A STUDY OF CORRELATION BETWEEN RHEUMATOID FACTOR AND ISCHEMIC HEART DISEASE IN RHEUMATOID ARTHRITIS INDIVIDUALS

Dissertation submitted to
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CONTENTS

COIMBATORE MEDICAL COLLEGE & HOSPITAL

CERTIFICATE

This is to certify that the Dissertation entitled "**A STUDY OF CORRELATION BETWEEN RHEUMATOID FACTOR AND ISCHEMIC HEART DISEASE IN RHEUMATOID ARTHRITIS INDIVIDUALS",** submitted by **Dr.Palanivelrajan.S,** Post-Graduate in General Medicine, Coimbatore Medical College, to The Tamilnadu Dr. M.G.R. Medical University is a record of a bonafide research work carried out by him under my guidance and supervision from September 2007 to September 2009.

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DECLARATION

I solemnly declare that the Dissertation titled "***A STUDY OF CORRELATION BETWEEN RHEUMATOID FACTOR AND ISCHEMIC HEART DISEASE IN RHEUMATOID ARTHRITIS INDIVIDUALS***", was done by me at Coimbatore Medical College & Hospital during the period from September 2007 to September 2009 under the guidance and supervision of my unit chief Prof. Dr.M.Ramaswamy.

This dissertation is submitted to The Tamilnadu Dr. *M.G.R.* Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch *I*) in General Medicine – March 2010

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acknowledgement

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introduction

INTRODUCTION

Ischemic heart disease (IHD) is a leading cause of death in the western world and increased incidence in our country also. Most of the subjects with IHD have one or more traditional risk factors including diabetes, smoking history, hypertension, obesity, a family history of IHD and hyperlipidimia[1]. In recent years new risk factors for IHD have been identified, including the presence of inflammation as demonstrated by raised highly sensitive C-reactive protein (hs-CRP)[2]. Subjects with chronic inflammatory diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus also have a greatly increased risk of developing IHD[3].

The autoantibody rheumatoid factor (RF) is strongly associated with RA, may be present in subjects many years before they develop RA[4] and its presence confers a risk of developing RA that increases with increasing titre[5]. However RF is associated with other autoimmune rheumatic disease, viral or bacterial infections and is present in as many as 15% of normal adults. [6]Recently, RF has been associated with an increased likelihood of developing IHD in patients with inflammatory polyarthritis.

Presence of RF in general population may identify the subjects with a similar immune pathology to patients with RA ,who may also share an increased likelihood of developing IHD and that RF may have special role in the pathogenesis of IHD.

To explore this, the study was conducted to find out whether the presence of RF was associated with increased risk of IHD among general population.

Aim of the study

AIMS AND OBJECTIVES

1. To analyse the RF as an independent and additional risk factor for IHD in general population.
2. To compare the association of RF as a risk factor in male and female population with relevance to high and low titres.

Review of literature

REVIEW OF LITERATURE

The coronary circulation is unique in that it is responsible for generating the arterial pressure that is required to perfuse the systemic circulation and yet at the same time has its own perfusion impeded during the systolic portion of the cardiac cycle. Because myocardial contraction is closely connected to coronary flow and oxygen delivery, the balance between oxygen supply and demand is a critical determinant of the normal beat to beat function of the heart. When this relationship is acutely disturbed by disease affecting coronary blood flow, the resulting imbalance can immediately precipitate a vicious cycle, where by ischemia-induced contractile dysfunction precipitates hypotension and further myocardial ischemia. IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world.

IHD is the most common, serious, chronic, life-threatening illness in the world wide. A high fat and energy-rich diet, smoking, and a sedentary lifestyle are associated with the emergence of IHD. In the United States and Western Europe, it is growing among low-income groups rather than high-income groups (who are adopting more healthful lifestyles), while primary prevention has delayed the disease to later in life in all socioeconomic groups.

Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD. With urbanization in the developing world, the prevalence of risk factors for IHD is increasing rapidly in these regions such that a majority of the global burden of IHD is now occurring in low-income and middle-income countries. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India. Given the projection of large increase in IHD throughout the world, IHD is likely to become the most common cause of death worldwide by 2020.

Central to an understanding of the pathophysiology of myocardial ischemia is the concept of myocardial supply and demand. Under normal conditions, for any given level of a demand for oxygen, the myocardium will be supplied with oxygen-rich blood to prevent underperfusion of myocytes and the subsequent development of ischemia and infarction.

The major determinants of myocardial oxygen demand are heart rate, myocardial contractility, and myocardial wall tension (stress). An adequate supply of oxygen to the myocardium requires a satisfactory level of oxygen-carrying capacity of the blood (determined by the inspired level of oxygen, pulmonary function, and hemoglobin concentration and function) and an adequate level of coronary blood flow. Blood flows through the coronary arteries in a phasic fashion, with

the majority occurring during diastole. About 75% of the total coronary resistance to flow occurs across three sets of arteries:

(1) large epicardial arteries

(2) prearteriolar vessels

(3) arteriolar and intramyocardial capillary vessels.

In the absence of significant flow-limiting atherosclerotic Obstruction, the normal coronary circulation is dominated and controlled by the heart's requirements of oxygen. This need is met by the ability of the coronary vascular bed to vary its resistance (and, therefore, blood flow) considerably while the myocardium extracts a high and relatively fixed percentage of oxygen. Normally, intramyocardial resistance vessels demonstrate an immense capacity for dilation. For example, the changing oxygen needs of the heart with exercise and emotional stress affect coronary vascular resistance and in this manner regulate the supply of oxygen and substrate to the myocardium (*metabolic regulation*). The coronary resistance vessels also adapt to physiologic alterations in blood pressure in order to maintain coronary blood flow at levels appropriate to myocardial needs (*autoregulation*).

By reducing the lumen of the coronary arteries, atherosclerosis limits appropriate increases in perfusion when the demand for flow is augmented, as occurs during exertion or excitement. When the luminal reduction is severe, myocardial perfusion in the basal state is reduced. Coronary blood flow can also be limited by spasm, arterial thrombi, and, rarely, coronary emboli as well as by ostial narrowing due to aortitis. Congenital abnormalities, such as origin of the left anterior descending coronary artery from the pulmonary artery, may cause myocardial ischemia and infarction in infancy, but this cause is very rare in adults.

Myocardial ischemia can also occur if myocardial oxygen demands are markedly increased and when coronary blood flow may be limited, as occurs in severe left ventricular hypertrophy due to aortic stenosis. The latter can present with angina that is indistinguishable from that caused by coronary atherosclerosis largely owing to subendocardial ischemia. A reduction in the oxygen-carrying capacity of the blood, as in extremely severe anemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself but may lower the threshold for ischemia in patients with moderate coronary obstruction.

Not infrequently, two or more causes of ischemia coexist, such as an increase in oxygen demand due to LV hypertrophy secondary to hypertension and a reduction in oxygen supply secondary to coronary

atherosclerosis and anemia. Abnormal constriction or failure of normal dilation of the coronary resistance vessels can also cause ischemia. When it causes angina, this condition is referred to as *microvascular angina.*

From a practical viewpoint, the cardiovascular risk factors that have emerged from such studies fall into two categories: those modifiable by lifestyle and/or pharmacotherapy and those that are essentially unmodifiable. The weight of evidence supporting various risk factors differs. For example, hypercholesterolemia and hypertension certainly predict coronary risk, but other so-called nontraditional risk factors, such as levels of homocysteine, lipoprotein (a) or infection, remain controversial. One must further distinguish factors that actually participate in atherogenesis from those that may merely serve as markers of risk without direct involvement in pathogenesis. The following Lists the risk factors recognized by the current National Cholesterol Education Project Adult Treatment Panel- III. The sections below will consider some of these risk factors and approaches to their modification.

- Cigarette smoking
- Hypertension (BP ≥ 140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol[<1.0 mmol/L (<40 mg/dL)]
- Diabetes mellitus

- Family history of premature CHD
    - CHD in male first-degree relative <55 years
    - CHD in female first-degree relative <65 years
- Age (men ≥45 years; women ≥55 years
- Lifestyle risk factors
    - Obesity
    - Physical inactivity
    - Atherogenic diet
- Emerging risk factors
    - Lipoprotein(a)
    - Homocysteine
    - Prothrombotic factors
    - ***Proinflammatory factors***
    - Impaired fasting glucose
    - Subclinical atherogenesis

Ischemic heart disease is most often due to atherosclerotic coronary artery disease. The importance of inflammation in atherosclerosis is also supported by the finding of inflammatory cells in atherosclerotic lesions . The following conditions are

associated with inflammatory/ proinflammatory factors- identified as probable causative factors for IHD.

1) Rheumatoid arthritis

2) Systemic lupus erthymatosus

3) Antiphospholipid antibody syndrome

4) Vassculitis producing other connective tissue disorders

Of these inflammatory/ proinflammatory factor, RF is one of the independent and additional risk factor for IHD.

ROLE OF RHEUMATOID FACTOR IN IHD:

The association of RF with IHD provides evidence of an importance of inflammation and raises the possibility that autoimmune mechanisms may play a part. The present study cannot determine whether RF is a non-specific marker of inflammation or is involved directly in pathogenesis of atherosclerosis in the subjects included. However , RF appears to cause direct tissue damage in RA as a constituent of immune complexes[13], perhaps by activating complement. It might cause damage to the vascular endothelium in the same way.

