor for RA. Population study by Goodson et al<sup>48</sup> found smoking increases the risk of cardiovascular disease before the onset of seropositive inflammatory polyarthritis. Hutchinson et al.<sup>49</sup> 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.<sup>50</sup>

### 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 atherosclerosis.<sup>51</sup> 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 rapidly 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.<sup>52</sup>

### 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.<sup>53</sup> 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.<sup>14</sup>

### 6. Hypertension

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

### 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.<sup>56</sup> 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.<sup>57,58</sup> Proinflammatory cytokines such as IL-6 and TNF- $\alpha$  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 triglycerida.<sup>30,59</sup>

### 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.<sup>59</sup> Proinflammatory cytokines play a role in glucose intolerance and insulin resistance. Increasing TNF- $\alpha$  levels generating a state of chronic hyperglycemia. TNF- $\alpha$  that aggravate insulin

sensitivity plays a role in chronic complications of diabetes.<sup>60</sup> These proinflammatory cytokines cause insulin resistance through its ability to reduce the activity of the insulin receptor tyrosine kinase. TNF- $\alpha$  also directly inhibit insulin dependent-glucose uptake on muscle tissue framework.<sup>61</sup>

### 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  $\geq$  60mm / h, vasculitis and pulmonary disease RA.<sup>4</sup>

### 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.<sup>14,62,63</sup>

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.<sup>64</sup> Baseline CRP is a predictor of cardiovascular mortality in patients with polyarthritis. In a cohort study for 10 years, Goodson et al<sup>65</sup> found CRP levels  $\geq$  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<sup>2</sup>) had a risk of death was significantly higher cardiovascular compared to non-RA patients with a normal BMI.<sup>66</sup> 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  $\geq$  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  $< 20$ .<sup>67</sup>

### 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.<sup>68,69</sup> Lopez-Longo FJ et al<sup>70</sup> 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%).<sup>70</sup>

### 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 atherosclerosis.<sup>71,72</sup> 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.<sup>72,73</sup>

### 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.<sup>31</sup> Thrombocytosis, which is one factor contributing to hypercoagulable state, often found in RA patients. Proinflammatory cytokines (IL-6, IL-1, and TNF- $\alpha$ ) 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.<sup>59,74</sup>

### 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.<sup>75-77</sup>

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.<sup>78,79</sup> 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.<sup>76,80</sup>

Common carotid artery thickness (CIMT)  $\geq 0.60$  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.<sup>79,81-83</sup>

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.<sup>77</sup> 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.<sup>76</sup>

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<sup>84</sup> 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<sup>41</sup> 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<sup>85</sup> 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<sup>86,87</sup> 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 cerebrovascular 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. <sup>4</sup>

Evans et al<sup>88</sup> discovered 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.<sup>52</sup> 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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# Association Between Adiponectin Levels with Markers of Atherosclerosis In Patients with Rheumatoid Arthritis

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## ABSTRACT

**Background:** Several studies have shown that atherosclerosis underlying processes of Cardiovascular disease (CVD), increased in rheumatoid arthritis (RA) and occurred early (premature). The cause of accelerated atherosclerosis in RA are still unknown. Adipokines have known that the adipokines play a role in the pathophysiology of RA and CVD. Accumulation of visceral fat associated with dysregulation of adipokines that influence the development of the atherosclerotic and disruption plaque. Obesity and pathological changes in fat mass and fat dysfunction as well as a change in the pattern of secretion of proinflammatory adipokines, may have a correlation between heart disease and rheumatic diseases. Adiponectin is one of the most widely-studied adipokines. In RA, adiponectin is involved in the pathophysiology of RA that produces of various proinflammatory and prodestructive molecules. So far, adiponectin has been known to provide anti-atherosclerotic effects in patients with non-RA. But, several recent studies in RA patients get opposite results in which increased levels of adiponectin are associated with increased prevalence of atherosclerosis. The effect of adiponectin on atherosclerosis in patient with RA is still unknown.

**Objective:** to determine the relationship of adiponectin with atherosclerosis in patients with rheumatoid arthritis.

**Methods:** This is a cross-sectional study conducted on outpatients of the rheumatology clinic at Cipto Mangunkusumo General Hospital from January until April, 2013. Subjects consisted of 50 patients were diagnosed based on ACR 1987/EULAR 2010 criteria. The collection of data obtained by consecutive sampling and evaluated the patients' medical data that included age, long-suffering of RA, body mass index (BMI), lipid profile, rheumatoid factor levels, levels of anti-cyclic citrullinated peptide (anti-CCP), C-reactive protein (CRP), erythrocyte sedimentation rates (ESR), blood pressure, fasting blood glucose, 2 hour post prandial blood glucose, ECG, examination of serum adiponectin levels and bilateral carotid ultrasound to measure the carotid artery intima media thickness.

**Results:** From the results of the 50 patients studied, obtained 28 (56%) of patients had increased levels of adiponectin. Atherosclerosis was found in 13 (26%) subjects. The median value was 9.46  $\mu\text{g/ml}$  with the lowest levels of 4  $\mu\text{g/ml}$  and the highest levels of 24  $\mu\text{g/ml}$ . The Spearman's test showed no

significant correlation between adiponectin serum and atherosclerosis in patients with RA ( $p = 0.706$  and  $r = 0.055$ ). The analysis results of the correlation of adiponectin with atherosclerosis based on age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, dyslipidemia showed no significant correlation.

**Conclusion :** From this study, researchers found no statistically significant correlation between adiponectin levels with marker of atherosclerosis (CIMT) in patients with rheumatoid arthritis

**Keywords :** Adiponectin, Atherosclerosis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by the involvement of articular and extra-articular. Cardiovascular disease (CVD) is the most important cause of mortality and morbidity of patients with RA.<sup>1</sup> CVD causes almost 50% to more deaths in patients with RA.<sup>2</sup> Several studies have shown that atherosclerosis underlying processes of CVD, increased in RA and occurred early (premature). But the cause of accelerated atherosclerosis in RA are still unknown. The increased risk of CVD in RA can not be fully explained by traditional risk factors such as age, sex, smoking, hypertension or type 2 diabetes (DM).<sup>3</sup>

In contrast to the general population, the risk of CVD in patients with RA particularly elevated in younger patients and female gender. Low body mass index ( $<20 \text{ kg/m}^2$ ) was also associated with a higher cardiovascular mortality. This may be correlated with increased inflammatory cytokines leads to a catabolic process.<sup>1</sup>

It remains unclear how the traditional risk factors interact with non-traditional risk factors to increase CVD in RA. However, some traditional risk factors, such as: men, sex, smoking and previous cardiovascular events, seems to have a relationship with the occurrence of CVD in patients with RA, but its contribution to the rate of CVD seems weak.<sup>4</sup>

In addition to traditional risk factors, chronic systemic inflammation has been shown to be an important factor in the development of atherosclerosis. Increased systemic inflammation in patients with RA is one of the non-traditional factors that will increase the cardiovascular risk in RA.<sup>5</sup> RA is a prototype of a chronic systemic

inflammatory disease. And interestingly, there are similarities between the inflammatory pathways in atherosclerosis and RA.<sup>1</sup>

Although traditional risk factors are also involved in the pathogenesis of cardiovascular disease in patients with RA, but does not fully explain how the increased cardiovascular risk in this population. Classical risk factors such as obesity might explain the increased risk of CVD in patients with RA.<sup>6</sup> It is well known that adipokines play a role in the pathophysiology of RA and CVD. Visceral fat accumulation associated with dysregulation of adipokines that influence the development of atherosclerotic and disruption plaque. Obesity and pathological changes in fat mass and fat dysfunction as well as a change in the pattern of secretion of proinflammatory adipokines, could be one of the link between heart disease and rheumatic diseases. Indeed, the incidence of CVD is increased in obese individuals with rheumatic disorders.<sup>7</sup>

Since the discovery of leptin in 1994, adipose tissue is no longer considered as a passive reservoir for storage energy.<sup>8</sup> Adipose tissue is an endocrine and metabolic organ that is very active and produce large amounts of bioactive peptides.<sup>8,9</sup> These molecules known as adipokines and substantially can modulate the metabolic cardiovascular risk factors including insulin resistance and atherogenesis, and inflammatory and immune responses. Leptin and adiponectin are the most studied adipokines.<sup>8</sup>

At the individual non-RA, adiponectin is anti-inflammatory, anti-atherogenic, anti-diabetic,<sup>11, 12, 13</sup> repair and production of metabolic risk decrease with increasing adiposities.<sup>8, 10</sup> High levels adiponectin are favorable factor because it will decrease the progression of atherosclerosis.<sup>14</sup>

The above findings are very opposite, considering the increased adiponectin level in RA, while the incidence of atherosclerosis in RA also increased. In contrast to the properties of adiponectin as an anti-inflammatory in a non-RA population. In contrast to RA, adiponectin is involved in the pathophysiology of RA, which produce a variety of proinflammatory and prodestructive molecule.<sup>8, 15-18</sup> Most studies in patients with RA have shown an increase in the serum concentration of adiponectin, and adiponectin is also produced in the inflamed joints.<sup>8, 15, 19</sup> Several studies have also shown that adiponectin is involved in the development of RA.<sup>8, 15-18, 20, 21</sup> These finding support the involvement of adiponectin in the immune response in RA. Adiponectin may play a role in the pathophysiology of rheumatoid arthritis that adiponectin can be a potential new therapeutic targets by performing inhibition of adiponectin.<sup>22</sup>

Is the RA could modify the effect of adiponectin on risk of atherosclerosis, is currently unknown. Therefore, this study required for the management of RA and inhibition of adiponectin on the possible use of RA (as a new therapeutic target),<sup>18</sup> so that can explain how the inhibitory effect of adiponectin on cardiovascular risk in patients with RA. Adiponectin has anti-inflammatory effects on blood vessels and on metabolic pathways and is a cardiovascular protective factor. Therefore, when inhibition therapy of adiponectin is done systematically, may provide cardiovascular consequences

unintended opposite. Giving inhibitor of adiponectin through intra-articular pathways is more advisable because theoretically it can limit the proinflammatory effects of adiponectin on the joints but do not eliminate the anti-inflammatory effects on blood vessels and cardiovascular.<sup>23</sup>

Carotid Intima-Media Thickness (CIMT) is an important marker for early subclinical atherosclerosis. CIMT is also a strong predictor for future cardiovascular events in individuals RA and non-RA.<sup>24, 25</sup> In individuals non RA, adiponectin levels are inversely related to CIMT, where low adiponectin levels will increase progression of atherosclerosis, thereby increasing the risk of cardiovascular disease (CVD). Shargorodsky et al found that serum levels of adiponectin are associated with early atherosclerosis assessed by CIMT in obese patients non-RA.<sup>14</sup> So adiponectin is also an independent predictor marker of early subclinical atherosclerosis in obese individuals non-RA. Measurement technique of Carotid IMT can be considered as a valid marker of early atherosclerosis in asymptomatic patients and is a predictor of mortality and morbidity of the cardiovascular disease.<sup>23-25</sup>

## METHODS

### Study Design

The research design was a cross-sectional study design using primary data obtained from anamnesis, physical examination, and investigation. The study was conducted between January until April 2013, at Polyclinic Rheumatology, Department of Internal Medicine, Cipto Mangunkusomo Hospital (RSCM), Jakarta.

### Patients

Total sample consisted of 50 patients with new and old RA who have been diagnosed RA based on the ACR 1987/EULAR 2010 criteria who visited rheumatology outpatient clinic at the Cipto Mangunkusomo Hospital (RSCM). Sampling were collected using a consecutive sampling method. The inclusion criteria were patients with RA who fulfilled ACR 1987/EULAR 2010 criteria, age > 16 years when diagnosed and are willing to follow the study. The exclusion criteria were patients with type 2 diabetes, hypertension, patients with a history of myocardial infarction, stroke or peripheral artery disease and treatment with ACE-inhibitor drugs.

