TITLE: THE ROLE OF RHEUMATOID FACTOR IN THE DIAGNOSIS OF RHEUMATOID ARTHRITIS

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1. Abstract:

1.1 Rheumatoid Factors:

Rheumatoid factors (RF) are autoantibodies directed against the Fc portion of IgG. Rheumatoid factor is a well-established diagnostic and prognostic test in Rheumatoid Arthritis. High titer IgM RF is relatively specific for the diagnosis of RA in the context of a chronic polyarthritis, and was for decades the sole serologic criterion widely used in the diagnosis of RA.

Patients with rheumatoid arthritis (RA) follow a variable disease course with regard to outcome measures such as functional status or radiological assessment of joint damage. Early identification of patients with RA and, in particular, those likely to assume a more rapidly destructive form of disease, is important because of the possible benefit from early, aggressive intervention with disease modifying agents. This realization has prompted the investigation and measurement of numerous biologic "markers" in blood and joint fluids that may serve as

indicators of prognosis and the response to therapy. Although some of the markers under consideration are accessible in routine practice, many are in the stage of experimental evaluation and require access to specialized technology and customized reagents.
RF also occurs in other diseases. As an example, some connective tissue diseases, such as systemic lupus erythematosus (SLE) and primary Sjögren's syndrome, may be associated with the presence of RF. In addition, RF levels may be elevated in patients with certain infections, such as malaria, rubella, hepatitis C, and following vaccinations. It has little predictive value in the general population; however, since the overall disease prevalence is relatively low. Rheumatoid factor may have some prognostic value with regard to disease manifestations and activity, and the severity of joint erosions. Seropositive RA (ie, RA associated with a positive rheumatoid factor test) is often associated with more aggressive joint disease, and is more commonly complicated by extra-articular manifestations than seronegative RA

1.2 Anti-CCP Antibodies:

Among the many biologic markers that have been assessed for usefulness in estimating disease, activity and prognosis of rheumatoid arthritis, only a few have found a role in clinical practice. At present the main clinically useful biologic markers in patients with RA are rheumatoid factors and antibodies to citrullinated peptides, for both diagnosis and prediction of functional and radiographic outcomes, as well as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for AA functional and radiographic outcomes.

Anti-CCP testing is a clinically useful tool in diagnosis or exclusion of RA in patients with polyarthritis. Patients with an established diagnosis of RA who have a positive test for RF, anti-CCP antibodies, or both are at a higher risk of developing erosive joint damage and functional impairment. As a result, such patients should receive anti-rheumatic therapy that suppresses disease activity early in the course of their

disease. Diagnoses other than RA should be considered in patients who are both RF and anti-CCP antibody negative. Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is no role for screening asymptomatic individuals for either RF or anti-CCP antibodies.
Presently, the main clinically useful biologic markers in patients with RA are rheumatoid factors and antibodies to citrullinated peptides Anti CCP Antibody test for both diagnosis and prediction of functional and radiographic outcomes.

1.3 Combination of Rheumatoid Factor and Anti-CCP Antibodies:

Testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than is achievable by testing for either antibody alone. Those with early arthritis who are RF or anti-CCP antibody positive are at an increased risk of developing RA and erosive joint disease, while those with neither of these markers are less likely to develop joint damage. Thus, earlier intervention with disease modifying antirheumatic drug (DMARD) therapy may be warranted in those with positive markers, while symptomatic treatment (e.g. with nonsteroidal anti-inflammatory drugs) may be appropriate for those lacking both RF and anti-CCP antibodies when first seen.

1.4 Findings:

Diagnoses other than RA should be considered in patients who are both RF and anti-CCP antibody negative. Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is no role for screening asymptomatic individuals for either RF or anti-CCP antibodies.

2. METHODOLOGY:

This dissertation is aimed to identify the role of rheumatoid factor in the diagnosis of rheumatoid arthritis and the value of biologic markers that have been assessed for usefulness in estimating disease activity and prognosis of rheumatoid arthritis, particularly the use of anti-CCP antibodies test in diagnosing early rheumatoid arthritis.

Access to numerous articles and case studies relevant to my dissertation was collected by using separate electronic databases and search engines which include: Pub Med, Medline, E Medicine, Medscape, Up-to-date and Athens/Oxford library search base.

The following journals were also consulted for the topic on rheumatoid factor including: “Arthritis and Rheumatism”, “British Journal of Rheumatology”, “Up-to-Date Journal”, “Journal of Rheumatology”, “American Journal of Medicine”, and the “New England Journal of Medicine”

Several key words and terms helped to define the initial search and was used to gather different abstracts and articles to finalise the topic.
The search terms employed were as follows:
Rheumatoid factor
Pathogenesis rheumatoid factor
Predictive and prognostic values of Rheumatoid factor
Rheumatoid factor Titer
Anti-CCP Antibodies

After the initial search strategy yield with articles and research studies on rheumatoid arthritis, rheumatoid factor and Anti CCP antibodies, over 1000 articles were narrowed by using “Rheumatoid Factor” to get the relevant information on finalizing this dissertation.

3. BACKGROUND

In this dissertation, the following issues will be addressed:

- Markers that are used in clinical practice as in the diagnosis of Rheumatoid arthritis.
- The role of Rheumatoid Factor its role as a screening test in the diagnosis of rheumatoid arthritis and the use of other diagnostic markers particularly the value of Anti CCP Antibody test in the diagnosis of early rheumatoid arthritis.
- Predictive and Prognostic Values of Rheumatoid Factor.
- When is it useful to measure Rheumatoid Factor?
- Combination of RF and anti-CCP antibodies tests as initial screening test in the diagnosis of Seronegative polyarthritis and in the diagnosis of early Rheumatoid Arthritis.

Rheumatoid factors (RFs) are antibodies specific enough to be used as diagnostic and prognostic markers of rheumatoid arthritis (RA). They often appear many years before the onset of clinical RA.