There is circumstantial evidence for this: Atherosclerotic plaques contain immunoglobulins and complements suggesting immune complex activity[15]. In addition the lack of relationship between IHD and the autoantibodies ANA and ACA suggests that the association between

RF and IHD may not be due to non-specific polyclonal B-cell activation secondary to inflammation, but the unique role of RF in the pathogenesis of atherosclerosis/IHD.

This is further supported by the association of RF with IHD in subjects with inflammatory arthritis[7]. There is also an intriguing possibility that the pathological process involved in IHD such as atheroma formation, may generate inflammatory tissue capable of producing RF. Infections cause inflammation and can induce RF production, although this is usually short lived. Chronic infections that induce persistent RF is rare. Acute infections are associated with an increased risk of cardiovascular events, perhaps by inducing circulating cytokines or an autoimmune response[16].

RHEUMATOID ARTHRITIS (RA):

RHEUMATOID ARTHRITIS is a chronic multisystem disease of unknown cause. Although there are a variety of systemic manifestations, the characteristic feature of established RA is persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution.

The prevalence of rheumatoid arthritis (RA) is ~ 0.8% of the population. Women are affected approximately three times more often than men. The prevalence increases with age, and sex differences diminish in the older age group. RA is seen throughout the world and

affects all races. The onset is more frequent during the fourth and fifth decades of life, with 80% of all developing the disease between the ages of 35 and 50.

The cause of RA remains unknown. The class II major histocompatibility complex allele HLA-DR4 and related alleles are known to be major genetic risk factors for rheumatoid arthritis(RA). Genetic risk factors do not fully account for the incidence of RA. The environmental factors also play a role in the etiology of the disease. It has been suggested that RA might be a manifestation of the response to an infectious agent in a genetically susceptible host.

Microvascular injury and an increase in the number of synovial lining cells appear to be the earliest lesions in rheumatoid synovitis. Before the onset of clinical symptoms, the perivascular infiltrate is predominantly composed of myeloid cells, whereas in symptomatic arthritis, T cells can also be found, although their number doesnot correlate with symptoms.

Light-microscopic examination discloses a characteristic constellation of features, which include hyperplasia and hypetrophy of the synovial lining cells; focal or segmental vascular changes, including microvascular inury, thrombosis and neovascularization; edema; and infiltration with mononuclear cells, often collected into aggregates around small blood vessels. The rheumatoid synovium is characterized by the

presence of a number of secreted products of activated lymphocytes, macrophages and fibroblasts. The propagation of RA is an immunologically mediated event. The inflammatory process in the tissue is driven by the CD4+ T cells infiltrating the synovium.

The systemic manifestations of RA can be accounted for by release of inflammatory effector molecules from the synovium. These include IL-1, TNF, and IL-6, which account for many of the manifestations of active RA, including malaise, fatigue, and elevated levels of serum acute-phase reactants. The importance of TNF in producing these manifestations is emphasized by the prompt amelioration of symptoms following administration of a monoclonal antibody to TNF or a soluble TNF receptor Ig construct to patients with RA. In addition, immune complexes produced within the synovium and entering the circulation may account for other features of the disease, such as systemic vasculitis.

Characteristically, RA is a chronic polyarthritis. Specific symptoms usually appear gradually as several joints, especially those of the hands, wrists, knees, and feet, become affected in a symmetric fashion.

RA is a systemic disease with a variety of extraarticular manifestations. It is estimated that as many as 40% of patients may have extraarticular manifestations, and in ~15% these are severe. On occasion, extraarticular manifestations may be the major evidence of disease activity and source of morbidity. As a rule, these manifestations occur in

individuals with high titres of autoantibodies to the Fc component of immunoglobulin G (rheumatoid factor) or with antibodies to CCP. Although the frequency of patients with severe extra articular manifestations appears to be declining, these patients have an increased mortality compared to other persons with rheumatoid arthritis or age-matched normal controls.

Rheumatoid vasculitis , which can affect nearly any organ system, is seen in patients with svere RA and high titres of circulating rheumatoid factor. Rheumatoid vasculitis in its most aggressive form, can cause polyneuropathy and mononeuritis multiplex, cutaneous ulceration and dermal necrosis, digital gangrene, and visceral infarction. While such widespread vasculitis is very rare, more limited forms are not uncommon, especially in patients with high titres of rheumatoid factor. Neurovascular disease presenting either as a mild distal sensory neuropathy or as mononeuritis multiplex may be the only sign of vasculitis. Cutaneous vasculitis usually presents as crops of small brown spots in the nail beds, nail folds, and digital pulp. Larger ischemic ulcers, especially in the lower extremity, may also develop. Myocardial infarction secondary to rheumatoid vasculitis has been reported as has vasculitic involvement of lungs, bowel, liver, spleen, pancreas, lymph nodes, and testes.

Evidence of asymptomatic pericarditis is found at autopsy in 50% of cases. Pericardial fluid has a low glucose level and is frequently

associated with the occurance of pleural effusion. Although pericarditis is usually asymptomatic, on rare occasions death has occurred from tamponade. Chronic constrictive pericarditis may also occur. More recently, an increased incidence of congestive heart failure and death from cardiovascular disease has been associated with RA.

THE 1987 REVISED CRITERIA FOR THE CLASSIFICATION OF RHEUMATOID ARTHRITIS :

These criteria demonstrate a sensitivity of 91-94% and a specificity of 89% when used to classify patients with RA compared with control subjects. Failure to meet these criteria, however, especially during the early stages of the disease, does not exclude the diagnosis.

1.GUIDELINES FOR CLASSIFICATION

a. Four of seven criteria are required to classify a patient as having rheumatoid arthritis (RA)
b. Patients with two or more clinical diagnoses are not excluded.

2.CRITERIA*

a. **Morning stiffness**: stiffness in and around joint lasting 1 h before maximal improvement.

b. **Arthritis of three or more joint area:** the 14 possible joint areas involved are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints.

c. **Arthritis of hand joints:** arthritis of wrist, metacarpophalangeal or proximal interpahalangeal joint.

d. **Symmetric arthritis:** simultaneous involvement of the same joint areas on both sides of the body.

e. **Rheumatoid nodules:** subcutaneous nodules over bony prominences, extensor surfaces, or juxtaarticular regions observed by a physician.

f. **Serum rheumatoid factor:** demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.

g. **Radiographic changes:** typical changes of RA on posteroanterior hand and wrist radiographs that must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

criteria a-d must be present for atleast 6 weeks.

criteria b-e must be observed by a physician.

Patients with rheumatoid arthritis have an increased prevalence of IHD. This is most likely in those people with the autoantibody RF, which are strongly associated with RA but is also present in up to 15% of all adults. Atherosclerotic plaque is a complex inflammatory lesion characterized by an infiltrate of macrophages and T cells[1]. Intra plaque immune cells are activated and involved in mediating tissue injury[5]. T-cell cytokines can drive macrophage activation in atherosclerotic lesions and can also regulate the acute-phase response[1]. Indeed, T cells in patients with acute coronary syndromes (ACS) are skewed toward the production of interferon (IFN)-γ, a potent monocyte activator largely derived from a distinct subset of CD4+ T cells[6,7] that, in contrast to classic CD4+ helper T cells, lacks the co-stimulatory molecule CD28[8]. CD4+CD28null T cells are clonally expanded in ACS and invade the unstable atherosclerotic plaque[9].

Moreover, CD4+CD28null T cells have cytotoxic capability, can effectively kill Endothelial cells *in vitro*, and may contribute to endothelial cell injury in coronary plaque[10]. Expansion of CD4+CD28null T cells was initially described in patients with rheumatoid arthritis (RA), a chronic autoimmune disease of unknown etiology[11]. RA is characterized by chronic inflammation and hyperplasia of synovial tissue.

More importantly, it is a quintessential systemic disease that can manifest in most major organ systems[12].

T cells play a central role in the Immune pathogenesis of RA and are the key regulators of the chronic destructive joint lesions[13]. In addition, patients with RA have abnormalities in T-cell homeostasis that affect the entire pool of T cells[14,15]. One of the consequences of dysregulated T-cell homeostasis is the emergence of large clonal CD4+CD28 null T-cell populations that are auto reactive and cytotoxic, and infiltrate synovial tissue[15]. The highest frequency of CD4+CD28null T cells is found in severe RA, particularly in patients with rheumatoid vasculitis[11,16].

When the inflammatory process in RA spreads to extra-articular sites, such as mid-size arteries and capillaries, morbidity and mortality are clearly increased[17]. The inflammatory mechanisms in RA may enhance atherogenesis in several ways. C-reactive protein, a useful marker of disease activity, is elevated in RA and has prognostic value. It may also participate directly in endothelial injury by sensitizing endothelial cells to T-cell mediated cytotoxicity.

Circulating cytokines in RA, such as TNF-α, result in endothelial activation and up-regulation of adhesion molecules. Indeed, endothelial dysfunction is frequently present in RA patients, even in the absence of identifiable Cardiovascular risk factors and improves with anti-TNF-α

therapy . Cytokines will also non-specifically activate monocytes and other cells of the innate immune system. RA is characterized by the expansion of auto reactive T-cell clones that typically lack CD28. The frequency of such CD4+CD28 null T cells correlates with disease severity with respect to erosive progression and extra-articular manifestations. The frequency in the RA with CAD cohort (median 3.5%) was higher than in historical controls of patients with RA and absence of extra-articular manifestations, suggesting that CV co-morbidity in RA is correlated with disease severity and that CD4+CD28null T cells may be involved in the Cardio Vascular complications of RA. CD4+CD28nullT cells have been directly implicated in the pathogenesis of coronary artery disease. Persistent activation of such auto reactive cells in RA may result in a vicious cycle of cytokine release, mononuclear cell activation and tissue injury.