### Assessments

Necessary data were collected by performing anamnesis, physical examination, laboratory tests and carotid ultrasound. Included in the assessment were clinical variables such as age, disease duration of RA, Body Mass Index (BMI), lipid profile, rheumatoid factor levels, levels of anti-CCP, levels of anti CRP, and ESR, blood pressure, fasting blood glucose, 2-hour post-prandial, ECG, and serum adiponectin levels examination. The concentration of serum adiponectin [ $\mu\text{g}/\text{ml}$ ] were measured using Human Adiponectin ELISA kit according to the manufacturers' instructions. The normal value of total adiponectin concentration in plasma 3.58 to 9.66  $\mu\text{g}/\text{ml}$  for women and 2.54 to 6.06 for  $\mu\text{g}/\text{ml}$  for males. Carotid ultrasound is done by one person radiologist using ultrasound

B-mode brand Philips Sonos 5500. Standard normal values of Carotid Intima-Media Thickness (CIMT) is  $\leq 1.0$  mm.<sup>26</sup>

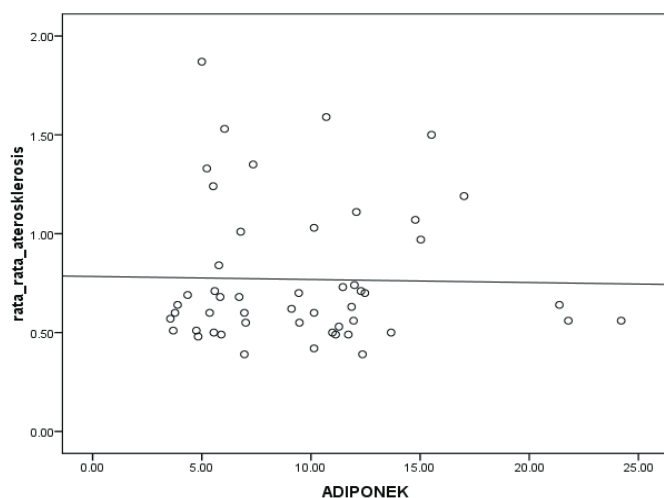
### Statistical Analysis

The data collected were analyzed using computer applications with SPSS version 15.0. Descriptive and analytical data will be presented in the form of text, tables, and pictures as appropriate.

### RESULTS

Of the 50 subjects involved in this study, 56% (28 patients) subjects had high serum adiponectin levels. Mean adiponectin levels could not be determined because the data distribution is not normal. While the median value is 9.46  $\mu\text{g} / \text{ml}$  with the lowest levels of 4  $\mu\text{g} / \text{ml}$  and the highest levels of 24 $\mu\text{g}/\text{ml}$ . The total of male subject (2 patients) have high adiponectin levels.

Bivariate analysis was done to see the correlation of independent variabel, namely adiponectin levels with the dependent variable, namely atherosclerosis. All variables were analyzed had a abnormal distribution, so the Spearman correlation statistical test was used. The results of correlation test between adiponectin levels and atherosclerosis showed a very weak correlation Alt value of  $p=0706$  and  $r=0.055$ . Furthermore, the relationship of adiponectin levels and atherosclerosis were analyzed by age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, and dyslipidemia, but none of which showed significant results.



**Figure 2.** The relationship between the adiponectin levels and average value of atherosclerosis

### DISCUSSION

In this study, obtained 28 subjects (56%) had high levels of adiponectin. With a higher proportion (56%) indicate that adiponectin plays an important role in the pathogenesis of RA.

At the individual non-RA, adiponectin is inversely related to atherosclerosis. Adiponectin has been shown to play a key role in obesity, inflammation, insulin resistance and atherosclerosis, but little is known about their contribution to individual with RA. As shown in this study, the adiponectin levels in patients with RA showed no-significant correlation

with the intima media thickness of the carotid artery. It is a marker of early atherosclerosis. The relationship of adiponectin and atherosclerosis were then analyzed by age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, dyslipidemia, but none of which showed significant results. The results of this study have the same results with the results obtained by Gonzalez et al.<sup>25,27</sup> and Dessein et al.<sup>22</sup>, that there is no correlation between adiponectin and intima media thickness of the carotid artery.

Serum concentration of adiponectin was not associated with atherosclerosis and cardiovascular event rates in RA.<sup>7,20,27,28</sup> It should be noted that in this case, the presence of autoimmunity may change the effects of adiponectin on metabolic risk and cardiovascular disease.<sup>22</sup>

So also with the incidence of CVD in RA, because not all patients with RA will experience the same CVD events. This difference is thought to be caused by the presence of genetic susceptibility to atherosclerosis which may also play a role. HLA-DRB1\*0404 is a predisposing gene for RA and is associated with more severe RA disease. RA patients with HLA-DRB1\*0404 gene-shared epitope-positive have a higher cardiovascular mortality compared with the epitope-negative.<sup>29</sup>

Patients with RA had an increased prevalence of premature atherosclerosis and insulin resistance, are associated with accelerated coronary atherosclerosis.<sup>28</sup> Prevalence of CVD in RA may be higher than DM type 2.<sup>30</sup> This study found no correlation between adiponectin with other cardiovascular risk factors such as age, disease duration, ESR, rheumatoid factor, DAS 28, CRP, BMI, and dyslipidemia. Other researchers also found that adiponectin was not correlated with several risk factors for atherosclerosis such as coronary calcium scoring<sup>28</sup>, HOMA IR,<sup>12,28</sup> total cholesterol, LDL kolesterol levels, systolic and diastolic blood pressure<sup>12</sup>. However, adiponectin correlated negatively with high levels of inflammation and plasma glucose.<sup>12</sup> Rho et al also found high concentrations of adiponectin in patients with RA, but adiponectin was not associated with coronary calcification and insulin resistance.<sup>28</sup>

In another study Gonzalez obtained the different results. High levels of inflammation associated negatively with circulating adiponectin, and low adiponectin concentration is more correlated independently with an overview of the metabolic syndrome (dyslipidemia and high plasma glucose levels). These findings are similar to those reported in non-RA subjects, and these increase the possibility that adiponectin contributes to atherogenesis in RA and subsequently involve in cardiovascular disease in patients with RA.<sup>12</sup>

Adiponectin has been associated as a protective factor for atherosclerosis in individual non-RA. However, in this study found no relationship between adiponectin and atherosclerosis. This may be due in patients with RA, the effect of adiponectin in atherosclerosis may be obscured by other inflammatory mediators that have pro-atherogenic effect whose levels are elevated in RA.

Adiponectin play an important role in the pathogenesis of RA, but plays small role in the pathogenesis of subclinical atherosclerosis in RA and inhibition of systemic adiponectin



would not change the overall cardiovascular risk in patients with RA.<sup>22</sup> In the context of adiponectin as a therapeutic target for RA, this provides new opportunities for the provision of adiponectin inhibitors through the systemic pathways. Because adiponectin is not associated with atherosclerosis in patients with RA, we don't need to worry about giving systemic inhibitors of adiponectin will eliminate the protective effect of adiponectin in the cardiovascular. So that the provision of adiponectin inhibitors can be done through the systemic pathways.

Another consequence of the results of this study also shows that levels of adiponectin have not been able to replace the use of ultrasound to measure CIMT as a predictor of atherosclerotic events in particular and the incidence of cardiovascular disease is common in patients with RA who do not exhibit clinical symptoms of cardiovascular disease.

The management to prevent CVD should be supported as much as possible. The main cause abnormal accumulation of fat mass and adiponectin dysfunction is poor nutrition and lifestyle habits, such as overeating and lack of physical activity. Therefore, the first approach to manage CVD in rheumatic disease is lifestyle modification and other therapeutics intervention that lead to decrease of fat mass and fat dysfunction to decrease cardiovascular mortality in patients with RA.<sup>7</sup>

From the data above, we need other efforts to prevent CVD. Therefore, we also need to know the other risk factors that will lead and aggravate cardiovascular disease in RA. In general population, cardiovascular mortality the same as RA was also associated with CRP and ESR.<sup>1</sup> TNF- $\alpha$  and IL-6 is a pro-inflammatory cytokine that also show the independent predictive role for cardiovascular events in the future.<sup>29</sup> These cytokines have an important role in the pathogenesis of RA and have high concentration in patients with RA. In addition, the duration and disease activity, the involvement of many joints, the presence of rheumatoid factor (RF), rheumatoid nodules and extra-articular manifestations are also a specific determinant of CVD events in patients with RA.<sup>31</sup> All of this suggests that systemic inflammation is not treated it can cause damage before injure the joints. And long-term exposure to systemic inflammation increases the risk of CVD. So the use of anti-rheumatic drugs are effective in suppressing the inflammation that will be able to reduce the risk of CVD events and one of prevention CVD in RA.<sup>1</sup> Besides, it is also required close monitoring of serum lipid levels that would changes adiponectin production or inhibit its effect in RA.<sup>22</sup>

### Limitations of Research

One of limiting factors in this study was adiponectin which had measured in this study are total adiponectin. Whereas adiponectin has several isoforms that may have a different biological function, and there is the opposite function. Although more studies show pro-inflammatory function of adiponectin in patients with RA, but the relationship between adiponectin and RA is not fully understood yet. So that further studies are needed which refers to the role of adiponectin isoforms.

Serum adiponectin levels may not be the same as the joint adiponectin levels.<sup>20</sup> Adiponectin produced locally by intra-articular adipocytes, may play a role in the degradation of extracellular matrix components.<sup>15</sup> These raise an assumption that the serum adiponectin levels may not reflect the actual activity of adiponectin in a particular tissue. Alternatively, increased production of adiponectin in autoimmune disease or in chronic inflammatory conditions may be secondary to inflammation - due to the catabolic response that occurs in RA.<sup>15,32,33</sup>

### CONCLUSION

In this study, we found no statistically significant correlation between adiponectin levels with marker of atherosclerosis (CIMT) in patients with rheumatoid arthritis

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# The Effect of Vitamin D Supplementation on Disease Activity and Neutrophil-Lymphocyte Count Ratio in Systemic Lupus Erythematosus Patients with Hypovitaminosis D : A Preliminary Study

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## ABSTRACT

**Background :** Previous studies showed a significant role of Vitamin D in modulating inflammation and immune abnormality in SLE. The correlation between vitamin D supplementation and SLE disease activity remains controversy. Neutrophil-Lymphocyte count Ratio (NLCR) as an inflammation marker was significantly increased in SLE patients.

**Objective :** To evaluate the effect of vitamin D supplementation on disease activity and neutrophil-lymphocyte count ratio (NLCR) in SLE patients with hypovitaminosis D.

**Methods :** This is a pre-post test study without control group using a consecutive sampling method. SLE patients were enrolled from Rheumatology Clinic of Hasan Sadikin General Hospital from November 2013-March 2014. Subjects received vitamin D3 2000 IU/day for 3 months. Data was analyzed using Wilcoxon test.

**Results :** We analyzed 28 subjects with 89,3% of vitamin D deficiency and 10,7% of vitamin D insufficiency, which converted to 25% of vitamin D deficiency, 32,1% vitamin D insufficiency and 42,9% normal vitamin D plasma level at the end of the study. After supplementation, Mexican Systemic Lupus Erythematosus Disease Activity Index (MEX-SLEDAI) and NLCR was significantly decreased (median 4(3-8) to 2(0-6) and median 2,95(1,17-7,27) to 2,28 (1,07-4,87),  $p < 0,001$ , respectively). SLE organ involvement such as mucocutan, hematology and renal also high BMI ( $> 23 \text{ kg/m}^2$ ) were risks of hypovitaminosis D. Vitamin D supplementation increased mean 25(OH)D serum level by 164,7%, 46,7% decreased of MEX-SLEDAI, and 24,2% decreased of NLCR ( $p < 0,001$ ). Nine subjects (32,1%) achieved remission, 19 subjects (67,9%) at disease persistence and no subjects experienced flare up after supplementation.

**Conclusion :** The effects of vitamin D3 2000 IU/day supplementation for 3 months are reduced disease activity and NLCR in SLE patients with hypovitaminosis D. The role of NLCR as a simple inflammation marker in this pilot study needs further investigation.

Systemic Lupus Erythematosus (SLE) is a chronic systemic autoimmune disease marked by autoantibody tissue deposition, tissue damage and heterogen clinical manifestation. Prevalence

of SLE in the United States is 10-400 in 100.000 people, with women to men ratio 9-14 : 1.<sup>1</sup> There was lack of data for prevalence of SLE in Indonesia. Rheumatology Clinic Hasan Sadikin General Hospital, Bandung in West Java recorded new cases of SLE between 2003-2005 were 6,4% from 3025 patients, which increased to 9,07% from 4037 patients in 2011 and 11,54% from 27.496 patients in 2012.<sup>2,3</sup>

Pathogenesis of SLE is multifactorial (genetic, environment and hormonal). Clinical manifestation of SLE developed through autoimmune predisposition, autoantibody formation, then disease exacerbation, remission, disease damage and comorbidity caused by chronic inflammation. Two main disease domain in SLE are disease activity and disease damage. Disease activity represent a reversible manifestation of disease which is the important parameter of SLE treatment.<sup>4,5,6</sup>

Vitamin D induces chemotaxis, macrophage phagocytosis, *Treg* activity, inhibits B cell differentiation and proliferation, and inhibits autoantibody production. The role of vitamin D in the immune system is the reversal of immune abnormalities in SLE. In vivo and in vitro studies showed beneficial effect of vitamin D supplementation on SLE immune abnormalities.<sup>7-14</sup>

SLE patients are at risk for hypovitaminosis D due to chronic steroid and hydroxychloroquine usage, mucocutaneous and renal involvement, antibody to vitamin D, sun avoidance and VDR gene polymorphysm.<sup>9,14-17</sup> However, the correlation and overall effect of vitamin D on disease activity remain unclear from the available clinical data.<sup>10-13,18-22</sup>

Hematologic involvement has been found in 50-70% SLE patients, which is mainly leukopenia (46%), consist of 75-93% lymphopenia and 47% netropenia.<sup>4,23</sup> In severe disease activity, leukopenia and lymphopenia can be found.<sup>24</sup>

Neutrophil-lymphocyte count ratio (NLCR) has been evaluated and used as inflammatory marker in various diseases.<sup>25,26,27</sup> NLCR was significantly higher in SLE patients than normal subjects (2,52 vs 1,64,  $p = 0,007$ ).<sup>24</sup> The role of NLCR in SLE disease activity monitoring is unknown.