Rheumatoid factors are antibodies directed against the Fc portion of IgG. Rheumatoid factors (RF) are autoantibodies directed against the Fc portion of IgG. The rheumatoid factor (RF) as initially described by Waaler and Rose in 1940 and as currently measured in clinical practice is an IgM RF, although other immunoglobulin types, including IgG and IgA, have been described. Seropositive RA (ie, RA associated with a positive rheumatoid factor test) is often associated with more aggressive joint disease, and is more commonly complicated by extraarticular manifestations than seronegative RF.

There is no single clinical, radiologic, or serologic test that enables a diagnosis of RA to be made with certainty. As with other autoimmune rheumatic diseases, the diagnosis depends upon the aggregation of characteristic symptoms, signs, laboratory data, and radiologic findings.

The main clinically useful biologic markers in patients with RA include rheumatoid factors, anti-cyclic citrullinated peptide (anti-CCP) antibodies, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Measurement of anti-CCP antibodies also may be useful in the differential diagnosis of early polyarthritis.

3.1. The prevalence of Rheumatoid Factor.

The reported sensitivity of the RF test in RA has been as high as 90 percent. However, population-based studies, which include patients with mild disease, have found much lower rates of RF-positive RA (26 to 60 percent) [122].

In Finland the prevalence of RF positive RA in adults was reported to be 0.7%[114].The annual incidence has varied from 32 to 42 per 100 000 in different studies during the past two decades, [115] and was highest in eastern and lowest in western Finland. [116]. In the absence of arthritis the prevalence of positive and strongly positive RF reactions was 2.1% and 1.0%, respectively. A recent study from Finland suggested that daily coffee consumption was associated with an increased prevalence of "false positive" RF reactions and seemed to be a risk factor for RF positive RA[117].

In England the prevalence of a "false positive" RF reaction was higher in polluted areas than less polluted areas[118].

The prevalence of positive RF has been reported to be high in Pima Indians, [119] related to the high incidence of RA among the Pima[120] and declining in line with the temporal trends in RA[121].

The prevalence of RA is 0.5–1% among adults in Europe, but it seems to be much lower in some Asian and African populations [113].

RF is considered an early marker since its presence is linked with an increased risk of developing Rheumatoid Arthritis (RA) in people with mild arthritic symptoms.Among the many biologic markers that have been assessed for usefulness in estimating disease activity and prognosis of rheumatoid arthritis, only a few have found a role in clinical practice. At present, the main clinically useful biologic markers in patients with RA are rheumatoid factors and antibodies to citrullinated peptides for both diagnosis and prediction of functional and radiographic outcomes, and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for aiding in ongoing assessment of disease activity and predicting functional and radiographic outcomes. Patients with rheumatoid arthritis (RA) follow a variable disease course with regard to outcome measures such as functional status or radiological assessment of joint damage. Rheumatoid factor became part of the classification criteria of RA almost 50 years ago. A variety of autoantigen-autoantibody systems has been described over the years.

Patients with rheumatoid arthritis (RA) follow a variable disease course with regard to outcome measures such as functional status or radiological assessment of joint damage. Early identification of patients with RA and, in particular, those likely to assume a more rapidly destructive form of disease, is important because of the possible benefit from early, aggressive intervention with disease modifying agents. This realization has prompted the investigation and measurement of numerous biologic "markers" in blood and joint fluids that may serve as indicators of prognosis and the response to therapy. Although some of the markers under consideration are accessible in routine practice, many are in the stage of experimental evaluation and require access to specialized technology and customized reagents. Rheumatoid factor may have some prognostic value with regard to disease manifestations and activity, and the severity of joint erosions. Seropositive RA (i.e., RA associated with a positive rheumatoid factor test) is often associated with more aggressive joint disease, and is more commonly complicated by extra articular manifestations than seronegative RA. Whether RF has a

physiologic function is uncertain though some potentially beneficial activities have been suggested.

There is currently no clear consensus regarding the indications for ordering the RF. The overall utility of this test may be historically overestimated and the pre-test probability of RF-associated disease as well as confounding inflammatory disorders should be considered. RF should not be used as a diagnostic test in patients who have arthralgias but no other symptoms or signs of a rheumatic disease. Repeat testing of RF may be useful if a patient's diagnosis remains uncertain. Higher titers of RF have higher positive predictive value for RA. Seropositive disease and higher titers of RF are associated with more severe RA, measurement of RF has limited prognostic value in the individual patient with RA.

At present, the main clinically useful biologic markers in patients with RA are rheumatoid factors and antibodies to citrullinated peptides Anti CCP Antibody test for both diagnosis and prediction of functional and radiographic outcomes, therefore testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than is achievable by testing for either antibody alone.

4. FINDINGS TO DATE

Rheumatoid factors are antibodies directed against the Fc portion of IgG. The rheumatoid factor (RF) as initially described by Waaler and Rose in 1940 and as currently measured in clinical practice is an IgM RF, although other immunoglobulin types, including IgG and IgA, have been described.The presence of RF can be detected by a variety of techniques such as agglutination of IgG-sensitized sheep red cells or bentonite or latex particles coated with human IgG, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA) or nephelometry [1-6].

Measurement of RF is not standardized in many laboratories (leading to problems with false positive results) and no one technique has clear advantage over others. Testing for RF is primarily used for the diagnosis of rheumatoid arthritis; however, RF may also be present in other rheumatic diseases and chronic infections.

4.1. PATHOPHYSIOLOGY — The origin of RF is incompletely understood [7,8]. An abnormal immune response appears to select, via antigenic stimulation, high-affinity RF from the host's natural antibody repertoire [9]. This may occur in rheumatic diseases, such as rheumatoid arthritis (RA), and in a number of inflammatory diseases characterized by chronic antigen exposure, such as subacute bacterial endocarditis (SBE). The development of RF after such infections has suggested that they represent an antibody response to antibodies that have reacted with microbes. This possibility is supported by experimental evidence showing that mice immunized with IgM coated VSV (vesicular stomatitis virus) develop rheumatoid factors [10].

Normal human lymphoid tissue commonly possesses B lymphocytes with RF expression on the cell surface. However, RF is not routinely detectable in the circulation in the absence of an antigenic stimulus.