However, we cannot exclude the possibility that the high CD4+CD28null T cells levels in RA with CAD patients is reflective of an increased RA disease severity in these patients. Addressing this issue further will require comparing RA patients that are matched for disease severity.

The impact of severe RA on mortality may be mediated via reduced physical activity that will compromise cardio respiratory fitness. This might contribute to higher Cardio vascular mortality in RF-positive

RA patients. Disability has been shown to be a predictor of all-cause and Cardiovascular mortality in early inflammatory polyarthritis and established RA.

More severe RA is also associated with a higher cumulative inflammatory disease burden. Atherosclerosis is now accepted to be an inflammatory condition, and elevation of inflammatory markers including high-sensitivity C-reactive protein (CRP) has been associated with the subsequent development of Cardio vascular events in the general population, and histological study has identified the presence of inflammatory cells in atherosclerotic plaque in the general population. If atherosclerosis is promoted by chronic low-grade inflammation, as suggested by Ridker, it is plausible that atherosclerosis may be accelerated in chronic systemic inflammatory conditions like RA[15]. A previous study of the Rochester RA cohort demonstrated that cumulative inflammation measured using the erythrocyte sedimentation rate (ESR) was associated with subsequent Cardio vascular events. In addition, modest elevations in baseline CRP were associated with subsequent Cardio vascular mortality in patients with early inflammatory polyarthritis who were registered with the Norfolk Arthritis Register.

Effective drug therapy, which reduces inflammation in RA, has been shown to reduce all-cause and CVD mortality, and responders to anti-tumor necrosis factor-a therapies were found to have a lower

incidence of myocardial infarction than non-responders. Therefore RF-positive patients may have increased ischemic heart disease mortality because they have increased levels of chronic inflammation, and suppression of this inflammation may lead to improved survival.

Other factors associated with RF status and severity of RA include anti-CCP status and presence of the HLA-DRB1 shared epitope. High titers of anti-CCP predicted mortality in a study of RA patients in Finland. A recent study reported that, while RF status and anti-CCP status were each associated with mortality in inflammatory polyarthritis, possession of both markers did not confer a higher mortality risk. In addition there was a significant interaction between these 3 variables in the models predicting mortality. Therefore mortality outcome in inflammatory arthritis appears to be associated with variables that promote more severe disease.

It has been hypothesized that circulating immune complexes and RF might have a direct effect on endothelial cells to promote atherosclerosis. Dessein, *et al* reported that RF and interleukin 6 were associated with biomarkers of endothelial dysfunction in RA patients, even after adjusting for traditional CVD risk factors. Impaired nitrate-mediated vascular dilation was found to be associated with circulating levels of immune complexes in RA, and this has been suggested to be one

of the mechanisms by which atherosclerosis is promoted in RA. It is interesting to note that B lymphocytes have been identified in atherosclerotic plaques of RA patients[51], while in atherosclerotic plaques of non-rheumatoid patients T lymphocyte infiltration is observed. Therefore there is some modest evidence that RF may be involved in the pathogenesis of atherosclerosis in RA.

Excess mortality in RA is largely confined to those who are RF-positive. It is still unclear whether RF itself contributes to the reduced life expectancy of patients with RA, or whether it is simply a marker for more severe disease and higher cigarette smoking exposure. Early use of disease modifying antirheumatic drugs and use of biologic agents to suppress inflammatory disease is likely to influence the life expectancy of these patients, and it will be interesting to explore whether cardio vascular disease outcomes in patients treated with B cell suppression are improved. However, it is likely that a combined approach is required, with modification of lifestyle factors, as well as suppression of the inflammatory disease process, to improve the mortality outcome in RF-positive subjects.

RA is characterized by chronic inflammation and hyperplasia of synovial tissue. More importantly, it is a quintessential systemic disease that can manifest in most major organ systems. T cells play a central role

in the immunopathogenesis of RA and are the key regulators of the chronic destructive joint lesions. In addition, patients with RA have abnormalities in T-cell homeostasis that affect the entire pool of T cells. One of the consequences of dysregulated T-cell homeostasis is the emergence of large clonal $CD4^{+}CD28^{null}$ T-cell populations that are auto reactive and cytotoxic, and infiltrate synovial tissue. The highest frequency of $CD4^{+}CD28^{null}$ T cells is found in severe RA, particularly in patients with rheumatoid vasculitis. When the inflammatory process in RA spreads to extra-articular sites, such as mid-size arteries and capillaries, morbidity and mortality are clearly increased.

Because the chronic inflammatory process and immune dysregulation in RA have features in common with those involved in atherosclerosis, they could predispose patients with RA to accelerated CAD. Several studies have documented an increased risk of atherosclerosis and myocardial infarction in patients with RA[18-20]. In addition, RA is associated with a reduced life expectancy, primarily because of excessive deaths from cardio vascular disease[21-25]. RA is a heterogeneous disease, and the disease phenotype itself is predictive of mortality; patients with more severe clinical disease have higher mortality rates[26]. Overall mortality is also increased in patients who are positive for the autoantibodies, rheumatoid factors[27,28]. In addition, the extent of

inflammation in RA has been linked to an increased risk of cardio vascular mortality[29]. The number of swollen joints, independent of traditional cardio vascular risk factors, is predictive of cardio vascular related deaths among Pima Indians with RA[30]. The strongest association with increased cardio vascular mortality is seen in patients with extra-articular manifestations of RA[17].

Inflammation is part of the process of atherosclerotic disease, and patients with inflammatory diseases, such as rheumatoid arthritis and systemic lupus erthymatosus, are at increased risk for cardiovascular events. Among patients with rheumatoid arthritis, testing positive for circulating rheumatoid factor (RF) represents an added risk for ischemic heart disease.RF may be present in 15% of the general population without clinical rheumatoid arthritis. This factor may be acquired through the presence of other autoimmune disease or previous bacterial infections. In addition, it appears that smokers have higher rates of testing positive for RF. The current study examines whether RF represents an independent risk factor for ischemic heart disease in a general population of patients.

In the general population, the presence of advanced atherosclerosis on angiography is predictive of a worse prognosis. The extent of atherosclerosis determined by angiography has not been studied in RA. Indirect evidence of accelerated atherosclerosis in RA comes from studies

using carotid artery intima medial thickness as a marker of atherosclerotic burden and vascular risk. Increased intima-media thickness was independent of traditional Cardio vascular risk factors but was related to RA disease activity, duration and severity.Data presented here suggest that the acceleration of atherosclerotic disease in RA holds for multiple vascular beds, lending support to a systemic disease mechanism.

Patients with RA have a significantly higher prevalence of angina pectoris. Also, women with RA have a significantly increased risk of myocardial infarction compared with those without RA. This excess of Cardio vascular disease in RA cannot be explained by the traditional Framingham risk factors and probably arises from the underlying disease and/or its treatment. There is no evidence that disease-modifying antirheumatic drug (DMARD) therapy increases mortality in RA. Corticosteroids can cause dyslipidemia, hyperglycemia and hypertension but may also control inflammation in RA. Studies have attempted to define the impact of steroids on mortality in RA but the results are inconsistent.DMARD treatment can actually improve the outcome in RA. Choi and colleagues have demonstrated that methotrexate-treated patients had a 70% reduction in CV deaths compared with those who did not receive disease-modifying therapy. Other DMARDs such as sulfasalazine, penicillamine, hydroxychloroquine, and gold did not confer

this protection. Thus, the RA disease process itself likely contributes to accelerated CAD.

The inflammatory mechanisms in RA may enhance atherogenesis in several ways. C-reactive protein, a useful marker of disease activity, is elevated in RA and has prognostic value[37]. It may also participate directly in endothelial injury by sensitizing endothelial cells to T-cell mediated cytotoxicity[10]. Circulating cytokines in RA, such as TNF-α, result in endothelial activation and up-regulation of adhesion molecules[38]. Indeed, endothelial dysfunction is frequently present in RA patients, even in the absence of identifiable CV risk factors[39] and improves with anti-TNF-α therapy[40]. Cytokines will also non-specifically activate monocytes and other cells of the innate immune system. RA is characterized by the expansion of auto reactive T-cell clones that typically lack CD28[11]. The frequency of such $CD4^{+}CD28^{null}$ T cells correlates with disease severity with respect to erosive progression[41] and extra-articular manifestations. The frequency in the RA with CAD cohort (median 3.5%) was higher than in historical controls of patients with RA and absence of extra-articular manifestations[11], suggesting that CV co-morbidity in RA is correlated with disease severity and that $CD4^{+}CD28^{null}$ T cells may be involved in the CV complications of RA.$CD4^{+}CD28^{null}$ T cells have been directly implicated in the pathogenesis of coronary artery disease[6]. Persistent activation of such autoreactive cells in RA may result in a

vicious cycle of cytokine release, mononuclear cell activation and tissue injury.However, we cannot exclude the possibility that the high $CD4^{+}CD28^{null}$ T cells levels in RA with CAD patients is reflective of an increased RA disease severity in these patients. Addressing this issue further will require comparing RA patients that are matched for disease severity but are disparate for CAD.