In this study, we evaluated the effects of vitamin D supplementation toward disease activity and NLCR as simple inflammation marker in SLE patients with hypovitaminosis D.

## METHODS

This was a pre-post design study without control group (quasi-experimental study) to assess the effect of 3-month vitamin D supplementation on disease activity and NLCR. Samples were collected using consecutive sampling from admissions method from Rheumatology Clinic, Outpatient Department Hasan Sadikin General Hospital, Bandung. This study was held from November 2013 until March 2014. The inclusion criteria were fulfilling the 2012 SLICC SLE diagnostic criteria<sup>28</sup>, age 14-55 years old, disease activity score using Mexican-SLEDAI (MEX-SLEDAI) more than 2 until 9, and vitamin D serum level using 25(OH)D (the best indicator for vitamin D status) of less than 30 ng/mL. The exclusion criteria were chronic kidney disease stage 4-5 patients, patients with chronic liver disease, subjects with disease flare, acute infection and chronic inflammation other than SLE during the study, patients received high dose corticosteroid (equivalent to prednisone > 30 mg/day) in the last 30 day, pregnant and breast-feeding, hypolipidemic and anticonvulsant consumption, subjects with active tuberculosis and/or on TB treatment, and history of vitamin D supplementation during the last 3 month was excluded from the study. The study was approved by the Ethical Committee of the Hasan Sadikin General Hospital, Bandung. All patients agreed to participate and signed informed consent at the beginning of the study.

Vitamin D serum level was assessed by *Enzyme-linked Immuno Sorbent Assay* (ELISA) 25(OH)D serum level examination. Hypovitaminosis D defined as vitamin D insufficiency (21–29 ng/mL) or deficiency (< 20 ng/mL).<sup>31</sup> SLE disease activity was measured using *Mexican SLEDAI* (MEX-SLEDAI), with scores classified as follows: 0-1 for remission, 2-5 represented mild disease activity, 6-9 was moderate and more than 10 as severe disease activity. Disease flare defined as  $\geq 3$  score increment. Remission defined as more than 3 scores reductions and less than 3 scores changes as disease persistence.<sup>6,29,30</sup> NLCR was obtained from absolute neutrophil count divided by absolute lymphocyte count attained from leukocyte differential count<sup>25-27</sup> Chronic kidney disease (CKD) stage 4-5 defined as glomerular filtration rate  $\leq 29$  ml/minute/1,73m<sup>2</sup> for more than 3 months by Cockcroft-Gault equation.<sup>32</sup> Previous liver disease, physical examination and elevated transaminase needed to assess chronic liver disease.<sup>33</sup> Fitzpatrick skin type score was evaluated to classify skin coloration and response to sun exposure.<sup>34</sup> The duration of ultraviolet exposure (minute/day) held from interview with study subjects.

Subjects received 2000 IU/day vitamin D3 (cholecalciferol) for 3 months based on clinical data from previous study that showed 100% SLE patients in our Rheumatology clinic was vitamin D deficiency (median 25(OH)D serum level was 3,84 ng/mL).<sup>22</sup> American College of Rheumatology (ACR) recommended 50.000 IU/week of vitamin D for 8 weeks, continued with 2000-4000 IU/day for maintenance. ACR also stated 2000 IU/day of vitamin

D was sufficient to achieve optimal vitamin D status (30-60 ng/mL) in normal subjects. Vitamin D available in Indonesia was supplied as vitamin D3 (cholecalciferol) 400 IU/soft capsule. During the study, we supplement study subjects with 5 soft capsule/day. We monitored every patients monthly to evaluate symptoms, SLE disease activity, compliance and any side effects to vitamin D supplementation. After 3-month supplementation (vitamin D serum level is not recommended to be remeasured for less than 3 months)<sup>31,35</sup>, we repeated the measurement of 25(OH)D serum level and NLCR. Data analysis started with *Shapiro-Wilk* normality test ( $n < 50$ ) for quantitative data. The comparison of MEX-SLEDAI and NLCR at baseline and after supplementation were analyzed using paired T-test or Wilcoxon's test as appropriate using SPSS for window ver 17.

## RESULTS

We enrolled 33 eligible SLE patients. During this study, 1 subject reported skin rash, 2 subjects with nausea-vomiting and 2 subjects were excluded due to uncompliance to supplementation. At the end of the study, 28 subjects available to be analyzed. Table 1 showed that the prevalence of SLE among the study subjects was higher in women (92,9%). Mean age was 30,7 $\pm$ 10,5 years old. Median disease duration was 21,25 months (4 -156 months). Median Body Mass Index (BMI) was 21,25 kg/m<sup>2</sup> (16,1 - 41,1 kg/m<sup>2</sup>). Frequency of SLE manifestation consisted of 92,9% mucocutaneous, 25% musculoskeletal, 67,9% hematology, 57,1% renal, 17,9% vaskulitis, 21,4% neuropsychiatric (NPSLE) and 14,3% serositis. Baseline Median (25(OH)D) serum level was 9,24 ng/mL (3-24,64 ng/mL). All subjects (100%) received methylprednisolone. Other SLE medications were chloroquine (57,1%), cyclophosphamide (14,3%), azathioprine (39,3%) and cyclosporine (3,5%). Only age ( $p=0,261$ ) and vitamin D level after supplementation ( $p=0,170$ ) were distributed normal ( $p > 0,05$ ). Baseline median MEX-SLEDAI score and NLCR were 4 (3 – 8) and 2,95 (1,17 - 7,27) (Table 2).

**Table 1.** Baseline characteristics of patients (n=28)

Characteristics	n = 28
<b>Sex (n, %)</b>	
Male	2 (7,1%)
Female	26 (92,9%)
<b>Age (years)</b>	
Mean $\pm$ SD	30,7 $\pm$ 10,5
<b>SLE disease duration(months)</b>	
Median (Range)	30,5 (4-156)
<b>Body Mass Index / BMI (kg/m<sup>2</sup>)</b>	
Median (Range)	21,3 (16,1-41,1)
<b>SLE manifestation (n,%)</b>	
Mucocutan	26 (92,9%)
Musculoskeletal	7 (25%)
Hematology	19 (67,9%)
Renal	16 (57,1%)
Vaskulitis	5 (17,9%)
NPSLE	6 (21,4%)
Serositis	4 (14,3%)

<b>SLE medications (n, %)</b>	
Corticosteroid	28 (100%)
Chloroquine	16 (57,1%)
Azathioprine	11 (39,3%)
Cyclophosphamide	4 (14,3%)
Cyclosporine	1 (3,6%)
<b>UV exposure (minute/day)</b>	
Median (Range)	15 (5-60)
<b>Skin colour (n %) (Fitzpatrick skin type score)</b>	
2	5 (17,9%)
3	11 (39,3%)
4	7 (25%)
5	4 (17,9%)
<b>Sunblock application SPF 30 (n, %)</b>	
Applying	19 (67,9%)
Not applying	9 (32,1%)
<b>Vit D Compliance (%)</b>	
Median (Range)	96,7 (90-100)
<b>Baseline 25(OH)D serum level (ng/mL)(n,%)</b>	
Insufficiency (20-29)	3 (10,7 %)
Deficiency (<20)	25 (89,3 %)
Severe Deficiency (<12)	19 (67,9%)

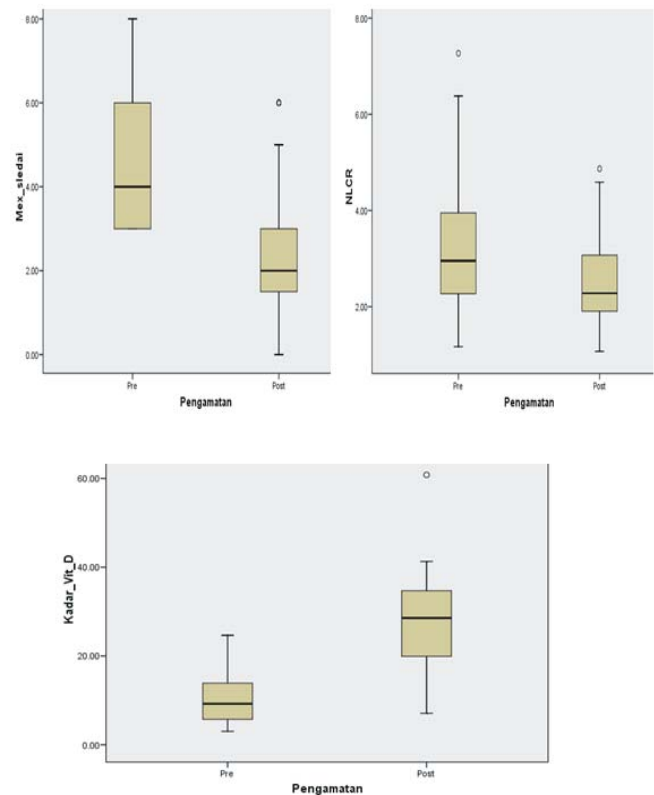
### The effects of vitamin D supplementation on MEX-SLEDAI and NLCR

Table 2 showed 3-month vitamin D supplementation resulted in statistically significance decreased disease activity ( $p < 0,05$ ). There was 46,7% decrease in MEX-SLEDAI, 24,2% decrease in NLCR, simultaneously with 164,7% increase in mean 25(OH)D serum level after supplementation.

**Table 2. Vitamin D (25(OH)D) serum level, MEX-SLEDAI dan NLCR Pre and post**

Variables	Before cholecalciferol supplementation (pre)	After cholecalciferol supplementation (post)	pre&post changes	p-value*
<b>MEX-SLEDAI</b>				
Median (Range)	4 (3-8)	2 (0-6)	Decrease	0,000
			46,7%	
<b>NLCR</b>				
Median (Range)	2,95 (1,17-7,27)	2,28 (1,07-4,87)	Decrease	0,000
			24,2%	
<b>25(OH)D (ng/mL)</b>				
Mean $\pm$ SD	10,2 $\pm$ 5,8	27 $\pm$ 12,1	Increase	0,000
			164,7%	

**Note \*** : p-value submitted from Wilcoxon test,  $p < 0,05$  as level of significance.



**Figure 1.** MEX-SLEDAI, NLCR and 25(OH)D serum level pre and post.

The effect of vitamin D supplementation (along with SLE immunosuppressive therapy) on disease activity comprised of 32,1% subjects with disease remission, 67,9% experienced persistence and no subject with disease flare during observation. (Table 3)

**Table 3.** MEX-SLEDAI after cholecalciferol supplementation

MEX-SLEDAI decreasing $\geq 3$ (remission) (n,%)	MEX-SLEDAI decreasing $< 3$ (persistent) (n,%)	MEX-SLEDAI increasing $\geq 3$ (flare up) (n,%)
9 (32,1%)	19 (67,9%)	-
TOTAL		28 (100%)

There were 89,3% subjects with vitamin D deficiency at baseline. After 3-month cholecalciferol supplementation, 25% subjects remains deficiency but 42,9% subjects achieved optimal vitamin D serum level. (Table 4)

**Table 4.** Characteristics of 25(OH)D serum level pre and post

	Before cholecalciferol supplementation (pre) n=28	After cholecalciferol supplementation (post) n=28
<b>25(OH)D serum level (ng/mL)</b>		
Normal (30-60)	-	12(42,9%)
Insufficiency (20-29)	3(10,7%)	9 (32,1%)
Deficiency (<20)	25 (89,3%)	7 (25%)
Severe deficiency (<12)	19 (67,8%)	5 (17,8%)

## DISCUSSION

This is a pre-post design study without control group (quasi-experimental study) to assess the effect of 3-month vitamin D supplementation on disease activity and NLCR in SLE Patients. This study design was selected because we found limitation in obtaining placebo or control group as comparison. On the first month follow-up, one subject reported skin rash, which is concluded as hypersensitivity reaction (co-evaluation with Dermatovenereologist). Moreover, two subjects reported gastrointestinal intolerance (nausea and vomiting). On the second month, two other subjects reported compliance less than 90%. Those five subjects' participation were discontinued from our study.