Modified IgG could be a stimulus to RF production and could be an important component of RA pathogenesis; this concept is supported by studies that observed an association of RF and more severe RA with autoantibodies to advanced glycated end product-damaged IgG or agalactosyl IgG [11,12].

Costimulation of B cells, perhaps mediated by toll-like receptors (TLRs), may allow B cells with low affinity receptors for IgG to become activated. TLRs are components of the innate immune system, and they provide signals after engaging various bacterial and viral products [13,14]. Studies in patients with RA have enhanced our understanding of the origin of RFs:

- CD14-positive cells (monocytes) from the bone marrow stimulate RF-producing B cells [15]. Furthermore, RF found in the peripheral blood probably originates within the bone marrow [16].
- Synovial fluid RF may be produced by synovium-derived CD20-negative, CD38-positive plasma cells [17].
- Circulating B cells require interleukin-10 (IL-10) for RF production [18].
- In RF-negative patients with RA, B cells capable of RF production are fewer in number and less responsive to T cell help than in RF-positive patients with RA. In one study, for example, the frequency of RF+:IgM+ B cells was increased more than 50-fold in seropositive patients (7 to 20 percent of IgM+ B cells versus well under 1 percent in normals; patients with seronegative RA had intermediate values (1.5 to 6 percent of IgM+ B cells) [19].

- Production of RF is also associated with the shared epitope of HLA DRB1*0401 [20]. Cigarette smoking, a risk factor for more severe RA, is associated with an increased prevalence of RF [21]. RFs possess significant heterogeneity related to mutations within heavy and light chain genes [22]. Thus, IgM RFs from patients with RA react with a variety of antigenic sites on autologous IgG [23]. They also react against immunoglobulins found in many

cellular and tissue antigens, but may have different biologic activity in different hosts and anatomic locations. As an example, one report of RF derived from synovial tissue lymphocytes in a patient with RA found specificity for gastric gland nuclei and smooth muscle; in contrast, RF derived from a control patient's peripheral blood did not show this pattern of reactivity [24].

Possible functions — The function of RF is poorly understood [23]. Possible functions include:

- Binding and processing of antigens embedded in immune complexes.
- Presentation of antigens to T lymphocytes in the presence of HLA molecules.
- Immune tolerance.
- Amplification of the humoral response to bacterial or parasitic infection.
- Immune complex clearance.

The role of RFs in the pathogenesis and perpetuation of RA or other rheumatic diseases is unknown. A high correlation for RF has been noted among identical twins with RA, suggesting that genetic factors influence both RF function and disease development [25]. However, some studies have shown that patients with RF-negative RA have HLA susceptibility alleles similar to those in RF-positive patients [26,27]. There may therefore be a similar immunogenetic predisposition to RA in these patients that is independent of RF.

IgG and IgA RFs are occasionally present in patients with RA in the absence of IgM RF [28,29]. Measurement of these non-IgM RFs is not widely available. However, they may be of prognostic value, since there is evidence suggesting that IgG, IgA, and 7S IgM RFs are associated with more severe disease [30-34]. This risk appears to be independent of HLA alleles associated with severe disease [35].

4.2. CLINICAL DISORDERS ASSOCIATED WITH RF POSITIVITY.

A positive RF test can be found in rheumatic disorders, nonrheumatic disorders, and healthy subjects [36].

Rheumatic disorders — Patients may have detectable serum RF in a variety of rheumatic disorders, many of which share similar features, such as symmetric polyarthritis and constitutional symptoms. These include [36]:

- Rheumatoid arthritis — 26 to 90 percent
- Sjögren's syndrome — 75 to 95 percent
- Mixed connective tissue disease — 50 to 60 percent
- Mixed cryoglobulinemia (types II and III) — 40 to 100 percent
- Systemic lupus erythematosus — 15 to 35 percent
- Polymyositis/dermatomyositis — five to 10 percent

Other autoantibodies, including anti-cyclic citrullinated peptides (anti-CCP), may be present in patients with suspected or established RA who are RF-negative [37]. The optimal clinical use of anti-CCP antibody testing and its relationship to RF testing remain uncertain [38].

Nonrheumatic disorders — Nonrheumatic disorders characterized by chronic antigenic stimulation (especially with circulating immune complexes or polyclonal B lymphocyte activation) commonly induce RF production .Included in this group are [36]:

- Indolent or chronic infection, as with SBE or hepatitis B or C virus infection. As an example, studies have demonstrated that hepatitis C infection, especially when accompanied by cryoglobulinemia, is associated with a positive RF in 54 to 76 percent of cases [39-42]. RF production typically ceases with resolution of the infection in these disorders. These molecules may be produced by activated hepatic lymphocytes [43Inflammatory or fibrosing pulmonary disorders, such as sarcoidosis.
- Malignancy.

- Primary biliary cirrhosis.

Healthy individuals — Rheumatoid factors have been found in up to four percent of young, healthy individuals [44]. The reported incidence may be higher in elderly subjects without rheumatic disease, ranging from three to 25 percent [45,46]. Part of this wide range may be explained by a higher incidence of RF among the chronically ill elderly as compared to healthy older patients [47]. When present, RF is typically found in low to moderate titer (1:40 to 1:160) in individuals with no demonstrable rheumatic or inflammatory disease.

Population-based studies have shown that some healthy people with positive RF develop RA over time, especially if more than one isotype is persistently elevated [57]. Retrospective study of stored blood samples collected as part of routine blood donation, has demonstrated that nearly 30 percent of those who later develop RA have serum RF present for a year or more prior to diagnosis (median 4.5 years) [58]. Likewise, among military recruits who are diagnosed with systemic lupus erythematosus, the presence of IgG or IgM RF in banked serum often precedes development of arthritis [59]. However, most asymptomatic persons with a positive RF do not progress to RA or SLE; as a result, measurement of RF is a poor screening test for future rheumatic disease [60].