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SYSTEMIC LUPUS ERTHTYMATOSUS

Atherosclerotic disease is common in systemic lupus erthymatosus and is the result of multiple pathogenic mechanisms that include traditional risk factors as well as SLE-related factors. Endothelial dysfunction and arterial stiffness contribute significantly to the atherogenic process. Accelerated atherosclerosis is a significant cause of morbidity and mortality in systemic lupus erthymatosus. Both arteritis and atherosclerosis can involve the coronary arteries of young patients suffering from SLE. Coronary arteritis, though rare, occurs in association with active vasculitis in other organs such as skin, spleen, kidneys, etc. Coronary spasm in SLE patients is rare, and when it occurs, it is usually in relation to the two common pathological processes mentioned above.

Systemic lupus erthymatosus is an autoimmune disorder affecting multiple organ systems. Patients with systemic lupus erthymatosus exhibit a bimodal pattern of mortality, with those who have had the disease for 5 to 10 years being at increased risk of cardiovascular disease,particularly myocardial infarction. Elevated levels of conventional cardiovascular risk factors promote vascular damage resulting in impairment of normal endothelial function. In addition,

autoantibodies directed against oxidized lipoproteins, along with chronic secretion of inflammatory cytokines and suppression of fibrinolytic parameters, are thought to increase atherogenesis. It is no longer a matter of dispute that SLE patients have an increased risk of developing atherosclerotic cardiovascular disease, particularly before the age of 50. The incidence of coronary heart disease in women with SLE aged 35–44 years has been estimated to be 50- fold greater than in the general population, and the cumulative prevalence of CAD in SLE patients was 8.9%. Early detection and management of atherosclerosis may reduce the morbidity and improve the survival of patients with SLE.

Etiologies of myocardial damage in SLE patients include premature atherosclerotic disease, antiphospholipid antibody syndrome, coronary artery spasm, coronaryartery vasculitis and restenosis after percutaneous revascularization procedures. The following discussion will focus on the diagnosis and pathogenesis of coronary artery disease with an emphasis on premature atherosclerosis and coronary vasculitis in patients with SLE.

Coronary artery vasculitis remains an infrequent complication of SLE. Prior to the widespread use of coronary angiography, coronary vasculitis was a post mortem diagnosis. Coronary angiography has helped in evaluating patients with suspected coronary vasculitis. It has been suggested that a rapid rate of progression of coronary lesions is more

suggestive of a vasculitic process and, therefore, single angiographic studies may be inadequate. One case report documented a tertiary referral center experience where only two patients younger than 35 years of age with coronary vasculitis were identified over a period of 40 years. A possible mechanism of arterial injury in SLE might be the development of auto-antibodies that may target the heart or the blood vessels. According to Dangas et al., there are increased auto-antibodies against actin and myosin during and after an acute coronary syndrome. The present case represents only the fourth case reported in detail with SLE and coronary artery disease in a patient younger than 21 years old. The diagnosis of coronary vasculitis secondary to SLE in this case is suggested by the documentation of the diagnosis of SLE, the absence of classic risk factors for atherosclerotic heart disease (no evidence of diabetes, hypertension, family history of CAD or smoking) and the occurrence of angina pectoris or myocardial infarction at a young age.

In addition to premature coronary artery disease, there was clearly a rapid change in the patient's anatomy after coronary artery bypass graft surgery with total occlusion of 3 out of 4 grafts over only a 4-month period. The fourth graft displayed segmental narrowing. This is higher than early occlusion rates reported in multiple trials. Also, the internal mammary artery of our patient displayed areas of fibrosis and intimal thickening per the operative report, precluding its use as a graft. These

events suggest vasculitis as a possible etiology for her deterioration, as is suggested from the pathology slide. Immune complex deposition in the coronary artery walls in patients with SLE have been documented via immunofluorescence studies and the relationship between inflammatory immunologic injury and atherosclerosis has been demonstrated experimentally. Similar immune complex deposition in coronary vessels of SLE patients may predispose to intimal thickening and atherosclerosis, thus increasing the frequency of myocardial infarction. Histologic findings at autopsy have displayed both neutrophilic and lymphocytic infiltration, fibrinoid necrosis and immune complex deposition.

The etiology of the accelerated atherosclerosis in SLE in not known, but it has been linked to inflammation and endothelial dysfunction, a consequence of the inflammatory process. Flow-mediated dilatation is a non-invasive method of measurement of endothelial dysfunction. It is based on the change in diameter of a conduit artery in response to increased flow, typically induced by a period of ischemia in the distal circulatory bed.

The formation of immune complexes in patients with SLE is strongly associated with acceleration of atherogenesis.The presence of autoantibodies to β2-glycoprotein-1 and HDL-associated protein and major antigen for anticardiolipin antibodies, is strongly associated with inflammation in patients with SLE as are autoantibodies to components

of oxidized LDL. In patients with SLE, immune complexes activate complement, which in turn acts on mast cells and basophilsto release vasoactive amines. These amines, which include histamine and 5-hydroxytryptamine, promote endothelial cell retraction and increased vascular permeability, induce the expression of endothelial adhesion molecules, and attract polymorphs that subsequently infiltrate the area of damage Thrombin and inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor–α are also involved in this process. Following the trigger of adhesion molecule expression, preformed P-selectin is rapidly but transiently translocated to the endothelial surface, and within hours E-selectin is also expressed . Subsequently, integrin molecules on the leukocytes bind to immunoglobulin superfamily receptors. For example, β2-integrins bind to intercellular adhesion molecule–1, and monocyte α4β1 integrin binds to vascular cell adhesion molecule–1 (VCAM-1). These molecules promote the capture and rolling of the leukocytes. Pro-oxidant molecules stimulate endothelial nuclear factor κB (NF-κB), thereby promoting expression of VCAM-1 and monocyte chemotactic protein–1 (MCP-1), and subsequently monocyte infiltration, by interaction with platelet-endothelial cell adhesion molecule. In diabetic patients, advanced glycosylation endproducts also mediate prolonged expression of NF-κB, and may be a mechanism for the similar increased risk of

cardiovascular complications.28 Nitric oxide induces the endogenous inhibitor of NF-κB, IκBα, which reduces expression of both VCAM-1 and MCP.

Advances in medical therapy and a better understanding of systemic lupus erythematosus (SLE) have contributed to a dramatic improvement in the long-term survival of patients. However, despite the overall long-term improvement, coronary artery disease remains a major cause of morbidity and mortality with an incidence that is approximately nine-fold greater than would be expected for this population. Following active lupus, coronary artery disease is the second most common cause of hospitalization for SLE patients. Manzi et al. found that, when controlled for age and gender, women with SLE who are 35–44 years old have a 50-times higher risk of myocardial infarction (MI). Previous autopsy studies have observed that severe coronary artery disease is present in as many as 40% of patients with SLE compared with only 2% of age-matched controls at the time of death.

ANTIPHOSPHOLIPIDS ANTIBODY SYNDROME :

The antiphospholipid syndrome (APS) is an acquired thrombotic disorder characterized by recurrent venous or arterial thrombosis or recurrent miscarriages, or both, associated with the presence in the serum of IgG or IgM anticardiolipin antibodies (aCL) and/or lupus anticoagulant

(LAC). APS may occur as a primary disorder (PAPS) or associated with connective tissue diseases, mainly systemic lupus erthymatosus (secondary APS).Primary and secondary APS are both associated with a significant increase of cardiovascular risk.

Atherosclerosis is an autoimmune/inflammatory disease associated with infectious, inflammatory, and autoimmune factors. Both humoral and cellular immune mechanisms have been proposed to participate in the onset and/or progression of atheromatous lesions. Heat-shock protein (hsp), oxidized low-density lipoprotein (LDL), and beta2-GPI have been reported to elicit humoral and cellular immune response in both experimental animals and humans.

Antiphospholipid (antibody) syndrome is a pathological condition that is also referred to as "Hughes syndrome." It originates from excess accumulation of blood clots by antiphospholipid antibodies. The syndrome may occur as a primary condition (primary APS) or along with the autoimmune disease, systemic lupus erthymatosus. SLE is a chronic disease that affects certain organs, blood vessels, or the skin. The main signs of APS include blotchy skin, migraine, memory loss, fatigue, deep vein thrombosis, pulmonary embolism, and stroke. Primary APS may affect heart valves and present with such damage in 30% of patients. In pregnant women with APS, miscarriages may occur.

The recognition that a number of SLE manifestations have a thrombotic rather than an inflammatory basis can be considered one of the most important recent contributions to rheumatology and immunology. The "anticardiolipin syndrome" described by Graham Hughes in the 1980s, which was subsequently renamed antiphospholipid (Hughes) syndrome, appeared as a frequent condition in patients with SLE but also was present in others without SLE or other autoimmune diseases. In such cases it was termed a "primary" APS (PAPS). Almost 20 years after its definition, APS has crossed over into many fields of medicine. However, the full spectrum of the syndrome has yet to be defined, though significant advances in the diagnosis and management of patients with APS have been made. In addition, a consensus about very important questions, such as the use of alternative tests for anticardiolipin (aCL) antibodies and lupus anticoagulant (LA) assays, the treatment of pregnancy failure, or the intensity of anticoagulant therapy, has not yet been achieved.