At the end of the study, we analyzed 28 subjects with women subjects in majority (92,9%), and mean age of  $30,7 \pm 10,5$  years old, which is in line with the epidemiology of SLE.<sup>2</sup> Baseline data showed mucocutaneous (92,9%), hematology (67,9%) and renal (57,1%) manifestation of SLE because vitamin D metabolism involves skin and kidney.<sup>31</sup> Also Bogaczewicz J et al<sup>12</sup> found that SLE patients with hematologic (leukopeni) and renal involvement had higher risk of vitamin D deficiency. Fifty percent subjects had BMI > 23 kg/m<sup>2</sup> (overweight) which increased the risk of hypovitaminosis D as vitamin D was sequestered in the adipose tissue.<sup>31</sup> Table 1 showed 100% subjects had corticosteroid, 39,3% subjects with Fitzpatrick skin type 3 and 67,9% applied sunscreen that also increased the risk of hypovitaminosis D.<sup>9,14-17</sup>

Initially, 89,3% subjects were vitamin D deficiency (25(OH)D < 20 ng/mL) and convert to 25% subjects after 3-month supplementation (table 4). We observed 42,9% subjects with normal vitamin D status, but 32,1% still in insufficiency after supplementation. Five subjects (17,8%) persist as severe vitamin D deficiency (< 12 ng/mL) due to less compliance, high BMI and gastrointestinal symptoms during the study. Robinson AB et al found that 400 IU per day vitamin D supplementation will increase mean 25(OH)D, but few subjects still hypovitaminosis D yet recommend higher dose of vitamin D, especially for patients with proteinuria and high disease activity.<sup>8</sup>

Table 2 demonstrate 46,7% decrease mean MEX-SLEDAI ( $p < 0,001$ ) and table 3 showed no subjects suffered flare up during study. According to a metaanalysis by Sakthiswary R et al<sup>18</sup>, there is a strong association between level of vitamin D and disease activity and no association with disease damage. Kurniati et al reported vitamin D 2000 IU/day followed by significant MEX-SLEDAI score decrease ( $6,85 \pm 2,71$  vs  $3,98 \pm 3,53$ ,  $p < 0,005$ ) without marked difference of  $1,25(\text{OH})_2\text{D}_3$  serum level.<sup>20</sup> Handono et al<sup>21</sup> also reported negative correlation between 25(OH)D serum level and disease activity ( $r = -0,659$ ,  $p = 0,000$ ). Altogether with Abou-Raya et al<sup>13</sup>, Borba et al<sup>19</sup> and Petri et al<sup>36</sup> whose reported significantly better inflammation marker after vitamin D3 supplementation, vitamin D3 2000 IU/day could be considered as "additional" therapy for SLE.

High risk hypovitaminosis D patients (such as overweight, darker skin colour, sun avoidance, sun screen application, mucocutaneous, hematologic and renal involvement and drugs) should be considered for early vitamin D status

examination, higher vitamin D supplementation and frequent monitoring of vitamin D serum level.<sup>35</sup>

We observed 24,2% decrease median NLCR, from 2,95 (1,17-7,27) to 2,28 (1,07-4,87)  $p < 0,001$ . Dan JQ dkk reported decrease NLCR after Radio Frequency Ablation in 178 hepatocellular carcinoma patients, which indicate better survival.<sup>37</sup> Wolfsminke et al observed that NLCR was not a useful predictive value in 440 severe malaria patients.<sup>38</sup> Oehadian et al reported significantly higher NLCR in SLE patients compared to normal (2,52 vs 1,64,  $p = 0,007$ ). Cut-off NLCR of  $\geq 1,93$  resulted in 70% sensitivity and 67% specificity to differentiate SLE and normal subjects.<sup>24</sup> Though our study result is consistent with Oehadian et al, but the role NLCR as a simple inflammation marker useful for disease activity monitoring in SLE still need further investigation.

Few subjects reported fatigue as part of baseline MEX-SLEDAI assessment (data not shown). Sterling et al reported fatigue as frequently undiagnosed disease burden but influenced the quality of life of SLE patients.<sup>39</sup> We observed that after vitamin D3 2000 IU/day for 3 months, those subjects reported less fatigue and one subjects can back to work (through patient interview).

Our study limitation were no placebo or control group and relatively short duration of study. We expected more apparent vitamin D effect on disease activity and NLCR in longer supplementation duration. Polymorphism of vitamin D receptor needed to investigated for 17,8% subjects persist in severe vitamin D deficiency.

## CONCLUSION

In the present study, there was a significant reduced disease activity and NLCR in SLE patients with hypovitaminosis D after the administration of vitamin D along with the main immunosuppressive SLE therapy. The role of NLCR as a simple inflammation marker in SLE disease activity monitoring needs to be further investigated. Furthermore, fatigue evaluation in SLE patients with objective measurement and the correlation with vitamin D supplementation also need further research.

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# Correlation between Severity of Knee Osteoarthritis and Serum Levels of *Cartilage Oligomeric Matrix Protein*

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## ABSTRACT

**Background:** The sensitivity of radiographic examination in the diagnosis and severity assessment of knee osteoarthritis (OA) is still low. Various attempts have been made to find more reliable indicators of cartilage damage. One potential marker is cartilage oligomeric matrix protein (COMP), a substance that in previous animal studies had been shown to be released in proportion to the extent of joint cartilage damage.

**Objective:** To evaluate the correlation between the severity of knee OA and serum level of COMP in human with normal renal function.

**Methods:** This was a cross-sectional study performed at the outpatient clinic in Department of Internal Medicine, Sanglah Hospital, Denpasar. The diagnosis of knee OA was based on the American College of Rheumatology (ACR) criteria. The degree of knee OA severity was determined by using the Kellgren-Lawrence criteria, while COMP values were checked by enzyme-linked immunosorbent assay (ELISA) method.

**Results:** Forty five patients who were recruited were examined: 19 (42.2%) were female and 26 (57.8%) were male. The mean age of patients was  $64.1 \pm 7.1$  years. There were 4.4%, 26.7%, 46.7%, and 22.2% patients who had grade 1st, 2nd, 3rd, and 4th degree joint damage based on the Kellgren-Lawrence score, respectively. Mean serum level of COMP was 1081.4 ng/mL. We found a significant correlation of the severity of knee OA with serum level of COMP ( $r = 0.41$ ,  $p = 0.005$ ).

**Conclusion:** Among the patients in this study, there was a significant correlation between the severity of joint damage in knee OA and serum level of COMP.

Osteoarthritis (OA) is the most common articular disease in humans.<sup>1</sup> World Health Organization (WHO) estimated 25% of people aged 65 years old around the world suffer from this disease.<sup>2</sup> Radiographic studies conducted in America and Europe reported the prevalence of knee OA in people aged 45 years or more is 14% in men and 22.8% in women.<sup>3</sup>

In Indonesia the prevalence of knee OA through radiologic findings reaches 15.5% in men and 12.7% in women.<sup>4</sup> Several studies conducted in Indonesia even shows a higher result

compared to America. A study done at the Internal Medicine outpatient clinic in Manado General Hospital (March 1994–November 1995) showed a prevalence of 36.81% and 37.55% in Surabaya.<sup>5</sup> Surveys conducted at the Rheumatology outpatient clinic of Sanglah Denpasar Hospital (2001 – 2002) demonstrated OA as the most frequent rheumatic cases (37%) where the majority of them were knee OA (97%).<sup>6</sup>

Osteoarthritis can affect many joints, more often the weight bearing joints such as hips and knees.<sup>3</sup> The prevalence of OA is expected to increase along with the increase of obesity as its major risk factor and a higher life expectancy. Pain, inflammation, and joint stiffness due to osteoarthritis may cause physical disability. In the United states, OA not only became the major cause of physical disability but also the expense incurred for this disease in 2001 reached 81 million dollars and an indirect cost of approximately 47 million dollars.<sup>7</sup> In Indonesia it is expected that 1-2 million elderly suffer handicap due to OA.<sup>4</sup>

To prevent the increasing number of handicap, an early diagnosis and accurate assessment of OA severity is needed. The current assessment is neither uniform nor objective due to its high dependency to the skill and experience of radiologists. By the time of diagnosis, OA has usually in an advance stage because conventional radiographs have limited capacity in detecting early stages of OA. This condition implies a higher failure in preventing physical disability. Therefore a marker that can detect cartilage damage as an objective assessment of OA is necessary, especially if it can predict early stages of this disease.

During the cartilage matrix turn over, both in normal and pathologic states, metabolites and fragments of the cartilage matrix will be released to blood and synovial fluid. One of these macromolecules is *cartilage oligomeric matrix protein* (COMP). The structure of this cartilage-specific protein is similar to trombospondin. COMP is known to stabilize articular cartilage matrix by binding to collagen and other extracellular components.<sup>7,8,9</sup> According to a study by Geng et al. (2008), Wistar rats deprived of COMP undergoes immediate arthritis reaction and later developing into severe chronic arthritis. Another study conducted in experimental animals that were made



OA, COMP was found to be expressed at the earliest phase of cartilage damage<sup>10</sup> and its level increases along with the grading of OA.<sup>11</sup>

The aim of this study is to evaluate the correlation between knee OA severity with serum levels of COMP in humans.

## METHODS

### Study Design

This was a cross sectional study. Samples were taken from the Internal Medicine Outpatient Clinic at Sanglah Hospital, Denpasar during 2010-2011.

### Samples recruitment

Sample inclusion criteria were patients who fulfilled the American Clinical Rheumatology (ACR) 1996 criteria for knee OA, aged more than 50 years old, and have agreed to participate by signing informed consent. Samples excluded in this study were patients with total articular space damage (no space left) from radiologic examinations, OA in joints other than knee, articular diseases other than OA, patients that were unable to stand without assistance, using or having used steroids for the last 2 weeks, and creatinine clearance below 60 ml/minute.

### Assessment

Knee OA severity was assessed according to the Kellgren Lawrence grading scale. Knee OA is classified into 5 grades (figure 1): grade 0 with normal radiologic findings; grade 1 with doubtful narrowing of joint spaces and possible osteophytic lipping; grade 2 with definite osteophytes and definite narrowing of joints space; grade 3 with moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour; and grade 4 with large osteophytes, marked narrowing of joints space, severe sclerosis and definite deformity of bone contour. Radiographic examination of patients was done in a standing position, where anteroposterior (AP) and lateral projection of both knees were taken. Radiographs were then examined by three qualified radiologists that had been tested with a reliability test (kappa test).



**Figure 1.** Kellgren Lawrence grading scale of knee OA

Sera for COMP were collected 3 hours after the patient woke up in the morning and rested approximately 30 minutes. To determine serum COMP levels, samples were examined with Human Cartilago Oligomeric Matrix Protein ELISA (Biovendor, Brno, Czech Republic) reagent. The examination using Biovendor reagent had a *limit of detection* (LOD) of 0,4 ng/mL.

## Statistical Analysis

Data normality of COMP levels were assessed using the Shapiro-Wilk test. Correlation between serum COMP levels, knee OA gradings, and age were analyzed with the Spearman and Pearson test according to the normality data. Relations of gender and serum COMP levels were assessed by T-test. Statistical significance used was  $p < 0,05$ . Linear regression multivariate tests were used to estimate serum COMP levels prediction using knee OA severity.

## RESULTS

Forty five patients enrolled in this study, of which 19 (42,4%) patients were male and 26 (57,8%) patients were female. Serum levels and knee x-ray were examined. Average age of sample was  $63.3 \pm 6.8$  years with a range between 50 to 85 years old. Most frequent education background was high school (60%) and most frequent occupation was civil servant or retired civil servants.

Most frequent OA grading based on Kellgren-Lawrence grading scale was grade 3. Mean serum COMP level was 1175,4 ng/ml. Mean body mass index (BMI) was 26,2 kg/m<sup>2</sup> also included as grade 1 obesity based on Western Pacific Region of WHO 2000 classification. Sample characteristics are shown in table 1.