4.3. RF titer — The titer of RF should be considered when analyzing its utility. The higher the titer, the greater the likelihood that the patient has rheumatic disease. There are, however, frequent exceptions to this rule, particularly among patients with one of the chronic inflammatory disorders noted above. Furthermore, the use of a higher titer for diagnosis decreases the sensitivity of the test at the same time as it increases the specificity (by decreasing the incidence of false positive results). In our study, for example, an RF titer of 1:40 or greater was 28 percent sensitive and 87 percent specific for RA; in comparison, a titer

of 1:640 or greater increased the specificity to 99 percent (ie, almost no false positive results) but reduced the sensitivity to eight percent [48].

4.4. Predictive value — The predictive value of RF testing has not been widely studied. As noted above, the sensitivity of RF in RA (ie, the proportion of patients with RA who are RF positive) has ranged from 26 to 90 percent. The specificity (ie, the proportion of healthy patients without RA who are RF negative) is reportedly 95 percent. As with any diagnostic test, however, the predictive value is also affected by the estimated likelihood of disease prior to ordering the test (ie, the pretest probability) and, with RF, the proportion of patients with a nonrheumatic disorder associated with RF production .

A study of consecutive tests ordered on unselected patients at the Beth Israel Deaconess Medical Center in Boston [48]. The positive predictive value of RF (the likelihood of having disease if the RF is positive) was only 24 percent for RA and 34 percent for any rheumatic disease. Thus, RF has a low positive predictive value if the test is ordered among patients with a low prevalence of RF-associated rheumatic disease or few clinical features of systemic rheumatic disease

RF testing also has modest positive predictive value among unselected patients presenting with arthralgia and arthritis. In patients with "undifferentiated" inflammatory arthritis the presence of RF was somewhat helpful in predicting the ultimate diagnosis of RA, although not as predictive as duration of symptoms for more than 12 weeks [49]. An earlier study found no predictive value for RF testing in such patients [50].

On the other hand, the negative predictive value of the RF (the likelihood of not having disease if the RF is negative) appears to be relatively high. In our study, the negative predictive value for RA and for any rheumatic disease was 89 and 85 percent, respectively [48]. It is important to appreciate, however, that the value of a negative test

depends upon the clinical setting. Suppose, for example, that a patient has an estimated 10 percent chance of RA, a negative RF test (assuming a sensitivity of 80 percent and specificity of 95 percent) will decrease the likelihood of RA from 10 percent to 2 percent. This small benefit may not justify performing the RF test.

The presence or absence of RF may have some value in predicting response to treatment. As an example, the anti-CD20, B cell depleting monoclonal antibody, rituximab, may be less effective for patients with seronegative than for those with seropositive RA [51].

4.5. Prognostic value — RF-positive patients with RA may experience more aggressive and erosive joint disease and extraarticular manifestations than those who are RF-negative [52,53]. Similar findings have been observed in juvenile rheumatoid arthritis [54]. These general observations, however, are of limited utility in an individual patient because of wide interpatient variability. In this setting, accurate prediction of the disease course is not possible from the RF alone.

Although some have suggested that erosive disease may be accurately predicted by analyzing the combination of HLA-DRB1 and RF status among patients with RA [55].These tests are of limited value in an individual patient as almost one-half of "high risk" patients had no erosions at one year.

Repeat testing of RF may be useful if a patient's diagnosis remains uncertain. However, there is no clear benefit to serial testing in a patient with established RA. In Sjogren's Disease, the disappearance of a previously positive RF may herald the onset of lymphoma [56] so some clinicians check RF repeatedly in their patients with Sjogren's Disease. The clinical utility of this practice, however, has not been critically assessed.

4.6. Anti-cyclic citrullinated peptide (CCP) antibodies.

An enzyme linked immunosorbent assays (ELISA) was developed to detect antibodies directed against filaggrin derived from human skin and has high specificity and sensitivity for the diagnosis of RA [61]. The target amino acid in filaggrin is citrulline, a post-translationally modified arginine residue [62]. Subsequently, an ELISA assay for the detection of antibodies to a cyclic peptide containing citrulline was made comercially available, which was easier to standardize, and also had high sensitivity and specificity for the diagnosis of RA. This became the assay for the detection of anti-cyclic citrullinated peptide (anti-CCP) antibodies.

Citrullinated proteins and peptides — Anti-citrullinated protein antibodies are highly specific for RA [96]. The citrullination is catalyzed by peptidyl arginine deiminase; arginine residues on fibrin and fibrinogen may be favored sites for deimination within rheumatoid joints [97-100]. Intracellular citrullinated proteins colocalized with the deimidase in 59 percent of RA synovial samples versus 17 percent of control samples [98]. However, citrullinated proteins may also be found in the synovium of other forms of arthritis, in nonsynovial tissue from patients with RA (e.g. pulmonary rheumatoid nodules), in the lungs of patients with interstitial pneumonitis, in brain from patients with multiple sclerosis, and in normal brain [101,102].

The RA-associated HLA-DRB1*0404 allele is also associated with production of antibodies to citrullinated fibrinogen, and T cell proliferation in response to fibrinogen peptides is frequent in RA patients but rare in controls [103]. In contrast, in another study the shared epitope was associated with antibodies to a citrullinated peptide derived from vimentin but not to a fibrinogen-derived citrullinated peptide [104].

Comparisons of the shared epitope (SE) frequencies on HLA-DRB1 alleles in healthy populations with RA patients who do or do not harbor anti-CCP antibodies have shown that the SE is associated only with anti-CCP-positive disease and not with anti-CCP-negative disease. This

indicates that the HLA-DRB1 alleles encoding the SE do not associate with RA as such, but rather with a particular phenotype, disease with anti-CCP antibodies [105].

A strong association between cigarette smoking, a known risk factor for RA, and the presence HLA-DBR1*0404 or other HLA alleles comprising the shared epitope has been noted for RA patients who have anti-citrulline antibodies [106,107]. As an example, in an epidemiologic study, the relative risk of developing RA was increased 20-fold in those who had two alleles for the SE, had ever smoked cigarettes, and were anti-cyclic citrullinated peptide (anti-CCP) positive [106]. Citrullinated proteins were present in the bronchoalveolar lavage fluid from the lungs of cigarette smokers, but were not demonstrated by immunostaining of fluid from nonsmokers. This study connects two important risk factors for RA, namely smoking and genetic predisposition conferred by carriage of the SE. It also raises the possibility that smoking-induced citrullinated proteins may serve as a link in the process, possibly as neoantigens. The lack of an association between smoking and risk of RA in those who are anti-CCP antibody negative, suggests that these disease subsets (anti-CCP positive versus anti-CCP negative) differ in their pathogenesis. However, a large collaborative study that included 2476 Caucasian RA patients from North America confirmed a strong association between the presence of anti-CCP antibodies and the shared epitope, but found only a weak association between anti-CCP formation and smoking [108]. On the other hand another study of 216 patients demonstrated a moderately strong association between anti-CCP and tobacco exposure, irrespective of the presence of the SE [109].