These autoantigens are expressed within atherosclerotic lesions. Immunization with the given autoantigens elicits an immune response that influences lesion progression. Atherosclerosis susceptibility can be transferred by autoantigen-sensitized lymphocytes from immunized animals. Patients with systemic lupus erthymatosus (SLE) and antiphospholipid syndrome (APS) have a high risk for atherosclerotic

cardiovascular events. The traditional risk factors fail to fully account for accelerated atherosclerosis in SLE and APS. Immunological alterations, such as antibodies to oxidized LDL, antiphospholipid antibodies (aPL), antibodies to beta-2 Glycoprotein (anti-beta2-GPL), anti-prothrombin antibodies, may play a role in premature atherosclerosis in SLE and APS. Antiphospholipid antibodies(aPLs) predict an increased risk for MI, and their levels are increased in young survivors of MI. ß2GP1 is a cofactor for antibody binding to cardiolipin, and recent studies indicate that many aCLs recognize oxidized CL (OxCL) and/or adducts of OxCL with ß2GP1.

The antiphospholipid antibody syndrome is characterized by both arterial and venous thrombosis and is common in SLE. In the recent studies, lupus anticoagulant showed a significant association with IHD in SLE. In addition, both aCLs and anti-ß2GPI antibodies tended to be associated with arterial disease in SLE. It is possible, therefore, that the increased risk of IHD in SLE is to some extent caused by thrombosis.

Thrombosis has been associated with the presence of a lupus anticoagulant(LAC) or antiphospholipid antibodies(APA) as part of a secondary antiphospholipid syndrome(APS). It has been noted that APA may promote cross-reactivity with anticardiolipin(aCL) binding to both the cardiolipin-protein complex and to oxidized low-density lipoprotein (LDL) cholesterol linking oxidation, inflammation, autoimmunity,

atherosclerosis and thrombosis. However, it has also been suggested that the development of the antibody is an epiphenomenon as part of an immune reaction to vascular injury. The precise role of APA in coronary artery disease in SLE patients remains unclear. In addition, most studies have been retrospective and screened patients for APA after a thrombotic event had occurred. Thus, it has been debated whether the observed associations are causative or whether they are only markers for an inflammatory or immune response causing vascular injury. Interestingly, Vaarala it al. designed a prospective 5-year study in which it was found that the APA levels were significantly higher in patients with MI than in age- and gender- matched controls, even after adjusting for conventional risk factors.

Recently many authors have been trying to find a correlation between the presence of aPL and thrombosis of coronary arteries, in the absence or limited arteriosclerotic changes. Prospective studies prove the close relationship between the presence of aPL and development of AMI and reinfarction. The frequency of AMI in APS varies, according to literature data. Some authors find out a connection between ACA and AMI in 21% of cases.

It is assumed that aPLs are a significant risk factor for AMI in selected patients. According to Adler et al, aPL precede the infarction, rather than follow it. The results he obtained regarding the frequency of

APS in AMI (38%) are a little higher, as compared with authors cited above. This could be attributable to proper initial selection of patients, suspected for APS. The increased values of ACA, ß2GP1 antibodies and CD31 registered in patients with AMI correlate well with the development of arterial thrombosis, and some disputable pathogenic mechanisms of arising of hyper coagulation in patients with APS. According to Galli et al, the presence of ACA and ß2GP1 antibodies in patients with systemic lupus erthymatosus is connected with a risk for development of arterial thrombosis. Many authors consider ß2GP1, which is the main co-factor of binding between ACA and cardiolipin, as one of the key structures. On the other hand, a direct formation of antibodies against ß2GP1 is also observed in APS. The importance of ß2GP1 is connected with its functions of a natural coagulant, namely the blocking of the contact system of coagulation, inhibition of adenosine diphosphate-depending aggregation and the synthesis of factor Xa from the activating platelets, as well as the inhibition of prothrombinase activity of inactivated platelets. Recently, there are reports that in patients with secondary APS, antibodies against ß2GP1 can be used as a target for immune mediated atherogenesis. Anti- ß2GP1 antibodies can trigger other mechanisms - to activate the endothelium cells and activate adhesion molecules such as ICAM-1, VCAM-1, and E-selectin.

The arising of thrombosis in APS is also associated with increased activity of thrombotic endothelium adhesion molecules CD31. CD31 is expressed on platelets, neutrophils, monocytes and endothelium cells, and it plays a significant role in their interaction. Apart from the signal function it has, CD31 also activates the ß-3 subgroup of integrins, which in turn play a crucial role in the adhesion of cells. It is not by chance that the flowcytometric investigation of the expression of CD31 on the circulating platelets is recommended as an important method for investigating thrombotic conditions. The increased expression of the marker in the chronic stage of myocardial infarction correlate well with the observation in cases of APS following thrombosis, and they prove the significance of CD31 in the pathogenesis of APS.

In conclusion, it is considered that number of studies carried out confirm the proposition that aPL play an important role in the pathogenesis of acute coronary incidences. The timely diagnosis of APS could improve the prognosis, prevention and treatment of patients in this risk group.

Materials and methods

MATERIALS

SUBJECTS :

Patients who are all positive to Rheumatoid factor (RF) attending RHEUMATOLOGY CLINIC, COIMBATORE MEDICAL COLLEGE HOSPITAL between September 2007—September 2009.

PERIOD OF STUDY :

September 2007— September 2009

DESIGN OF STUDY:

Cross sectional observational study

ELIGIBILITY CRITERIA:

All patients with RHEUMATOID ARTHRITIS (RF positive by ELISA)

EXCLUSION CRITERIA:

1. Chronic infection
2. Elderly patients (>60 years)
3. Patients with thyroid abnormality

INCLUSION CRITERIA:

1. Hypertension
2. Obesity
3. Diabetes mellitus
4. H/O smoking,
5. H/o IHD
6. Family h/o IHD

METHODOLOGY

One hundred patients with rheumatoid arthritis and with RHEUMATOID FACTOR positive attending RHEUMATOLOGY CLINIC, COIMBATORE MEDICAL COLLEGE HOSPITAL during the study period were evaluated for IHD by ECG and ECHO.

Those who are included in the study were evaluated for traditional risk factors like h/o Diabetes, smoking (in the past / present), family h/o IHD and they were clinically examined for hypertension, body mass index for Obesity and features of RA. Patient with BP >140/90 mmHg were considered as hypertensive in this study. Fasting blood for sugar and lipid profile were measured. They were also evaluated for RF positivity, high or low titres by ELISA. A resting 12 lead ECG was carried out for features of IHD. The following changes in the ECG were taken as marker of ischemia

1) The combination of ST elevation in atleast two contagious leads and reciprocal ST depression in atleast two contagious leads.
2) Inversion of T with ST still being elevated.
3) Presence of pathological Q waves.

STATISTICAL ANALYSIS:

Statistical analysis was done using standard formulae SPSS (Statistical Package for social sciences) in windows Dos version. Base line data like age, gender, RF, Traditional risk factors were collected. Patients were categorized on their RF positive with or without traditional risk factors and Ischemic changes.

The significance of association between the factors was collected using PEARSON CHI-SQUARE TEST and YATES Corrected CHI-SQUARE TEST. $P<0.05$ was taken as significant.

CRITERIA CONSIDERED IN THE STUDY

S.NO	PARAMETERS	VALUES
1	Obesity (BMI)	>23
2	Hypertension:	>140/90mmhg
3	Diabetes -Fasting blood sugar	> 110 mg/dl
4	Abnormal Lipid profiles;	
	VLDL:	>100 mg/dl
	LDL:	>100mg/dl
	HDL:	<40mg/dl
	TGL:	>160mg/dl
5	Rheumatoid factor; (BY ELISA technique)	
	HIGH TITRE:	>320 IU/ml
	LOW TITIRE:	<320 IU/ml

OBSERVATION & RESULTS

OBSERVATIONS AND RESULTS

1.	**TOTAL NUMBERS OF PATIENTS(n)**	100
	FEMALE	70
	MALE	30
2.	**AGE**	
	≤40YEARS	44
	41-60YEARS	56
3.	**ECG-ISCHEMIC CHANGES**	
	TOTAL	20
	A. WITH TRADITIONAL FACTORS	14
	MALE	10
	FEMALE	4
	B. ONLY RF POSITIVE	6
	MALE	5
	FEMALE	1
	HIGH TITIRE RF	4
	LOW TITIRE RF	2

AGE DISTRIBUTION:

Of the hundred patients with RF positivity , there were 70 females and 30 males, age distribution of those included in the study are showed in table no:1