**Table 1** Characteristics of based sample (N = 45)

Characteristics	n (%)*
Gender	
male	19 (42,2)
female	26 (57,8)
Age, years, mean (SD)	63,3 (6,8)
Education background	
No education	1 (2,2)
elementary	6 (13,3)
junior high school	2 (4,4)
high school	27 (60,0)
University	9 (20,2)
Work	
unemployed	8 (17,8)
labor	0 (0)
farmer	0 (0)
civil servants (PNS)	30 (66,7)
private sector	4 (8,9)
Military-police	3 (6,7)
BMI, kg/m <sup>2</sup> , mean (SD)	26,2 (4,2)
COMP level, ng/mL, mean (SD)	1081,4 (3,3)
COMP level, ng/mL, median (range)**	
Grade 0	0 (0)
Grade 1	868,4 (613,5–1123,3)
Grade 2	881,3 (683–1197,5)
Grade 3	11124,3 (673,6–2177,8)
Grade 4	1273,9 (816,9–2278,6)
Degree of Joint damage	
Grade 0	0 (0)
Grade 1	2 (4,4)
Grade 2	12 (26,7)
Grade 3	21 (46,7)
Grade 4	10 (22,2)

\* unless otherwise noted

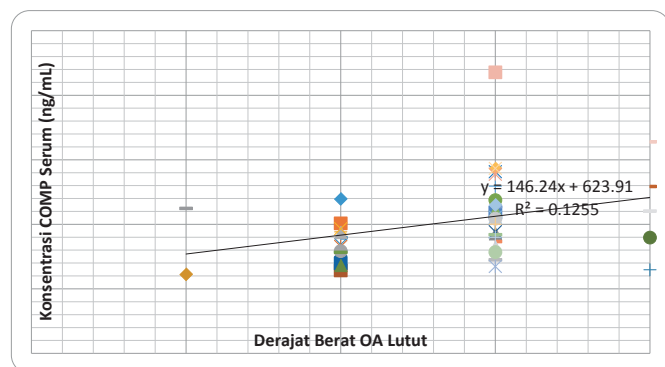
\*\* data distribution is not normal therefore described in median and range

### Reability of knee radiographs in determining severity of knee OA

Three radiologists were tested with a kappa test ( $k$ ) before assessing knee radiographs to determine OA grade based on Kellgren-Lawrence criteria. Assays were based on the readings of 20 samples of knee radiographs by two radiologists. The kappa value attained was 0,595. This was included an adequate criteria.<sup>12</sup>

### Correlation between severity of knee OA and serum COMP levels

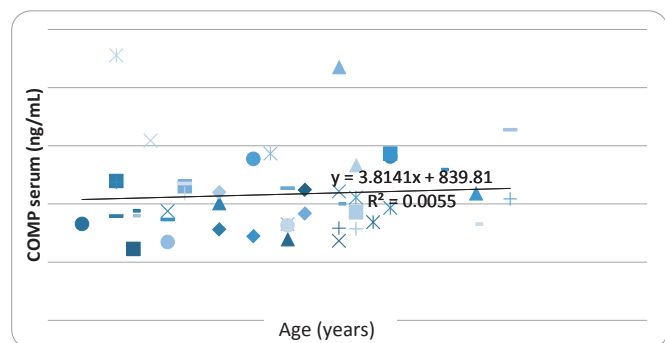
Positive correlations were found statistically significant, using the Spearman correlation test, with  $r = 0,41$  and  $p = 0,005$ . Therefore there was a tendency of increasing grade of knee OA along with increase COMP serum levels (figure 2).



**Figure 2** Relationship between knee OA severity grade (K/L) with COMP serum

### Correlation of Age and COMP serum level

Two methods were used to test the relationship between age and COMP serum levels. The first test was done by correlation test. The second test was done by test comparing COMP serum levels after they were categorized into 2 age groups of  $< 65$  years and  $\geq 65$  years old. In the correlation test a tendency of increase COMP serum levels with age was found, but with no significant correlation ( $r = 0,103$ ;  $p = 0,5$ ) (Figure 4).



**Figure 4** Relationship between age and COMP serum

The compare test of COMP serum in the age groups  $< 65$  years old and  $\geq 65$  years displayed no significant difference ( $t = -8,53$ ;  $p = 0,398$ ).

### Correlation of gender and COMP serum level

In this study, no significant difference was found of log10-COMP serum between male and female ( $t = 0,802$ ,  $p = 0,427$ ). However, the results show a higher COMP serum levels in male than female (Table 2)

**Table 2** COMP serum levels based on gender

Sex	Mean COMP serum (ng/mL)	p
Male	1.135,6 (391,4)	0.427
Female	1.041,7 (318,8)	

### Multivariate Analysis

Linear regression was used as the multivariate analysis to look at factors influencing COMP serum. From the analysis results, only knee OA severity grade ( $p < 0,25$ ) were eligible to be included in the multivariate analysis. Other variables such as gender and age could not be included because their  $p$  values were  $> 0,25$ . Based on the linear regression analysis, equation of COMP was obtained,  $COMP = 573 + 177,3$  (knee OA severity grade). The above equation is feasible because ANOVA test display  $p = 0,005$ . However, knee OA severity grading can only explain COMP serum concentration of 15,1% based on *adjusted R square* linear regression test dan *Anova* value.

### DISCUSSION

In a study done by Clark et al<sup>11</sup> COMP serum obtained from the control group was  $1.061,83 \pm 370.83$  ng/mL, whereas OA patient group was  $1.208,57 \pm 487,47$  ng/mL. Another study was done by Jordan et al<sup>13</sup> examining COMP serum levels corresponding the knee OA severity grade (K/L). After transforming the data using natural logarithm, the mean COMP serum levels in knee OA ( $\pm$ SD) is as follow; grade 0 of  $6.68 \pm 0.40$ , grade 2 of  $6.79 \pm 0.40$ , grade 3 of  $6.87 \pm 0.34$ , grade 4 of  $7.00 \pm 0.48$ . In this study, the distribution value of COMP levels was not normal with a mean COMP level in knee OA patients of 1.081,4 ng/mL ranging between 613,5 to 2.278,6 ng/mL. This data was lower when compared with the previous two studies.

Previous studies investigating the relationship between arthritis and serum COMP levels have been conducted in both experimental animals and humans. Experimental animals that were made to have arthritis demonstrated an increased level of COMP in late phase after further cartilage damage, but not at the beginning when inflammation peaked.<sup>14,15</sup> This study showed that increased COMP in blood was due to articular cartilage damage. In another study, elevated levels of COMP were found higher in experimental animals that had severe arthritis damage compared with mild damage.<sup>14,15</sup> This study implied severe degree of arthritis meant more COMP.

Research studying the relationship between OA and COMP serum levels in humans by Petersson et al<sup>16</sup> exhibited samples with no OA in previous radiologic examinations then later on had OA. They showed a higher concentration of COMP serum compared with those without OA after being follow up for three years.

A tendency of increasing knee OA severity grade along with COMP serum levels was found in this study and showed a correlation that was statistically significant. In Indonesia, research on the correlation between knee OA severity grade with COMP serum has never been conducted. The research done by Conrozier et al<sup>17</sup> was on the correlation between hip OA severity grade with COMP serum. In the study a significant correlation was found between COMP and joint space width (JSW) ( $r = 0,40$ ;  $p = 0,001$ ). COMP value was also connected to yearly mean narrowing (YMN) of the hips ( $r = 0,38$ ;  $p = 0,002$ ).

Researches related to knee OA had been done before, comparing the average levels of COMP serum in patients with different OA grading. One the researches was conducted by Clarck et al (1990) who compared COMP serum levels in OA patients and control group. As a result, patients with grade 3 and 4 knee OA had an average COMP serum of 21,3% higher ( $p = 0,013$ ) compared with the control group and patients with grade 2 knee OA had an average COMP serum 11,5% higher than the control group ( $p = 0,045$ ). Although average COMP serum levels tended to be higher in grade 3 - 4 knee OA than to grade 2 but this did not differ significantly.<sup>11</sup>

In this research, the average COMP serum levels were compared between groups of severe knee OA group (grade 3 and 4) with mild knee OA (grade 1 and 2) and obtained a significant difference ( $t = -3,04$ ;  $p = 0,004$ ). This data supported previous theory stating that higher grade OA had higher COMP serum level.

However, the use of serum COMP as a tool to assess the severity of knee OA, based on these results, can not be fully utilized because the levels of serum COMP vary in each grade of OA (a sample of grade 4 knee OA was found having a COMP level below the average COMP level of grade 2) (Figure 3).

Multivariate analysis (linear regression) showed that, although the equation on the influence of knee OA severity grading with COMP serum could be used, it could only explain as much as 15,1% COMP serum levels. Possibly, there are other factors influencing COMP levels that has not been investigated. Another cause may be the reability (or kappa) of determining knee OA from radiographs is not included as good criteria. In this study, the kappa value of radiographic readings in determining knee OA grade based on Kellgren Lawrence criteria was moderate. For further research, kappa values should be increased by training. Another alternative is by using better modalities such as MRI in assessing the severity of OA.

Besides the grading of knee OA severity, several other factors may affect serum COMP levels, such as age, sex, and impaired excretion due to kidney disease. Effect of impaired renal function can be ignored because patients with these conditions are excluded first.

There were a few of limitations in this study. One of the criteria used for inclusion OA samples was clinical in which the diagnosis of OA can only be made if there was a complaint. OA patients without clinical complaints are unlikely to be included as a study sample therefore affecting the COMP

serum levels obtained. Moreover, assessment of OA grade with knee radiographs using Kellgren-Lawrence criteria only achieve a reliability (kappa value= 0.6) of moderate.

## CONCLUSION

This study concluded that there was a significant correlation between knee OA severity grades with COMP serum levels. Strength criteria included moderate correlation ( $r = 0.41$ ). However, using serum COMP level to assess the severity of knee OA is not applicable because of varying level of serum COMP in each grade of OA. Further efforts to a better and objective assessment of OA severity can be made by increasing the value of kappa or using better modalities should another research is planned to cover the limitations in this research.

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# Avascular necrosis of the right femoral head in female patient with Systemic Lupus Erythematosus

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Avascular necrosis (also known as osteonecrosis, aseptic necrosis, or ischemic necrosis) represents collection of pathologic conditions from various etiologies causing impairment of blood supply to particular bone resulting in bone cellular death. Avascular necrosis remains a significant cause of morbidity in patients with systemic lupus erythematosus (SLE).<sup>1</sup> It often involves multiple joints in SLE, in which the femoral head is involved in most of these patients. Corticosteroids use is known as a major risk factor in the development of this complication.<sup>2-3</sup> We report this case due to its quite common occurrence in SLE patients. The early recognition of avascular necrosis is essential to prevent morbidity.

## CASE REPORT

A 24 year-old female patient presented to Emergency Department of Cipto Mangunkusumo General Hospital with chief complaint of pain in right hip two weeks prior to admission. She was difficult to move her right thigh and walk due to the severity of the pain. The pain was aggravated with movement and relieved by rest; thus, she had limitation of daily activities. There was no history of trauma or thrombotic episodes. She did not smoke cigarette and drink alcohol. She was not married. There was no family history of similar illness in her family.

The patient was diagnosed with SLE two months prior to admission. Her chief complaint was dark rashes all over her extremities. She was given methylprednisolone 32 mg/day, omeprazole 20 mg bid, folic acid qd, and vitamin D3 tid. Her rashes were improved with the medication, but she did not regularly visit the Allergy and Immunology Clinic in Cipto Mangunkusumo General Hospital.

The physical examination revealed moderately ill-looking. Her body weight was 45 kg and her height was 152 cm with body mass index (BMI) of 18.6 kg/m<sup>2</sup>. Her blood pressure was 110/70 mmHg, without tachycardia and tachypnea. Her body temperature was 37°C. She had no malar rash or stomatitis, but she had hyper-pigmented macula all over her extremities and an ulcer in sacral region 3 cm in diameter with clean base and no pus. There was no limb length discrepancy. She was difficult to move her right leg out and unable to raise that. Her physiological reflexes were intact. No pathological

reflexes noted during the examination. Other physical examinations were within normal limits.

Laboratory examination revealed hemoglobin of 10.2 gram%; haematocrit of 31%; white blood count (WBC) of 10,200 u/L, and platelet count of 314,000 u/L. The blood urea was 27 mg/dL and creatinine was 0.4 mg/dL. The electrolytes and liver transaminases were within normal limits. ANA was positive and anti-ds-DNA was 360.79. The erythrocyte sedimentation rate (ESR) was 110 mm/h. Her activated partial thromboplastin time (aPTT) was 35.4 sec (control 33.5 sec) and prothrombin time (PT) 14.1 sec (control 11.6 sec), which were normal. Radiography of the chest, pelvis, and lumbo-sacral were revealed no abnormalities. Her electrocardiography (ECG) was also within normal limits.