As citrullinated proteins are found in many sites of inflammation, it is not clear why patients with RA make such high titer antibodies to these proteins. As noted above, one hypothesis is that this antibody response is genetically mediated, but some patients with high titers of anti-CCP antibodies are SE negative. Another hypothesis is that in RA, unique citrullinated epitopes form, comprising the antigens to which most anti-citrullinated antibodies develop. In this respect some of these putative

epitopes, recognized by rabbit and mouse antisera, colocalize in RA synovium with PAD2 (peptidyl arginine deiminase), the enzyme that converts arginine to citrulline [101]. Extensive research continues to identify the "primary" citrullinated epitope(s) and to address the question of why patients with RA generate high titers of anti-CCP antibodies [110-112].

The increase in risk associated with smoking in individuals with the shared epitope may be affected primarily by citrullination of proteins in inflamed tissues. This was suggested in a study in which the association between smoking and RA was strongest (relative risk 21) among individuals with antibodies to citrullinated proteins as detected by the anti-cyclic citrullinated peptide (anti-CCP) assay [91]. In contrast, there was no evidence of an interaction between smoking and the shared epitope in patients who were anti-CCP antibody negative, including a subset who were anti-CCP negative but RF positive. Nor was an association noted between cigarette smoking, anti-CCP antibody status, or carriage of shared epitope in a study of 300 African American patients with RA [92].

Another study evaluated the genetic-environment-immune link in 515 Danish RA patients [93]. 309 had anti-CCP antibodies; of 456 tested, 262 had the shared epitope. The odds ratio (for RA) for those having both the shared epitope and having anti-CCP was 17.8. For the anti-CCP pos, shared epitope RA patients the odds ratio for those who smoked was 52.6 to 57.4 (vs 17.4 vs nonsmokers); for those who consumed alcohol the odds ratio was 10.5-27 (for non-drinkers the odds-ratio was 50.1); the odds ratio for those who drank coffee was 27.4-53.3 (v s 13.0 for non-coffee drinkers); and the odds ratio for women who used OC was 44.6 (vs 32.3 for non-users). Furthermore the odds ratio for anti-CCP pos, shared epitope homozygous who were unmarried was 177 and those without a job was 243. The authors concluded that smoking among

carriers of the shared epitope (either heterozygotes or homozygotes) accounted for 36 percent of all anti-CCP positive RA patients.

Some have interpreted these data to indicate that the shared epitope is a marker for anti-CCP antibodies rather than an independent risk factor for RA per se. Peptidyl arginase deiminase (PADI) is the enzyme that modifies arginine residues to citrulline. One haplotype in the PADI 4 gene leads to increased levels of the enzyme and susceptibility to RA in some Asian populations [94]. In a study from Korea of 341 RA patients, PADI4 haplotypes were associated with "seropositive" (eg anti-CCP) RA of short disease duration, while the shared epitope was associated with longstanding, seropositive RA [95].

As with RF, anti-CCP antibodies may be present prior to the appearance of symptoms of RA.

ELISA assays that detect anti-CCP antibodies have a sensitivity and specificity of 47 to 76 and 90 to 96 percent for RA, respectively [62-69]. The best data come from a meta-analysis of 87 studies in which the pooled sensitivity and specificity for the diagnosis of RA were 67 percent (95% CI 62-72 percent) and 95 percent (95% CI, 94-97 percent) for anti-CCP antibodies, compared to 69 percent (95% CI 65-73 percent) and 85 percent (95% CI, 82-88 percent) for IgM RF [63].

Test performance is dependent upon the characteristics of the assay kit. Higher values of sensitivity and specificity have been reported with a later generation assay compared to the original assay [68,70,71].

Measurement of anti-CCP antibodies also may be useful in the differential diagnosis of early polyarthritis [68]. Although anti-CCP antibody testing is more specific than RF for RA [63], positive results can occur in other diseases, including tuberculosis and several autoimmune rheumatic diseases [69,72-75]. As examples:

- An increased prevalence of anti-CCP antibodies has been noted in patients with active tuberculosis (TB). The rate in different studies has ranged from 32 to 39 percent [72,73] to as low as 7 percent [74].Many patients with TB and anti-CCP antibodies also have antibodies to a cyclic peptide that contains an unmodified arginine residue (CAP) [73]. This suggests that binding of the antibodies from patients with TB is determined by portions of the CCP peptide other than the citrulline moiety.
- In a study of 116 Japanese patients with rheumatic diseases other than RA, anti-CCP antibodies were detected in 15 percent of patients with SLE, 14 percent with Sjogren's syndrome, 23 percent with either polymyositis or dermatomyositis, and 6 percent with scleroderma [75]. However, the mean titers of anti-CCP antibodies among patients without RA were substantially lower compared with titers in the RA group. Similar observations were made in a large French cohort [69].

Testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than testing for either antibody alone. This was illustrated in a study that compared the results of serologic testing in 196 patients with a clinical diagnosis of RA and in 239 controls [64]. The main findings with respect to test performance were as follows:

- Anti-CCP — sensitivity 56 percent and specificity 90 percent
- IgM RF — sensitivity 73 and specificity 82 percent
- IgM RF and anti-CCP — sensitivity 48 and specificity 96 percent

Anti-CCP antibody-positive patients with early RA are at increased risk of progressive joint damage [83,84,63,76,77]. This was illustrated in a series of 145 such patients in which there was more radiographically apparent damage after five years of observation in those with detectable anti-CCP antibodies compared to those who were RF-positive [76]. The presence of anti-CCP antibodies was also predictive of more rapid

radiographic progression in two studies of 183 and 279 Swedish patients with early RA [84,77], and the BeSt trial in 508 Dutch patients [83].