TABLE NO-1 AGE DISTRIBUTION IN RELATION TO SEX

AGE	MALE	FEMALE
21-30	4	13
31-40	5	22
41-50	10	19
51-60	11	16

CHART NO-1 AGE DISTRIBUTION IN RELATION TO SEX

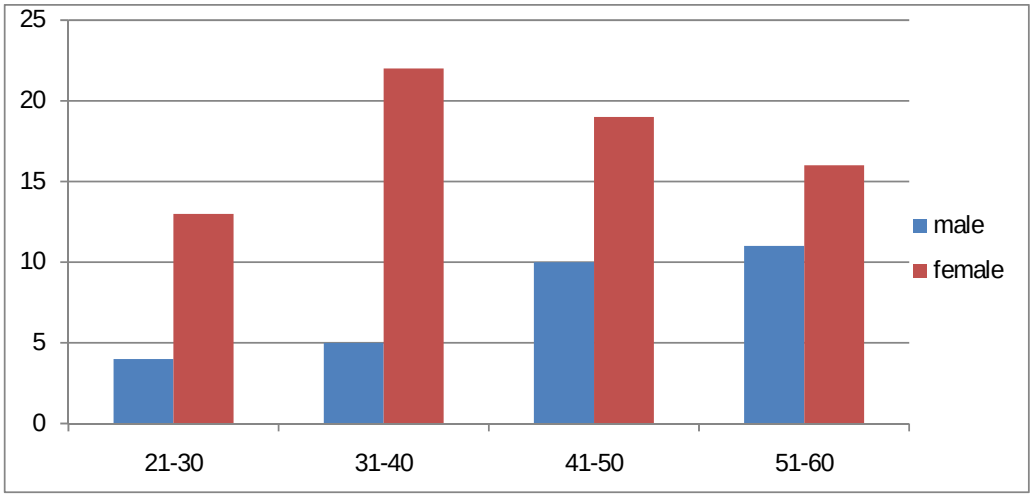


TABLE -2: ISCHEMIC CHANGES IN THE TOTAL

POPULATION UNDER STUDY IN PERCENTAGE:

ECG CHANGES	FREQUENCY	PERCENTAGE
PRESENT	20(100)	20%
ABSENT	80(100)	80%

CHART-2 : ISCHEMIC CHANGES IN RF POSITIVE PATIENTS

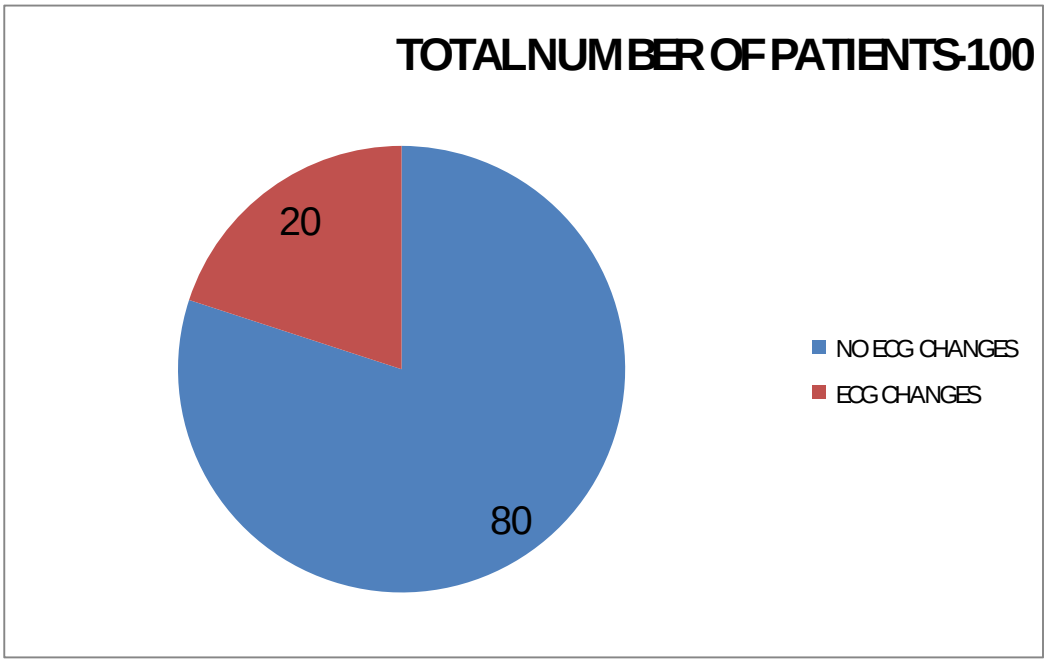


TABLE -3: AGE AND SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES OF RF WITH TRADITIONAL RISK FACTORS

AGE & SEX DISTRIBUTION OF ISCHEMIC CHANGES		
AGE	**MALE**	**FEMALE**
21-30	2	0
31-40	2	1
41-50	5	1
51-60	6	3

TABLE -4: AGE DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF INCLUDING TRADITIONAL RISK FACTORS:

ECG-ISCHEMIC CHANGES		
AGE	**NUMBERS**	**PERCETAGE**
<40 yrs	5(44)	25%
41-60yrs	15(56)	75%

$\chi 2=1.77$

P=0.18 NOT SIGNIFICANT

On comparing below 40age : 40-60age 1:1.77 ratio by chi square test, the P value is 0.18 which is > 0.05.so,it is not significant. The

association between age distribution in RF positive patients is not significant.

CHART-3: AGE DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF POSITIVITY WITH TRADITIONAL RISK FACTORS:

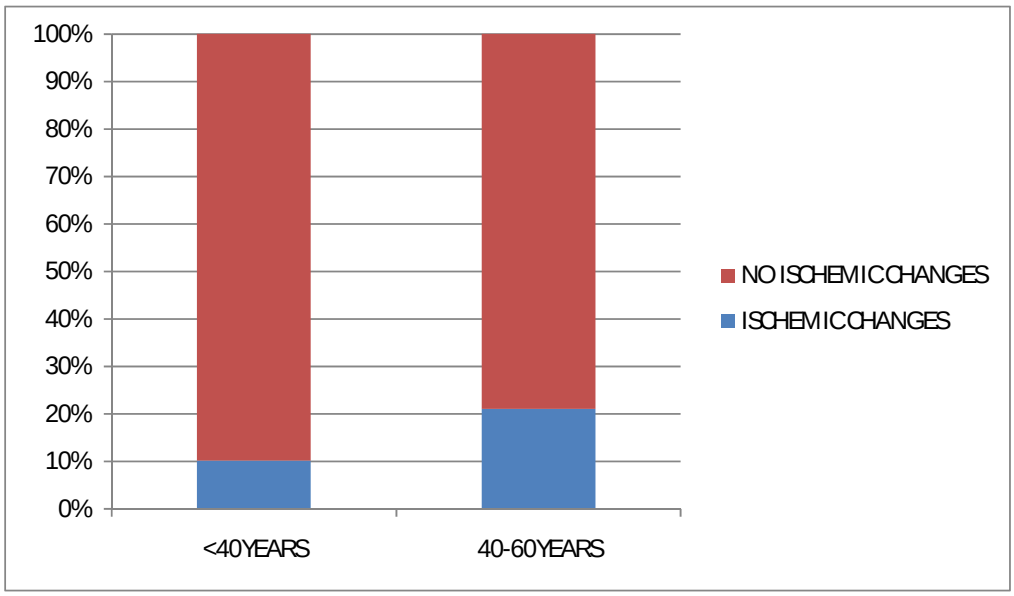


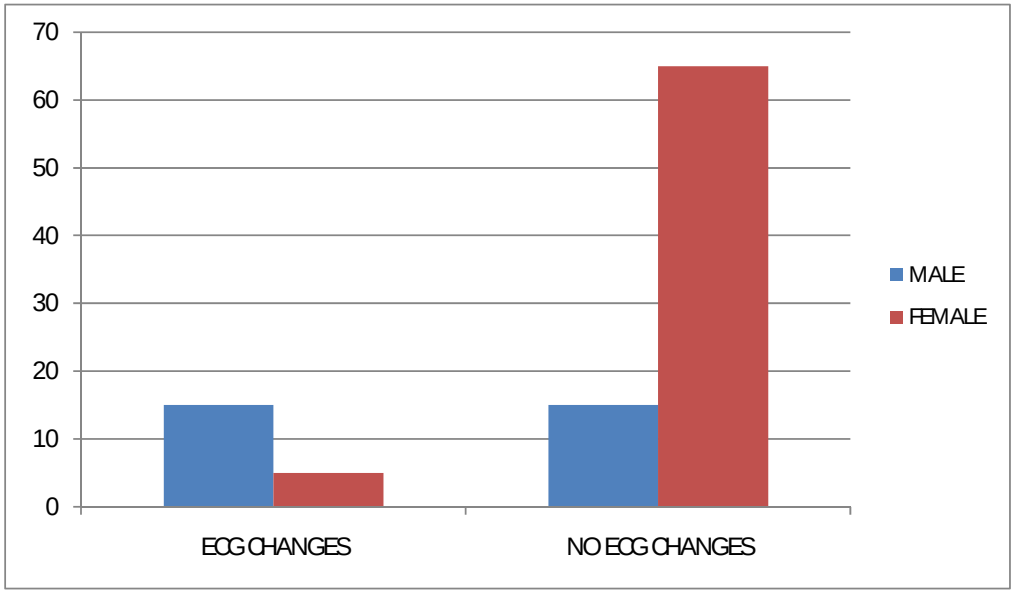
TABLE-5: SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES DUE TO RF WITH TRADITIONAL RISK FACTORS

ECG-ISCHEMIC CHANGES		
SEX	**PRESENT**	**ABSENT**
MALE	10(12)	2(12)
FEMALE	4(18)	14(18)

$\chi 2$= 8.49 / P=0.0035 (SIGNIFICANT)

The study shows that 83.33% of males and 28.57% of females with RF positive with traditional risk factors had ischemic changes . On comparing the male, female ratio (2.2:1) by chi square test, the P value is 0.0035. This indicating that males with RF and traditional risk factors have greater risk of IHD compared to females.