**Figure 1** : Pelvic radiography showed no abnormality on both femoral heads

The working diagnoses were suspected fracture of the right femoral head caused by suspected avascular necrosis, SLE, anemia, low intake, pressure ulcer, and immobilization. Then, she was given intravenous normal saline and Triofusin E 1000 per 24 hours, 1700 kcal diet per day, methylprednisolone tablets 8 mg bid, folic acid tablet qd, vitamin D3 tid, omeprazole 40 mg injection qd, tramadol 100 mg injection bid, heparine UFH 5000 units subcutaneously bid, ceftriaxone 2 g injection qd, and metronidazole 500 mg infusion tid. The patient was planned for pelvic magnetic resonance imaging (MRI) and consulted to the Department of Orthopedic and Traumatology. On fourth day of hospitalization, patient and her family decided to go home due to financial problems.

Four days after the discharge, patient went for pelvic MRI. The test revealed collapse of the right femoral head which suggested avascular necrosis of the right femoral head. She was then lost to follow-up and had never visited the hospital ever since.



**Figure 2** Patient's MRI showed collapse of the right femoral head (yellow arrow)

## DISCUSSION

Systemic lupus erythematosus is a multisystem, autoimmune disease of unknown etiology. It is characterized by immune dysregulation that results in the production of autoantibodies, generation of circulating immune complexes, and activation of the complement system. Pathogenesis of the disease is apparently multifactorial with genetics, environmental, hormonal, and possibly viral influences playing a role.<sup>4</sup>

Avascular necrosis (also known as osteonecrosis, aseptic necrosis, or ischemic necrosis) represents conditions that result in impairment of blood supply to particular bone resulting in bone cellular death. Avascular necrosis can lead to architectural collapse of the subchondral bone, joint incongruity, and degenerative arthritis. A definite association between avascular necrosis and SLE was first documented in 1960 by Dubois and Cozen. Avascular necrosis has continued to be a significant cause of morbidity in patients with SLE.<sup>1</sup> The incidence of avascular necrosis in SLE patients is 4-16% and often involves multiple joints. The femoral head is involved in 80% of these patients. Corticosteroids use is a major risk factor in the development of this complication.<sup>1,5</sup> A researcher, named Zizic concluded on the rarity of avascular necrosis in other steroid-dependent populations, such as asthma, dermatological disorder, and inflammatory bowel disease, when compared to SLE.<sup>5-7</sup> This finding suggests that additional factors specific to SLE itself may be responsible for avascular necrosis. Other features which have been associated with development of avascular necrosis in SLE include arthritis, central nervous system disease, vasculitis, hematologic abnormalities, Raynaud's phenomenon, and antiphospholipid antibodies.<sup>2-3,5</sup>

The pathogenesis of avascular necrosis in SLE is multifactorial. Some factors that may contribute are blood flow to the bone, vasculitis, and corticosteroid itself. The femoral head derives its blood supply from three sources: intraosseous cervical vessels, retinacular vessels, and the artery of the ligamentum teres. There are only few anastomoses to

the femoral head. Therefore, any disruption to the blood flow of one artery above cannot be compensated by the collateral vasculature.<sup>2,8</sup>

It is believed that vasculitis and increased tendency to thrombosis as components of lupus syndrome contribute to avascular necrosis in SLE.<sup>5</sup> Vasculitis is characterized by inflammation of the vessel wall and intravascular activation of polymorphonuclear (PMN) leukocyte and release of reactive oxygen species. These events may stimulate aggregation of PMN resulting in intravascular thrombus.<sup>2</sup> Mont et al found a high incidence of thrombophlebitis and vasculitis in patients with avascular necrosis. This suggests that the pathophysiological mechanisms of thrombotic and endothelial damage are involved in the development of avascular necrosis.<sup>9,10</sup> From history taking, patient mentioned no history of any thrombotic events, more over from blood examination revealed normal hemostatic examination.

The mechanism of steroid induced avascular necrosis is still not fully understood. Corticosteroids use at least 30 mg/day is a major risk factor in the development of this complication. McFarland and Frost suggested that corticosteroids may suppress osteoblastic function of the bone; and therefore impairs the host response to micro-fractures. Corticosteroids also exert some effect to fat metabolism, storage, and asymptomatic systemic fat emboli. Two hypotheses have been proposed in an attempt to explain the mechanism by which changes in fat metabolism after steroid administration can lead to avascular necrosis. The first suggests that altered fat metabolism causes an increase in the size of intraosseous adipocytes, leading to increased intraosseous pressure which compromises perfusion (through activation of the coagulation pathway) and results in ischemia. The second proposed mechanism is that altered fat metabolism results in increased serum lipid levels with subsequent occlusion of subchondral vessels by fat emboli. Animal studies have proposed that increased levels of serum lipids leads to lipid deposition in the femoral head, causing femoral hypertension and ischemia. Fisher and Bickel concluded that systemic fat emboli caused a mechanical vascular obstruction on avascular necrosis.<sup>1-2,5</sup>

Studies investigating avascular necrosis and steroid treatment yielded conflicting results concerning cumulative steroid dose, maximum daily steroid dose, route of administration, and duration. Aranow et al screened 62 SLE patients by MRI for avascular necrosis. Forty three of 62 patients took  $\geq 30$ mg/day of prednisone and nine patients (19%) had evidence of avascular necrosis. Patients who had taken  $< 30$ mg/day had no evidence of avascular necrosis. From another descriptive study done by Castro et al concluded that there was no significant difference between the avascular necrosis and non-vascular necrosis group in relation to the maximum daily corticosteroid dose, the cumulative steroid dose, or methylprednisolone pulse therapy.<sup>5,9</sup> The most possible contributing factor to avascular necrosis in this patient was steroid ingestion.

The process of avascular necrosis may appear before the symptoms. It causes pain upon standing, walking, or moving the affected bone and the pain relieved when resting. Due to

severe pain, some people remember the exact day and hour when the pain begin to emerge. Sudden arrival of the pain may occur when there is disruption of the blood supply to the bone. In avascular necrosis of the femoral head, the groin pain may radiate down to one side of the thigh or felt in the buttocks. The gait was antalgic, trying to reduce all motion of the thigh. As the disorder progress, the more likely a hip fracture occurs. The pain somehow increases, the thigh joint becomes stiff and reduces its range of movement.<sup>4,11</sup> This patient complained pain on her right hip accompanied with reduced motion at the hip.

Physical examination may reveal pain and limitation in passive range of motion of the hip, especially forced internal rotation. A distinct limitation of passive abduction may also be noted. Passive internal and external rotation of the extended leg (log roll test) and straight-leg raise against resistance may elicit pain as well.<sup>2</sup> This patient experienced limitation in passive abduction, internal, and external rotation of the leg.

Diagnosis of avascular necrosis can be done trough radiographic imaging. Antero-posterior and frog-leg lateral radiographs should be obtained as part of the work-up; however, early-stage avascular necrosis is not visible on radiographs. MRI should be performed when avascular necrosis of the femoral head is suspected but not obvious on radiographs.<sup>12-13</sup>

The successful treatment of patients with avascular necrosis is related directly to the stage of disease at the time of diagnosis. Staging plays an important role in diagnosis. Ficat and Arlet described the first staging system for avascular necrosis of femoral head in 1960. Hungerford and Lennox modified this staging system when MRI became available, adding stage 0 to the classification. Steinberg et al expanded this staging system, by dividing stage III lesions into femoral heads with or without collapse or hips with or without acetabular involvement. Ohzono et al incorporated the concept of location of the lesion with prognostic value. More recently, a new classification has been completed by The Association Research Circulation Osseus (ARCO), which joins the Ficat and Arlet staging system, the Hungerford-Lennox modification, Steinberg, and Ohzono staging systems.<sup>2,14-16</sup> We report this patient based on Ficat and Arlet staging (table 1).

**Table 1** Ficat and Arlet staging of avascular necrosis of femoral head<sup>14-16</sup>

Stage 0	No pain, normal radiographic finding, abnormal findings on MRI or bone scintigraphy
Stage I	Pain, normal x-ray finding, abnormal findings on MRI or bone scintigraphy
Stage II	Pain, cysts and/or sclerosis visible on x-ray, abnormal MRI or bone scintigraphy without subchondral fracture
Stage III	Pain, femoral head collapse visible on x-ray, abnormal MRI or bone scintigraphy, crescent sign (subchondral collapse) and/or slip-off in contour of subchondral bone
Stage IV	Pain, acetabular disease with joint space narrowing and arthritis visible on x-ray, abnormal MRI or bone scintigraphy

MRI, magnetic resonance imaging

MRI is representing the gold-standard of non-invasive diagnostic evaluation of avascular necrosis and become the most sensitive and specific means of diagnosing avascular necrosis. MRI has several advantages such as allows accurate staging by clearly depicting the size of the lesion; detection of asymptomatic lesions that are undetectable on plain radiographs, thus facilitating early treatment and better response; provides multi-planar imaging and excellent soft tissue resolution. Whole-body STIR (short tau inversion recovery) MRI permits the evaluation of the entire skeleton in a single examination that can be completed within a reasonable period of time.<sup>14,17</sup>

Characteristic MRI findings for avascular of the hip include a low signal intensity band (seen on T1 and T2 images) that demarcates a necrotic antero-superior femoral head segment. The extent and location of femoral head necrosis on MRI have been studied as predictors of femoral head collapse. Smaller lesions (less than one fourth the diameter of the femoral head) and more medial lesions (away from primary weight-bearing areas) predict a better outcome. The ability of MRI to detect the early stages of avascular necrosis may allow earlier intervention to ameliorate disease progression and to minimize more severe long-term sequelae.<sup>9,16-17</sup> From patient's pelvic radiography, there were no changes from the femoral head. So, it was decided to order more advance imaging modality of MRI. The MRI revealed collapse of the femoral head. Based on Ficat and Arlet staging, this patient was classified under stage III. Sometimes in stage III, anteroposterior radiograph may appear normal, like in this patient, but frog-leg lateral view often reveals a crescent sign under the subchondral bone.<sup>18</sup> Unfortunately, we did not perform the frog-leg lateral view in this patient.

Management of avascular necrosis consists of non-operative and operative measures. Non-operative management is often used for small, asymptomatic lesions in which subchondral bone collapse is absent. Non-operative measure usually results in an unfavorable prognosis. Most methods of non-operative treatment have involved restricted weight bearing, pharmacologic agents, and various external, biophysical modalities such as electromagnetic stimulation, extracorporeal shock-wave therapy, and hyperbaric oxygen. Restricted weight bearing with use of a cane or crutches has not been shown to affect the natural history of the disease and is useful only in controlling symptoms. Those biophysical modalities only provide symptomatic control without altering the course of the disease. Pharmacological intervention includes statin to lower the lipid level. Pritchett reported that at a mean of 7.5 years avascular necrosis of the femoral head had been developed in only 1% of patients who were taking high doses of steroids as well as various statin drugs.<sup>2,4,15,19</sup>

**Table 2** Recommendation of decision-making hierarchy for the treatment of patients with avascular necrosis of the femoral head<sup>12,18-21</sup>

Stage	Treatment
0 (asymptomatic, no radiographic changes)	Possible core decompression
I (no radiographic changes)	Core decompression, percutaneous drilling
II (pre-collapse)	Core decompression, percutaneous drilling, bone-grafting, osteotomies
III (crescent sign)	Hemiresurfacing, total hip arthroplasty
IV (joint deformity, acetabular involvement)	Total hip arthroplasty

Operative treatment (see table 2 for recommendation) of avascular necrosis of the femoral head can be categorized as either prophylactic measures (to retard progression) or reconstruction procedures (after femoral head collapse). The most commonly performed prophylactic surgical treatment is core decompression (removal of the inner layer of bone) and bone-grafting (healthy bone from one part of the patient to be transplanted in the diseased area; at present vascularized-grafts are used). Core decompression is usually performed in earlier stage of avascular necrosis. The goal is to decompress the femoral head and thereby reduce the intraosseous pressure in the femoral head, restore normal vascular flow, and subsequently reduce the hip pain. Bone-grafting may be effective, compared with core decompression, for larger lesions just before head collapse.<sup>14,15,18,20-21</sup>

There are some reconstruction procedures for avascular necrosis of femoral head such as total hip arthroplasty, osteotomy, limited femoral resurfacing arthroplasty, and bipolar arthroplasty. Most hips that undergo collapse ultimately require reconstruction. Prosthetic replacement offers the most predictable means of pain relief in advanced avascular necrosis. Total hip arthroplasty is a predictably effective treatment of avascular necrosis of the femoral head when the disease is progressed to Ficat and Arlet's stages III and IV.<sup>14,15,20-21</sup> This patient progressed into stage III based on Ficat and Arlet, so total hip replacement is mandatory in this case.