Among patients with early oligo- or polyarthritis, positive anti-CCP testing appears to predict an increased risk for radiographic progression in patients who are IgM-RF negative. This was demonstrated in a prospective study that included 178 such patients [78]. Radiographic progression (more than 5 units by Sharp score) was more frequent in the anti-CCP positive patients than those with a negative test result (40 versus 5 percent). The anti-CCP test correctly predicted whether or not there would be worsening radiographic damage in 83 percent. Similar findings have been noted in other studies [79-81].

A decrease in anti-CCP titers can be seen in patients treated effectively with nonbiologic or biologic DMARDs, but is less frequent and of a lesser magnitude than the decrease in IgM RF [82].

RF and anti-cyclic citrullinated peptide (anti-CCP) antibodies may be present in the blood prior to the appearance of arthritis [85-88].

The following observations illustrate the range of findings:

- In a cohort study of healthy individuals from Finland, 9 of 129 subjects with positive RF subsequently developed seropositive RA over a 10 year investigation period, as compared to only 12 of 7000 subjects with negative tests (7.0 versus 0.2 percent) [85].
- In a report of 83 patients with RA who had stored blood samples available as a result of blood donation or prenatal testing, the prevalence of anti-CCP antibodies was significantly higher in patients preceding diagnosis than in controls (34 versus 5 percent) [86]. There was also a significant increase in the prevalence of RFs of all isotypes (17, 19, and 33 percent for RF of IgG, IgM, and IgA isotype, respectively).
- In a case-control study of 79 patients with RA who had stored serum available from blood donations prior to the development of RA (1 to 51 samples per patient, dating up to 15 years prior onset

of RA), 49 percent had detectable anti-CCP and/or anti-IgM RF on at least one occasion and 41 percent had anti-CCP detectable when symptoms first develop [87].

Although these autoantibodies may represent clinically silent disease, the development of such autoantibodies can also be viewed as a risk factor for the later development of disease. The sensitivity of a positive anti-CCP assay and a positive RF in the 1.5 years prior to diagnosis has ranged from 18 to 30 percent and the specificity from 99 to 100 percent.

The following are some of the useful features of anti-CCP antibody assays:

- The sensitivity of enzyme-linked immunosorbent assays (ELISA) for anti-CCP antibodies is similar to that of testing for IgM RF, but the specificity of a positive anti-CCP antibody assay is higher, in the range of 90 to 96 percent.
- Anti-CCP antibodies predict erosive disease more effectively among patients with RA than do assays for RF [89,90].
- Testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than is achievable by testing for either antibody alone.
- ELISA testing for anti-CCP may be useful in the differential diagnosis of early stage RA, particularly in the ability to distinguish RA from primary Sjögren's syndrome or SLE. It may also be valuable in identifying those patients with early RA who are at increased risk of progressive joint damage.
- Among patients with early oligo- or polyarthritis, anti-CCP testing appears to be of predictive value in the IgM-RF negative subgroup. Anti-CCP testing is a clinically useful tool in diagnosis or exclusion of RA in patients with polyarthritis.
- In contrast to RF, anti-CCP antibodies are rarely present in the serum of patients with HCV infections.

5. FUTURE

Widely available tests that may predict functional and radiographic outcomes in patients with rheumatoid arthritis (RA) are: serum IgM rheumatoid factor (RF), serum anti-cyclic citrullinated peptide antibodies (anti-CCP), Erythrocyte sedimentation rate (ESR), and C reactive protein (CRP).Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is no role for screening asymptomatic individuals for either RF or anti-CCP antibodies. Patients with synovitis of less than six weeks duration do not meet current ACR criteria for RA. Those with early arthritis who are RF or anti-CCP antibody positive are at an increased risk of developing RA and erosive joint disease, while those with neither of these markers are less likely to develop joint damage. (Thus, earlier intervention with disease modifying antirheumatic drug (DMARD) therapy may be warranted in those with positive markers, while symptomatic treatment (e.g. with nonsteroidal anti-inflammatory drugs) may be appropriate for those lacking both RF and anti-CCP antibodies when first seen.).Diagnoses other than RA should be considered in patients who are both RF and anti-CCP antibody negative. Patients with an established diagnosis of RA who have a positive test for RF, anti-CCP antibodies, or both are at a higher risk of developing erosive joint damage and functional impairment. As a result, such patients should receive anti-rheumatic therapy that suppresses disease activity early in the course of their disease. Other tests may also have prognostic importance, but are either still investigational or have limited clinical availability.

Anti-CCP antibody-positive patients with early RA are at increased risk of progressive joint damage. The combination of IgM RF and anti-CCP have a sensitivity 48 and specificity 96 percent respectively as compared to IgM RF of sensitivity 73 and specificity 82 percent. Among patients with early oligo- or polyarthritis, positive anti-CCP testing appears to

predict an increased risk for radiographic progression in patients who are IgM-RF negative. Widely available tests that may predict functional and radiographic outcomes in patients with rheumatoid arthritis (RA) are: serum IgM rheumatoid factor (RF), serum anti-cyclic citrullinated peptide antibodies (anti-CCP), Erythrocyte sedimentation rate (ESR), and C reactive protein (CRP).Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is no role for screening asymptomatic individuals for either RF or anti-CCP antibodies. Measurement of anti-CCP antibodies also may be useful in the differential diagnosis of early polyarthritis.
Therefore testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than testing for either antibody alone in patients with oligoarthritis or polyarthritis.