CHART-4: SEX DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF INCLUDING TRADITIONAL RISK FACTORS:



In the present study, a total of 20 patients had ischemic changes in the ECG. Among the patients, there were 15 males and 5 females. The proportion of patients with ischemic changes in ECG were higher for males accounting for 50% of the male population in the study.

TABLE 6: AGE AND SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES DUE TO RF WITHOUT TRADITIONAL RISK FACTORS:

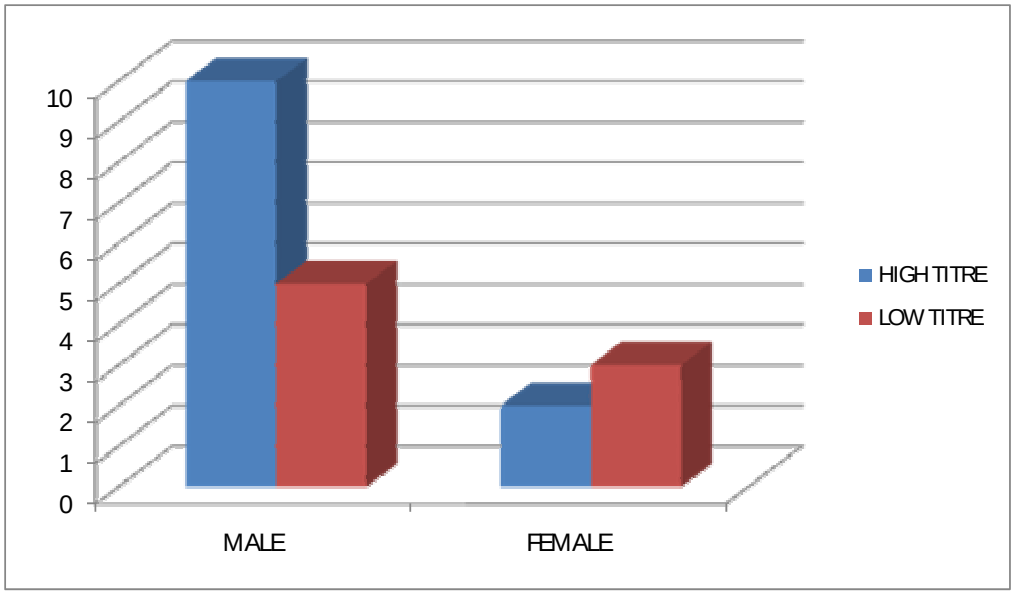
AGE DISTRIBUTION	RF WITHOUT TRADITIONAL RISK FACTORS- ECG CHANGES		
	MALE	FEMALE	TOTAL
21-30	1(3)	0(12)	1(15)
31-40	1(2)	0(20)	1(22)
41-50	1(6)	1(13)	2(19)
51-60	2(7)	0(7)	2(14)

A total of 6 patients had ischemic changes in the ECG in the study population without having any traditional risk factors. Among the 6 patients, there were 5 males and only one female.

TABLE-7: SEX DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF POSITIVITY WITH VARYING TITRES:

ISCHEMIC CHANGES IN ECG(N=20)			
MALE(15)		FEMALE(5)	
RF-HIGH TITRE	RF-LOW TITRE	RF-HIGH TITRE	RF-LOW TITRE
10 (50%)	5 (25%)	2 (10%)	3 (15%)

CHART-5: SEX DISTRIBUTION OF ISCHEMIC CHANGES IN RELATION TO RF POSITIVITY WITH VARYING TITRES:



In the present study there were 20 patients who had RF positivity with Ischemic changes in ECG. 15 were males and 5 were females. Of these 10 males and 2 females had high titre of RF with ischemic changes. Thus the majority of patients with high titre of RF along with ischemic changes are males.

TABLE- 8: SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES IN LONE RF POSITIVE AND TITRES

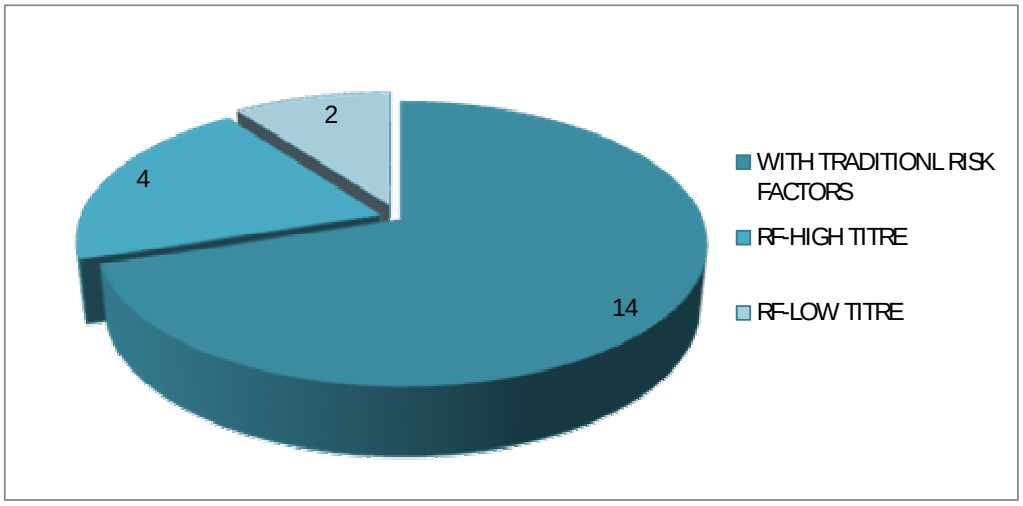
SEX	RHEUMATOID FACTOR	ECG ISCHEMIC CHANGES			
		PRESENT		ABSENT	
		NUMBER	PERCENT	NUMBER	PERCENT
MALE	HIGH TITRE	4	100%	_	_
	LOW TITRE	1	7.14%	13	92.86%
FEMALE	HIGH TITRE	0	_	18	100%
	LOW TITRE	1	3%	33	97%

Subjects with ischemic changes with RF positivity alone without the presence of traditional risk factors were tabulated above with sexual differentiation and also with respect to varying titres of RF.

TABLE- 9: SEX DISTRIBUTION IN RELATION TO ISCHEMIC CHANGES IN LONE RF POSITIVE AND TITRES:

ISCHEMIC CHANGES IN ECG(N=6)			
MALE(5)		**FEMALE(1)**	
RF-HIGH TITRE 4 (80%)	RF-LOW TITRE 1 (20%)	RF-HIGH TITRE 0	RF-LOW TITRE 1

CHART-6 : ISCHEMIC CHANGES IN ECG IN RELATION TO LONE RF POSITIVE AND TITRES



In the present study Lone RF without traditional risk factors was seen in only 5 male patients, with only one female patient .Of the 5 male patients 4 had high titre RF (>320). Considering the association of traditional risk factors a an additional risk factor with RF positivity, 14 had ischemic changes.

In men

5/30 ==16.66%

CONFIDENCE INTERVEL= 4 – 28

$\chi^2_{\text{YATES CORRECTED}}$ **P**=0.01 (significant)

In study population

5/100== 5%

CONFIDENCE INTERVEL= is 1.7-5.4.

$\chi^2_{\text{YATES CORRECTED}}$ **P**=0.01 (significan**)**

TABLE-10 : ISCHEMIC CHANGES IN RELATION TO RF WITH AND WITHOUT TRADITIONAL RISK FACTORS IN PERCENTAGE:

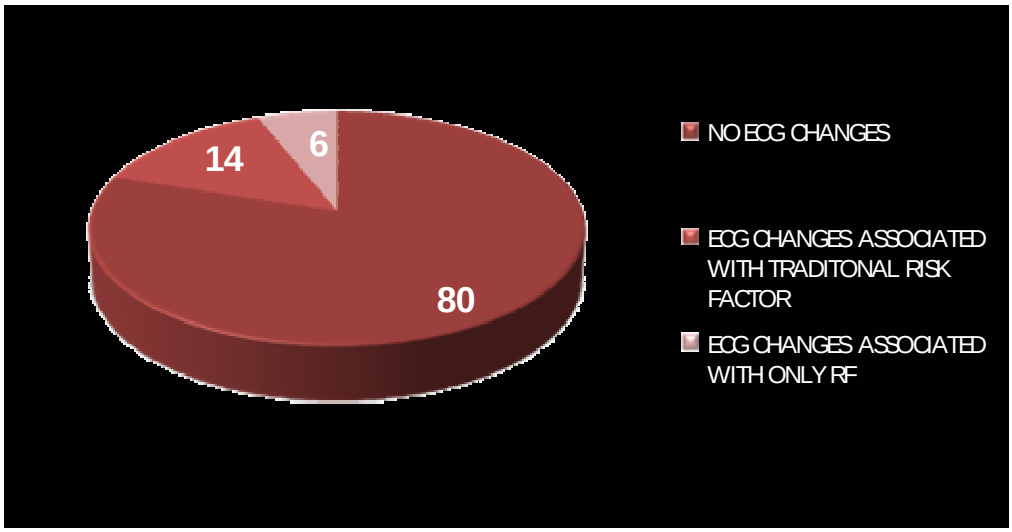
RF WITH TRADITIONAL RISK FACTORS	ECG ISCHEMIC CHANGES			
	POSITIVE		NEGATIVE	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Present	14	50%	14	50%
Absent	6	8.33%	66	91.66%

$\chi 2$= 19 .35; P=0.00001 (significant)

Subjects with ischemic changes in RF positive with traditional risk factors are 50 % without traditional risk factors are 8.33 % . On

comparing these values by chi square test , P value is 0.0001which is statistically significant.