## SUMMARY

We have reported a case of avascular necrosis of the femoral head in female patient with systemic lupus erythematosus. Steroid might contribute as one factor for the development of avascular necrosis. According to the staging, the patient should be treated with total hip replacement, but after establishing the diagnosis the patient was lost to follow-up.

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# Osteoarticular Tuberculosis: A Secondary Manifestations to Tuberculous Pleural Effusion

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Tuberculosis appears to be increasing throughout the world after years of continuous decline, despite the introduction of effective chemotherapy. This resurgence is related to the increasing number of patients immunocompromised by chemotherapeutic agents used to treat other diseases or Acquired Immunodeficiency Syndrome (AIDS); the appearance of multiple drug-resistant strains of tuberculosis, and aging population. Musculoskeletal tuberculosis arises from haematogenous seeding of the bacilli soon after the initial pulmonary infection.<sup>1</sup> Osteoarticular TB can occur in the knee - one study found of 1074 cases, 8.3 percent - or 90 cases - affected the knee.<sup>2</sup> The clinical symptoms are insidious onset, pain, swelling of the joint and limited range of movements. Investigations for suspected cases include: Mantoux test, radiological imaging, fine needle aspiration biopsy, surgical biopsy, bacteriological examination, histopathological examination, and polymerase chain reaction (PCR) of a suitable specimen. The mainstay of treatment is multidrug antitubercular chemotherapy. The main reason for poor outcome is delayed diagnosis.<sup>1</sup>

We report a case of osteoarticular manifestation of tuberculosis infection affecting the left knee presenting in a man with a history of tuberculosis pleural effusion. This case highlights, firstly, osteoarticular disease is always secondary to a primary lesion in the lung and, secondly, the diagnosis of tubercular arthritis can be challenging, particularly in the presence of confounding factors such as preexisting arthritis. Ethical approval was not required for this case study.

## Case Report

A 22-year old man, presented to the rheumatology clinic with a painful and swollen left knee. His symptoms had gradually worsened over a period of one month whereby now he had a limited range of movement of the knee. The symptoms dated from a fall 1 month previously. The patient reported symptoms of respiratory infections. He denied any intravenous drug use or HIV risk factors and had good immune status. He recalled history of tuberculosis year ago and was on antitubercular treatment for 2 weeks (stop on his own due too abdominal symptoms). The initial physical examination revealed tachycardia (110 beats/minute), fever (38°C), arthritis of the left

knee and low Body Mass Index (BMI)16.5 kg/m<sup>2</sup>. Lung auscultation revealed signs of moderate rales. Examination of the left knee revealed a swollen warm knee, painful, restricted with reduced flexion ability and small amounts of effusion in the left knee joints (Figure 1).



**Figure 1.** Physical examination revealed painful swelling of the left knee

Automated blood counts demonstrated a total white cell count of  $13.37 \times 10^3/L$ , neutrophil segment of 91%, an erythrocyte sedimentation rate prolonged to 35 mm/hr and hypoalbuminemia (3.0g/dl). Sputum smears for AFB were negative. Chest radiography revealed infiltrates and pleural effusions of the left lung (Figure 2). On plain radiography, the affected knee appeared normal other than subtle soft tissue swelling (Figure 3). Patient underwent arthrocentesis of the left knee and a total of 4 mL of cloudy yellowish-coloured fluid was removed and sent for PCR, culture and microscopy. Culture yielded negative results, PCR was positive for M. TB, and no crystals were seen. Culture for acid-fast bacilli was not requested (lack of fluid sample). We concluded that this patient suffered from an acute monoarthritis due to osteoarticular tuberculosis. Patient reject for thoracocentesis and hospitalization. Antibiotic were given for respiratory infection symptoms and a referral was arranged to the hospital's tuberculosis clinic. A decision was made to start antitubercular treatment with isoniazid, rifampicin, pyrazinamide and ethambutol pending the culture results. The patient left against medical advice several hours later. Respiratory symptoms disappeared in a week under antibiotics. After 6 weeks of treatment, the patient showed improvement in his general health as well as reduction in the left knee swelling. At

the time of writing, he was continuing to follow up as an outpatient at the tuberculosis clinic.



**Figure 2.** Chest radiograph showing parapneumonic pleural effusion



**Figure 3.** Anteroposterior and lateral radiographs of the knee showing is unremarkable other than a subtle soft-tissue swelling

### Discussion

It is estimated that there are nine million people worldwide infected with the active form of TB and it is the direct cause of around two million deaths per year.<sup>3</sup> Tuberculosis is typically classified as pulmonary or extrapulmonary. About 60% of cases are pulmonary, and of the remainder about 7% involve bone or joints or both. Tuberculous arthritis is usually monoarthritis with a predilection for weight-bearing joints; however, up to 15% of cases are polyarticular.<sup>4</sup> In adults, TB shows a preponderance to the spine (40%), then the hip (25%), and finally the knee (8%).<sup>5,6</sup> While extrapulmonary manifestations of TB are common, accounting for around 15–20% of cases in immunocompetent patients, the first presentation of the disease as a joint infection is rare.<sup>7</sup> Primary bone infection with TB is less likely than hematogenous spread from a primary focus elsewhere.<sup>3</sup> Musculoskeletal tuberculosis arises from hematogenous seeding of the bacilli soon after the initial pulmonary infection.<sup>4</sup> Although, our patient showed respiratory symptoms, the rest of the symptoms were actually typical clinical initiation of specific synovitis of the knee: fever and painful swelling of the joint.

Culture of synovial fluid gives positive results in 79% of cases, but synovial biopsy may be required to grow the organism. In some cases the organism will not be seen on smear

or culture, but caseating granulomas will be demonstrated on histologic examination. For this reason histologic studies must be performed in cases in which microbiologic tests give negative results in order to confidently exclude tuberculosis as a cause of chronic arthritis. In our case, sputum smears for AFB were negative and PCR of the joint fluid confirmed the diagnosis. Plain radiographic findings of tuberculous arthritis are only seen after a latent period of about 3-4 weeks. Joint effusion and soft-tissue swelling are the only findings in early stages. In the late stages, the classic ‘Phemister triad’ of joint space reduction, juxta-articular osteoporosis and peripheral osseous erosions are described. Early changes are better demonstrated on MRI which has now become the mainstay of imaging in musculoskeletal tuberculosis.<sup>8</sup> Options for treatment once the diagnosis is confirmed must involve antituberculous chemotherapy, but surgery may be indicated to improve symptoms and quality of life in patients affected by joint infection. Unlike for pulmonary TB, the treatment for bone and joint disease is a lengthier process, often requiring twelve to eighteen months of chemotherapy.<sup>9,10</sup>

### Conclusion

Any case of acute arthritis is septic until proven otherwise, and any case of chronic arthritis ought to raise the suspicion of tuberculosis, particularly in a person from an endemic region. It remains a controversial topic whether one can ever truly describe a case of primary tuberculosis of a joint; however, there are cases, such as that presented here, which seem to manifest only as secondary manifestation to pulmonary tuberculosis.

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# Chronic Osteomyelitis of Wrist Joint in An Immunocompromised Host

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Osteomyelitis is heterogeneous in its pathophysiology, clinical presentation, and management. Osteomyelitis is generally categorized as acute or chronic based on histopathologic findings, rather than duration of the infection. Necrotic bone is present in chronic osteomyelitis, and symptoms may not occur until six weeks after the onset of infection.<sup>1</sup> Epidemiology of chronic osteomyelitis is less well characterized compared with acute osteomyelitis.

Adult osteomyelitis most commonly arises from open fractures, diabetic foot infections, or the surgical treatment of closed injuries. Hematogenous osteomyelitis accounts for approximately 20% of cases of osteomyelitis in adults. It is more common in males regardless of age. Although rare in adults, it most frequently involves the vertebral bodies.<sup>2</sup> *S. aureus* is the most common isolate in all types of bone infection and is implicated in 50-70% of cases of chronic osteomyelitis.<sup>3</sup>

## CASE REPORT

A 42-year old male came to hospital with progressive vomiting and weakness since two weeks before admission. The symptoms began three days after he got four kinds of drug from a doctor, as treatment for his chronic cough and abscesses on his right hand.

One and a half year ago, his right hand suddenly swelled. The swelling extended and reached his upper arm. He started to feel feverish, especially at night. Painful suppurating abscesses occurred on the back of his right hand a year later. The pus was white, thick, mixed with blood, but was not malodorous. Three months before admission, he noticed that his hand was “drop”. He could not move his right wrist. He had lost approximately 30 kilograms of body weight during his illness. Two weeks before admission, he consulted a doctor and was given four kinds of drug which had to be taken for six months. After a few days, he noted that his urine coloring turned red. The fever subsided and the pus diminished, but he started to feel nauseous and vomited, which was the main reason of his visit to the hospital.

Twenty years ago, distal part of the third finger of his right hand was accidentally cut by a machine. He did not realize that the finger was cut until he was told.

The patient had been married for 19 years and had a healthy 8-year old daughter. He once worked in a parking lot but had been jobless for six months. He had been smoking for about twenty years. He sometimes consumed alcoholic drinks. He also admitted that he had been doing free sex.

The patient looked ill and weak. He was 168 centimetres tall and weighted 39 kilograms. On examination, his blood pressure was 120/70 mmHg, heart rate of 120 bpm and respiratory rate of 28/minutes. His temperature was 37°C. The skin was dry and xerotic. There were multiple hypopigmented macules of various size with greasy white scales along the body. No anaesthetic or pain sensation on the lesions. He has noticeable paleness of his conjunctivae. Lagophthalmus could be seen when eyes were closed. No oral thrush was found. Percussion detected dullness below the fifth costae on both lungs. Lung auscultation revealed vesicular breath sound with crackles on both lungs. Heart rhythm was regular without murmurs or gallops. There was no abnormalities in the abdomen. There were bilateral pitting edema on the foot.

Local examination of the right hand noted that his wrist was slightly swollen, erythematous in appearance, and very tender to palpation. He could not move his wrist. There were deformity and subluxation of the joint to the ulnar side. There were also three atrophic scars on the dorsal of the wrist joint, which were once the pus-secreting abscesses. The distal segment of third finger of right hand was mutilated. Sensory of all fingers were considered intact.

On the anterior part of his right lower leg, there was a linear scar, about 14 centimetres long, without sign of inflammation. Enlargement of right auricularis magnus nerve and right ulnar nerve were palpated. Left lateral peroneus nerve and left posterior tibial nerve were also enlarged and tender to palpation. His toe nails had ragged appearance with yellow discoloration, onychodystrophy, and subungual hyperkeratotic.

Blood was obtained for initial laboratory analysis and the results were as follow: hemoglobin 11,1 g/dl; haematocrite 34%; leukocyte 12,200/μl, thrombocyte 574,000/μl, ESR 8 mm; MCV 73,3; MCH 24; MCHC 32,8, SGOT 27 U/l, SGPT 14 U/L, albumin 1,4 g/dL, globulin 2,7 g/dL, random blood glucose 87 mg/dl, CRP 48,3; sodium 124 meq/L; potassium 3,54 meq/L; and chloride 101

meq/L. Chest x-ray showed chronic active tuberculosis of the lungs with bilateral pleural effusion (Figure 1).



**Figure 1. Bilateral Pleural Effusion**

Plain film of right manus region gave an impression of septic arthritis of the right wrist joint with subluxation of distal segment of radiocarpal-ulnecarpal joint to the volar and ulnar sides, deformity of distal phalang of third finger, disused osteoporosis of manus bone, and calcification of soft tissues in volar side of distal antebrachii. There was also destruction in a third distal part of radius-ulnar (epi-metaphysis), carpal, and metacarpal, with less defined borders. Joint space was narrowing. These appearances were concluded as osteomyelitis (Figure 2).



**Figure 2. Radiologic photo of hands with osteomyelitis**

Based on clinical manifestations and initial workup, the patient was diagnosed with: osteomyelitis of wrist joint and pulmonary tuberculosis. He was treated with antimicrobial cefotaxime iv 1 gram tid and levofloxacin iv 500 mg qd, sucralfate 100 mg qid, omeprazole 1x40 mg iv, ondansetron 3x4 mg iv, and NaCl 0,9% 500 cc/8 hours. Antituberculosis drugs (ATD) were temporarily discontinued because of severe vomiting.