There is currently no clear consensus regarding the indications for ordering the RF. The overall utility of this test may be historically overestimated and the pretest probability of RF-associated disease as well as confounding inflammatory disorders should be considered.
Widely available tests that may predict functional and radiographic outcomes in patients with rheumatoid arthritis (RA) are: serum IgM rheumatoid factor (RF), serum anti-cyclic citrullinated peptide antibodies (anti-CCP), Erythrocyte sedimentation rate (ESR), and C reactive protein (CRP).
Patients with synovitis of less than six weeks duration do not meet current ACR criteria for RA. Those with early arthritis who are RF or anti-CCP antibody positive are at an increased risk of developing RA and erosive joint disease, while those with neither of these markers are less likely to develop joint damage.)
Thus, earlier intervention with disease modifying antirheumatic drug (DMARD) therapy may be warranted in those with positive markers, while symptomatic treatment (e.g. with nonsteroidal anti-inflammatory drugs) may be appropriate for those lacking both RF and anti-CCP antibodies when first seen. Diagnoses other than RA should be considered in patients who are both RF and anti-CCP antibody negative
Patients with an established diagnosis of RA who have a positive test for

RF, anti-CCP antibodies, or both are at a higher risk of developing erosive joint damage and functional impairment. As a result, such patients should receive anti-rheumatic therapy that suppresses disease activity early in the course of their disease. Other tests may also have prognostic importance, but are either still investigational or have limited clinical availability. Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is no role for screening asymptomatic individuals for either RF or anti-CCP antibodies.

Measurement of RF has little value as a screening test to diagnose or exclude rheumatic disease in either healthy populations or those with arthralgias. Healthy individual's individuals should not be tested for RF. Similarly we should not be using the RF as a diagnostic test in patients who have arthralgias but no other symptoms or signs of a rheumatic disease.

5.1 FUTURE RECCOMENDATIONS

- RF or anti-CCP antibodies test should be evaluated in the same clinical setting in which it is planned to be used. Diagnostic tests are most useful when applied in clinical situations in which the disease in question is reasonably likely to be present and unhelpful when the likelihood of disease is very low.
- Higher titers of RF have higher positive predictive value for RA. Although, in aggregate, seropositive disease and higher titers of RF are associated with more severe RA, measurement of RF has limited prognostic value in the individual patient with RA.
- The titer of RF should be considered when analyzing its utility. The higher the titer, the greater the likelihood that

the patient has rheumatic disease. There are, however, frequent exceptions to this rule, particularly among patients with one of the chronic inflammatory disorders.

- Most asymptomatic persons with a positive RF do not progress to RA or SLE; as a result, measurement of RF is a poor screening test for future rheumatic diseaseTesting for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than is achievable by testing for either antibody alone.
- Rheumatoid factor is detected in the setting of various rheumatic diseases, infections, other inflammatory diseases, and in some healthy people.
- The RF has a higher positive predictive value if ordered more selectively in patients with a modest or higher chance of having an RF-associated rheumatic disease such as RA or Sjögren's syndrome. Included in this group are patients with prominent morning stiffness, sicca symptoms, or arthralgia or arthritis in a rheumatoid distribution (i.e., symmetric polyarthritis involving small joints).
- ELISA testing for anti-CCP may be useful in the differential diagnosis of early stage RA, particularly in the ability to distinguish RA from primary Sjögren's syndrome or SLE. It may also be valuable in identifying those patients with early RA who are at increased risk of progressive joint damage.
- Anti-CCP antibody-positive patients with early RA are at increased risk of progressive joint damage.
- Among patients with early oligo- or polyarthritis, anti-CCP testing appears to be of predictive value in the IgM-RF negative subgroup.

6. CONCLUSION:

Rheumatoid factors are antibodies directed against the Fc portion of IgG. The rheumatoid factor (RF) as initially described by Waaler and Rose in 1940 and as currently measured in clinical practice is an IgM RF, although other immunoglobulin types, including IgG and IgA, have been described.

Widely available tests that may predict functional and radiographic outcomes in patients with rheumatoid arthritis (RA) are: serum IgM rheumatoid factor (RF), serum anti-cyclic citrullinated peptide antibodies (anti-CCP), Erythrocyte sedimentation rate (ESR), and C reactive protein (CRP).The presence of RF can be detected by a variety of techniques such as agglutination of IgG-sensitized sheep red cells or bentonite or latex particles coated with human IgG, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA) or nephelometry .

Measurement of RF is not standardized in many laboratories (leading to problems with false positive results) and no one technique has clear advantage over others. Testing for RF is primarily used for the diagnosis of rheumatoid arthritis; however, RF may also be present in other rheumatic diseases and chronic infections. High titer IgM RF is relatively specific for the diagnosis of RA in the context of a chronic polyarthritis, and was for decades the sole serologic criterion widely used in the diagnosis of RA. It has little predictive value in the general population; however, since the overall disease prevalence is relatively low. RF also occurs in other diseases.

Rheumatoid factor may have some prognostic value with regard to disease manifestations and activity, and the severity of joint erosions. Seropositive RA (i.e., RA associated with a positive rheumatoid factor test) is often associated with more aggressive joint disease, and is more commonly complicated by extra articular manifestations than seronegative RA. Whether RF has a physiologic function is uncertain though some potentially beneficial activities have been suggested.

There is currently no clear consensus regarding the indications for ordering the RF. The overall utility of this test may be historically overestimated and the pretest probability of RF-associated disease as well as confounding inflammatory disorders should be considered. RF should not be used as a diagnostic test in patients who have arthralgias but no other symptoms or signs of a rheumatic disease. Repeat testing of RF may be useful if a patient's diagnosis remains uncertain. Higher titers of RF have higher positive predictive value for RA. Seropositive disease and higher titers of RF are associated with more severe RA; measurement of RF has limited prognostic value in the individual patient with RA.

Widely available tests that may predict functional and radiographic outcomes in patients with rheumatoid arthritis (RA) are: serum IgM rheumatoid factor (RF), serum anti-cyclic citrullinated peptide antibodies (anti-CCP), Erythrocyte sedimentation rate (ESR), and C reactive protein (CRP)

Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is norole for screening asymptomatic individuals for either RF or anti-CCP antibodies.

Patients with synovitis of less than six weeks duration do not meet current ACR criteria for RA. Those with early arthritis who are RF or anti-CCP antibody positive are at an increased risk of developing RA and erosive joint disease, while those with neither of these markers are less likely to develop joint damage. Thus, earlier intervention with disease modifying antirheumatic drug (DMARD) therapy may be warranted in those with positive markers, while symptomatic treatment (e.g. with nonsteroidal anti-inflammatory drugs) may be appropriate for those lacking both RF and anti-CCP antibodies when first seen.

Diagnoses other than RA should be considered in patients who are both RF and anti-CCP antibody negative. As with RF, anti-CCP antibodies may be present prior to the appearance of symptoms of RA. Patients with an established diagnosis of RA who have a positive test for RF, anti-CCP antibodies, or both are at a higher risk of developing erosive joint damage and functional impairment. As a result, such patients

should receive anti-rheumatic therapy that suppresses disease activity early in the course of their disease.

Patients with an established diagnosis of RA who have a positive test for RF, anti-CCP antibodies, or both are at a higher risk of developing erosive joint damage and functional impairment. As a result, such patients should receive anti-rheumatic therapy that suppresses disease activity early in the course of their disease. Diagnoses other than RA should be considered in patients who are both RF and anti-CCP antibody negative. Patients with synovitis of less than six weeks duration do not meet current ACR criteria for RA. Those with early arthritis who are RF or anti-CCP antibody positive are at an increased risk of developing RA and erosive joint disease, while those with neither of these markers are less likely to develop joint damage thus earlier intervention with disease modifying antirheumatic drug (DMARD) therapy may be warranted in those with positive markers, while symptomatic treatment (e.g. with nonsteroidal anti-inflammatory drugs) may be appropriate for those lacking both RF and anti-CCP antibodies when first seen.

Measurement of RF has little value as a screening test to diagnose or exclude rheumatic disease in either healthy populations or those with arthralgias. There is currently no clear consensus regarding the indications for ordering the RF and therefore we should not be screening healthy individuals by testing for RF.

The overall utility of this test may be historically overestimated and the pretest probability of RF-associated disease as well as confounding inflammatory disorders should be considered. Rheumatoid factor is detected in the setting of various rheumatic diseases, infections, other inflammatory diseases, and in some healthy people. The RF has a higher positive predictive value if ordered more selectively in patients with a modest or higher chance of having a RF. Higher titers of RF have higher positive predictive value for RA. Although, in aggregate, seropositive disease and higher titers of RF are associated with more severe RA, measurement of RF has limited prognostic value in the individual patient with RA.

Testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than is achievable by testing for either antibody alone. ELISA testing for anti-CCP may be useful in the differential diagnosis of early stage RA, particularly in the ability to distinguish RA from primary Sjögren's syndrome or SLE. It may also be valuable in identifying those patients with early RA who are at increased risk of progressive joint damage. Earlier intervention with disease modifying antirheumatic drug (DMARD) therapy may be warranted in those with positive markers, while symptomatic treatment (e.g., with nonsteroidal anti-inflammatory drugs) may be appropriate for those lacking both RF and anti-CCP antibodies when first seen.

Among patients with early oligo- or polyarthritis, anti-CCP testing appears to be of predictive value in the IgM-RF negative subgroup. Anti-CCP testing is a clinically useful tool in diagnosis or exclusion of RA in patients with polyarthritis. Patients with an established diagnosis of RA who have a positive test for RF, anti-CCP antibodies, or both are at a higher risk of developing erosive joint damage and functional impairment. As a result, such patients should receive anti-rheumatic therapy that suppresses disease activity early in the course of their disease. Diagnoses other than RA should be considered in patients who are both RF and anti-CCP antibody negative. Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is no role for screening asymptomatic individuals for either RF or anti-CCP antibodies. Patients with synovitis of less than six weeks duration do not meet current ACR criteria for RA. Those with early arthritis who are RF or anti-CCP antibody positive are at an increased risk of developing RA and erosive joint disease, while those with neither of these markers are less likely to develop joint damage. Patients with an established diagnosis of RA who have a positive test for RF, anti-CCP antibodies, or both are at a higher risk of developing erosive joint damage and functional impairment. As a result, such patients should receive anti-rheumatic therapy that suppresses disease activity early in the course of their disease.

6.1 Summary and Recommendations:

- Rheumatoid factors are antibodies directed against the Fc portion of IgG. Normal human lymphoid tissue commonly possesses B lymphocytes with RF expression on the cell surface. However, RF is not routinely detectable in the circulation in the absence of an antigenic stimulus.
- How chronic infections and rheumatic diseases lead to increased RF in serum is uncertain, but one attractive hypothesis suggests costimulation of B cells with low affinity receptors for IgG through toll-like receptors by DNA or RNA containing immune complexes may play a role. Whether RF has a physiologic function is uncertain though some potentially beneficial activities have been suggested.

- Rheumatoid factor is detected in the setting of various rheumatic diseases, infections, other inflammatory diseases, and in some healthy people. There is currently no clear consensus regarding the indications for ordering the RF. The overall utility of this test may be historically overestimated and the pretest probability of RF-associated disease as well as confounding inflammatory disorders should be considered.

- Measurement of RF has little value as a screening test to diagnose or exclude rheumatic disease in either healthy populations or those with arthralgias.

- The RF has a higher positive predictive value if ordered more selectively in patients with a modest or higher chance of having an RF-associated rheumatic disease such as RA or Sjögren's syndrome. Included in this group are patients with prominent morning stiffness, sicca

symptoms, or arthralgia or arthritis in a rheumatoid distribution (i.e., symmetric polyarthritis involving small joints).

- The value of a negative RF (i.e., its negative predictive value) is limited by the incidence of RF-negative RA and the low prevalence of RF-associated rheumatic disease among all patients with arthralgia.

- Higher titers of RF have higher positive predictive value for RA.

- Although, in aggregate, seropositive disease and higher titers of RF are associated with more severe RA, measurement of RF has limited prognostic value in the individual patient with RA.

- Testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than testing for either antibody alone in patients with oligoarthritis or polyarthritis.

- Anti-CCP antibody-positive patients with early RA are at increased risk of progressive joint damage.
- Unless it is demonstrated that there is an intervention that effectively and safely reduces the risk of developing RA, there is no role for screening asymptomatic individuals for either RF or anti-CCP antibodies.

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