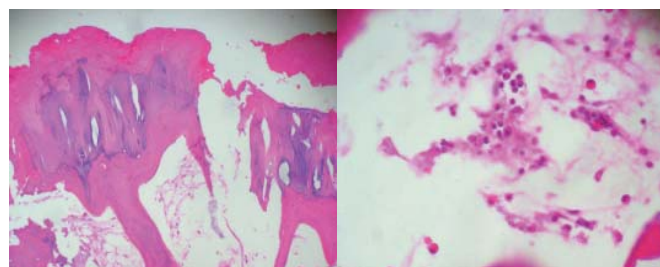
During follow-up, gram staining of sputum specimen

showed the presence of positive cocci and negative bacilli. Acid-fast staining of sputum resulted negative. Sputum culture could not be done at the moment for technical reason. AntiHIV screening test gave out negative result. CD4 cells count was low (198 cells/mm<sup>3</sup>).

TB drugs were then given by titration. After several days of titration the patient received full dose of antituberculosis drugs, which consisted of rifampicin 300 mg, isoniazid 300 mg, and ethambutol 1000 mg. Patient could not tolerate pyrazinamide because nausea and vomiting recurred with 500 mg of pyrazinamide. Streptomycin 750 mg im qd was then added into the regimen.

The hypopigmented macules were diagnosed as pityriasis versicolor and were given ketoconazole solution. After nearly three weeks of therapy, exfoliation of the skin became more visible. No itch, redness, or blisters. The skin disorder was diagnosed as pityriasis versicolor and was treated with ketoconazole and selenium sulfide 1,8% solution. During follow up, the skin lesions did not improve. Specimen from toe nails were also taken. KOH smears of skin specimen resulted negative, but acid-fast staining gave out positive result with bacterial index 15/6 and morphology index 0%. Patient was classified as lepromatous leprosy with grade II deformity and acute neuritis. He was treated with clofazimin 300 mg daily and dapson 100 mg daily. KOH smears of nails specimen discovered the presence of hyphae and arthrospore. Culture grew colonies of candida and *fusarium sp.*

Surgery was conducted during hospitalization. Surgical procedure included debridement, arthrodesis, and installation of T-plate. Intraoperative biopsy of the bone was performed, but bone culture could not be done. Histopathologic examination of biopsy specimen revealed bone tissues, necrotic bone/ sequestrum, and infiltration of chronic inflammatory cells and neutrophil. No signs of specific inflammation. The conclusion was chronic osteomyelitis (Figure 3). Patient was discharged after his condition improved.



**Figure 3. Histopathologic appearance**

## DISCUSSION

Diagnosis of chronic osteomyelitis was based on medical history, physical examination and diagnostic tests. According to patient's signs and symptoms, osteomyelitis had probably started 1.5 years ago when the swelling occurred. Osteomyelitis should be suspected in anyone with bone pain who has a past history of trauma or orthopedic surgery. Patients generally exhibit malaise, anorexia, weight loss, fever, night sweats, and often complain of persistent pain and drainage through sinus tract. Walenkamp described a classic history as cyclical pain, increasing to "severe deep tense pain with fever" that

often subsides when pus breaks through in a fistula.<sup>3</sup> In our patient, the presence of structural deformities of the right hand was noted. The hand looked swelled and erythematous. There were three atrophic scars, which were said to have been drained of pus on the dorsal side. Classically, the cardinal signs of inflammation are redness, tenderness, heat, and swelling. If these signs are noted on physical examination, it be concluded that an infection is present. However, as with the history, signs of an actual osteomyelitis are often difficult to be distinguished from those of an overlying soft tissue infection. Suspicion of a bone infection may be confirmed by the presence of exposed necrotic bone, surgical hardware, or active fistulas.<sup>3</sup> At the moment, there were no exposed bone, surgical hardware, or active fistulas found. Pus secretion had ceased to flow approximately ten days before admission.

Laboratory test indicating systemic inflammation should be a sensitive marker for infection. However, this should not be the case in chronic osteomyelitis, which is a disease characterized by devitalized tissues and a muted inflammatory response. The WBC counts and acute-phase reactants, such as ESR, ferritin, and CRP, are often normal in cases of chronic osteomyelitis.<sup>3</sup> His leukocyte, ferritin, and CRP were elevated, but his ESR was within normal limit. Nutritional parameters such as albumin, prealbumin, and transferrin, are helpful in the workup of a patient with suspected chronic osteomyelitis so that malnutrition can be identified and managed.<sup>3</sup>

Plain radiographs play a significant role in the workup of chronic osteomyelitis. Plain radiography has a reported sensitivity and specificity of 43% to 75% and 75% to 83% respectively. Radiographic findings of chronic osteomyelitis can be subtle and include osteopenia, thinning of the cortices, and loss of the trabecular architecture in cancellous bone. Sequestra appears radiodense relative to normal bone.<sup>3</sup> In our case, findings that were suggestive for osteomyelitis had been obtained from plain radiographs, so that other imaging modalities, such as CT or MRI, were considered unnecessary. In cases where plain radiographs failed to show characteristic features of osteomyelitis, a more sophisticated imaging modality should be pursued. Choices include CT, bone scintigraphy, and MRI (table 1). Ultrasound examination may also be helpful in detecting abscess and surface abnormalities of bone.

**Table 1** Accuracy of diagnostic imaging for the assessment of chronic myelitis<sup>4</sup>

Diagnostic methods	Sensitivity	Specificity
FDG-PET	96%	91%
Bone scintigraphy	82%	25%
Leukocyte scintigraphy	61%	77%
Bone + Leukocyte	78%	84%
MRI	84%	60%

According to Waldvogel, osteomyelitis can be classified into hematogenous or contiguous-focus, acute or chronic, and with or without vascular insufficiency. An alternative classification by Cierny and Mader (Cierny-Mader Staging

System) considers the quality of the host, the bone's anatomic nature, treatment factors, and prognostics factors. This classification system is helpful in determining if treatment should be simple or complex, curative or palliative, and limb sparing or ablative (table 2).<sup>5</sup>

**Table 2** Cierny-Mader Staging System of Osteomyelitis<sup>5</sup>

Anatomic type	Physiologic class
Stage 1: Medullary osteomyelitis	A host healthy
Stage 2: Superficial osteomyelitis	B host
Stage 3: localized osteomyelitis	Bs: systemic compromise
Stage 4 : diffuse osteomyelitis	Bl: local compromise
	Bls : local and systemic compromise

**Factors affecting immune surveillance, metabolism and local vascular**

Systemic factor (Bs): malnutrition, renal or hepatic failure, diabetes mellitus, chronic hypoxia, immune disease, extremes of age, immunosuppression or immune deficiency

Local factors (Bl): chronic lymphedema, venous stasis, major vessel compromise, arteritis, extensive scarring, radiation fibrosis, small vessel disease, neuropathy, tobacco abuse

In this case, the type of osteomyelitis was diffuse so it was classified into stage 4. Etiology of diffuse osteomyelitis includes trauma, hematogenous, or contiguous soft tissue infection. Chronic osteomyelitis in this patient was considered to be hematogenous because of the absence of open fracture or wounds in the hand. Patient was classified into physiologic class B because he had systemic compromised condition (malnutrition and immunodeficiency). Stage 4 requires debridement, stabilization, dead-space management, second-stage reconstruction, and antibiotics. The goal of treatment for a B host is to remove the compromising factors that distinguish them from an A host.<sup>6</sup>

Bone infection in the adult population is much more likely to be exogenous in origin than hematogenous because the predilection for bacterial seeding of bone ceases with closure of the epiphyses. For this reason, hematogenous osteomyelitis is rare in people beyond their teens, occurring only in immunocompromised hosts.<sup>3</sup> The possibility of patient having immune deficiency syndrome has been considered early on the course of treatment. The patient was undernutrition with low body mass index and hypoalbuminemia, but his HIV screening tests return negative though his CD4 cells count was low. Immunosuppression may occur as a biologic complication of another disease process. Diseases in which immunodeficiency is a common complicating element include malnutrition, neoplasms, and infections. Our patient was underweight and suffered for chronic infection. Deficient intake of protein, fat, vitamins, and minerals will cause some metabolic derangements that inhibit lymphocyte maturation and function. Deficient humoral immunity usually results in increased susceptibility to infection by pyogenic bacteria (otitis, pneumonia, meningitis, osteomyelitis), whereas defects in cell-mediated immunity lead to infection by viruses, atypical mycobacteria and other intracellular microbes. Immunodeficiency state is a significant predisposing factor

for lung tuberculosis, fungal infection, and leprosy suffered by the patient. On the contrary, chronic infection gives large contribution to the generation of immunodeficiency state.<sup>7</sup>

*Mycobacterium tuberculosis* is a very possible pathogenic cause of osteomyelitis of wrist joint in this patient. This form of TB presents typically 3-5 years after the initial respiratory infection, with the haematogenous spread at that initial infection. The infection usually originates in the metaphyseal bone marrow and crosses the epiphysis to the joint.<sup>8</sup> In this patient, chest x-ray is suggestive for tuberculosis with bilateral infiltrates and effusion. Those with CD4 counts < 200 cells/mm<sup>3</sup> are more likely to have atypical infiltrates (lower lobe predominance, adenopathy, absence of cavities), extrapulmonary disease in up to 60%, or disseminated disease.<sup>9, 10</sup> Acid-fast staining of sputum resulted negative for three samples. Negative smears are more likely to occur in person with low CD4 counts since organism-laden cavities are less likely to occur at low CD4 counts.<sup>10</sup> The fact that patient's condition improved after administration of antituberculosis drugs was a supporting evidence in the consideration of tuberculosis as the etiology. Once considered, a clinical diagnosis should be supported by mycobacterial culture from the affected area. Synovial fluid culture for *M. tuberculosis* reported a sensitivity of 79%, whereas synovial tissue culture had a sensitivity of 94%.<sup>11</sup>

Other potential agents are pathogens that commonly cause hematogenous osteomyelitis. A solitary pathogenic organism is usually recovered from bone. In adults, *Staphylococcus aureus* is the most common cause. It is isolated in 50% cases of hematogenous osteomyelitis.<sup>6</sup> We gave empirical antibiotic treatment with cefotaxime and levofloxacin. The available literatures on the treatment of osteomyelitis is inadequate to determine the best agent, route or duration of antibiotic therapy. Most studies treated patients for six weeks.<sup>12</sup>

Leprosy is another possible cause of osteomyelitis. The type of leprosy is lepromatous leprosy, in which the cell-mediated response to the organism is poor. It is well explained by the immune status of the patient. Bone changes in leprosy are divided into two groups, specific and secondary changes. Specific lesions are due to the direct involvement of bone by the organism, whereas secondary lesions are the result of trauma and infection. Specific bony lesions in leprosy are rare with an incidence of 3% to 5% among hospitalized patients.<sup>13</sup> Various studies have shown incidence of overall bone changes in leprosy to be ranging from 82.9 percent to 91 percent. The common sites of predilection for bone damage in leprosy are the small bones of hands and feet followed by bones of the face. Bone involvement is more common in lepromatous type.<sup>14</sup> But, leprosy mainly involves the proximal and the middle phalanges.

Confirmation of the presence of osteomyelitis requires a combination of radiologic, microbiologic and histopathologic tests. Histopathologic and microbiologic examination of bone is the gold standard for diagnosing osteomyelitis. In this patient, plain radiograph of wrist joint is sufficient to diagnose osteomyelitis of wrist joint. Unfortunately, microbiologic examination has never been performed. Specimen for microbiologic examination is planned to be taken at the same

time with debridement procedure. *Debridement* is delayed because of TB. Effective antibiotic therapy should be started before surgery for tuberculosis. ATD should be started at least three weeks before surgery. Dissemination of the disease has been reported when surgery was done without adequate chemotherapeutic coverage.<sup>15, 16</sup> In this case, postponement of surgical procedure takes longer than three weeks because the administration of antituberculosis drugs was interrupted due to drug induced hepatitis.

Diagnosis of chronic osteomyelitis can be definitively made only by intraoperative biopsy. Biopsy in our patient revealed chronic osteomyelitis without signs of specific inflammation. Histologic evidence of mycobacterial infection will need the presence of granulomatous inflammation, although its presence is not specific for mycobacterial infection. Granuloma formation is induced by interferon gamma, which is secreted by the CD4 + T cells. In HIV-infected people whose CD4+ T cells are progressively destroyed, the ability to form granulomas is occasionally retained with no apparent CD4+ T cells available. This patient was not infected by HIV, but his CD4+ T cells are below 200. It could be an explanation for the absence of granuloma in this patient. Culture of bone biopsy should have been done because it yields a microbiologic diagnosis in 94% of cases.<sup>17</sup> But this time it could not be done because of technical reasons.

## SUMMARY

This unusual case of osteomyelitis became more complicated because of the patient's immunodeficient condition. Regrettably, the case lacked of microbiological evidence. Despite the absence of granulomas in bone biopsy specimen, we could not decide whether osteomyelitis was caused by common microorganism or by *Mycobacterium sp.* Clinically, the patient's condition improved with the administration of ATD.

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