CHART-7: ISCHEMIC CHANGES IN RELATION TO RF WITH AND WITHOUT TRADITIONAL RISK FACTORS :



Discussion

DISCUSSION

In the study population, most of the RF positive patients clustered between 30-50 years. Dividing the study population with ischemic changes by ECG, by age, 25% were below 40 years and 75% were above 40 years. All of the above patients had RF positivity along with traditional risk factors and ischemic changes in the ECG.

In this study 30% were males and 70% were females. The M:F ratio was 1 : 2.33. 20 patients had ischemic changes in ECG constituting 15 males (50%) and 5 females (7.14%)patients of the total study population. This is concordant with Edwards C J et al[1] where the M:F ratio was 1 : 1.02 . Comparatively females were more common in present study population. This is because the patients selected were suffering from RA which is more common in females. Considering the ischemic changes, males were affected more than females though more number of female patients were included in the study. This is also similar to Edwards C J et al[1]

Evaluating the 20% (n=20) who were RF positive with ischemic changes, 14 patients had traditional risk factors(70%).The other 6 patients had only RF positivity without any other traditional risk factor. Among these 5 patients were males and there was only one female. This

indicates an association of RF and IHD a strong possibility especially in males.

Among the 10male patients who had RF positivity with traditional risk factors and ischemic changes, 6 patients had high titre of RF and 4 patients had low titre. Percentage wise 42.85% and 28.57% were having high and low titres of RF along with traditional risk factors causing IHD. This is concordant with both Edwards C J et al[1], Kenneth J Warrington et al[4.]

Among the 4 female patients who had RF positivity with traditional risk factors , 2 patients had ischemic changes with high titre of RF making up 12.5%. 2 patients had ischemic changes with low titre RF and traditional risk factors forming 12.5% This is disconcordant with both Edwards C J et al[1], Kenneth J Warrington et al[4.]

By these data this study shows that, RF with traditional risk factors have increased incidence of ischemic changes in males than females especially with high titre RF.

In this study only 6 patients had RF positivity without traditional risk factors along with ischemic changes and among them 5 were males and there was only one female. This is 27.7% of the total RF positive males without traditional risk factors in study population and 16.66% total male patients in the study population. Only one female patient had ischemic changes in ECG with lone RF without traditional risk factor.

This is 1.9% of the total RF positive females without traditional risk factors and 1.4% of the total female patients in the study. This study is in concordance with Edwards C J et al[1]

The long term Herfordshire Cohort study reported by Sydall H E et al[5] had similar results. RF positive male patients without traditional risk factors are vulnerable to IHD. Females with traditional risk factors did not have IHD – this is discordant with this study. Our study indicated that IHD may be associated with RF and traditional risk factors in females which is as in the study of Sydall H E et al[5]

Of these 5 male patients, 4 patients had high titre of RF positivity which is 80% and one patient had low titre of RF which is 20% .This suggested that a high titre of RF may have an increased incidence of IHD. This concurs with the earlier study by Edwards C J et al[1] and del Puente A et al[3]

In this study, Autoantibody RF which is risk factor for IHD in men is 16.66% (5 out of 30); confidence interval(CI) is 5-28 and 5% (5 out of 100) study population; This goes with many other similar studies from various parts of the world.

Most of the of the studies state the prevalence to be between 4-28%. Edwards C J et al[1]- 11.6%(in men), Kenneth J Warrington1 et al[4] - 1.97% (in general population).

From the observation and analysis of study, it is assumed that there is an association between high titre of RF and IHD. This association was significantly more in male patients.

This study has a number of potential limitations. The study is conducted with the maximum available resources in the hospital. The most important is the fact that this is a cross-sectional study and will need confirmation by a longitudinal cohort study.

conclusion

CONCLUSIONS

- RF can be considered as one of the risk factor for Ischemic heart disease in males.
- High titre RF alone can further increase the incidence of IHD.
- RF in association with other traditional risk factors increase the prevalence of IHD.
- Though more female patients have positive RF ,they are not vulnerable to IHD.

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annexures

PROFORMA

Name:

Age:

Sex:

OP No.

Address:

Presenting Complaints:-

H/o HT

H/o Diabetes Mellitus

H/o IHD

H/o Smoking

Family H/o IHD

Rhematalogical H/O

EXAMINATION:

Pulse:

BP:

CVS:

RS:

P/A:

CNS:

INVESTIGATIONS:

BLOOD GLUCOSE:

Fasting

Post prandial

S.LIPID PROFILE:

TOTAL CHOLESTROL

VLDL

LDL

HDL

TGL

BODY MASS INDEX :

RHEUMATOID FACTOR:

High titre

Low titre

ELECTROCARDIOGRAM:

ECHO :

ABBREVIATIONS

ACL	**:**	ANTI CARDIOLIPIN ANTIBODIES
AMI	**:**	ACUTE MYOCARDIAL INFARCTION
APS	**:**	ANTI PHOSPHOLIPID SYNDROME
BMI	**:**	BODY MASS INDEX
CCP	**:**	CITRULINATED CYCLIC POLYPEPTIDE
CHD	**:**	CORONARY HEART DISEASE
CRP	**:**	C-REACTIVE PROTEIN
CVD	**:**	CARDIO VASCULAR DISEASE
ESR	**:**	ERTHROCYTE SEDIMENTATION RATE
HDL	**:**	HIGH DENSITY LIPOPROTEIN
IHD	**:**	ISCHEMIC HEART DISEASE
LDL	**:**	LOW DENSITY LIPOPROTEIN
RA	**:**	RHEUMATOID ARTHRITIS
RF	**:**	RHEUMATOID FACTOR
SLE	**:**	SYSTEMIC LUPUS ERTHYMATOSUS
TGL	**:**	TRIGLYCERIDE
VLDL	**:**	VERY LOW DENSITY LIPOPROTEIN

MASTER CHART

SL NO	AGE	SEX	OP NO	RA	RF	TRADITIONAL RISK FACTORS						ECG CHANGES	ECHO CHANGES
						SMOKING	DM	HT	OBESITY	DYSLIPIDEMIA	FAMILY H/O IHD		
1	36	F	3079624	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
2	39	M	750108	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
3	50	F	586833	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
4	45	F	550576	YES	HT	NO	YES	YES	NO	NO	YES	YES	YES
5	44	F	527540	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
6	54	F	521345	YES	LT	NO	NO	YES	NO	NO	NO	NO	NO
7	50	F	484537	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
8	54	F	463799	YES	LT	NO	YES	YES	NO	NO	NO	NO	NO
9	51	M	460695	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
10	59	M	438081	YES	LT	NO	YES	YES	NO	NO	NO	YES	YES
11	37	M	429440	YES	HT	NO	NO	NO	NO	NO	NO	YES	YES
12	36	F	428996	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
13	40	F	426348	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
14	40	F	426348	YES	LT	NO	YES	NO	NO	NO	YES	NO	NO
15	50	M	417697	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
16	30	M	413188	YES	HT	NO	NO	NO	NO	NO	NO	YES	YES
17	39	F	402532	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
18	23	F	367392	YES	LT	NO	NO	YES	NO	NO	NO	NO	NO
19	44	F	353178	YES	LT	NO	YES	NO	NO	NO	NO	NO	NO
20	60	M	323451	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
21	57	M	323003	YES	LT	NO	NO	NO	NO	NO	NO	YES	YES
22	36	F	322646	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
23	36	F	322646	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
24	42	F	322568	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
25	27	F	322487	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO

SL NO	AGE	SEX	OP NO	RA	RF	TRADITIONAL RISK FACTORS						ECG CHANGES	ECHO CHANGES
						SMOKING	DM	HT	OBESITY	DYSLIPIDEMIA	FAMILY H/O IHD		
26	27	F	322487	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
27	33	F	322255	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
28	60	F	321701	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
29	32	M	320820	YES	HT	NO	NO	YES	YES	NO	YES	YES	YES
30	45	F	319398	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
31	60	F	317874	YES	LT	NO	NO	YES	NO	NO	NO	NO	NO
32	22	M	313872	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
33	47	M	311345	YES	HT	NO	YES	NO	YES	YES	NO	YES	YES
34	49	F	311345	YES	LT	NO	YES	NO	NO	NO	NO	NO	NO
35	52	F	311345	YES	LT	NO	YES	YES	NO	NO	NO	NO	NO
36	38	F	304966	YES	LT	NO	NO	NO	NO	NO	NO	YES	YES
37	42	M	304302	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
38	47	M	297630	YES	HT	YES	NO	YES	YES	NO	NO	YES	YES
39	59	M	293602	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
40	47	F	293378	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
41	30	F	291110	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
42	51	F	285012	YES	LT	NO	YES	NO	NO	NO	NO	NO	NO
43	54	M	281817	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
44	57	F	278180	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
45	56	F	256410	YES	LT	NO	YES	NO	YES	YES	NO	YES	YES
46	25	F	251880	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
47	38	M	228153	YES	LT	YES	NO	YES	NO	NO	NO	YES	YES
48	40	F	225554	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
49	60	F	218078	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
50	60	F	218078	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO

SL NO	AGE	SEX	OP NO	RA	RF	TRADITIONAL RISK FACTORS						ECG CHANGES	ECHO CHANGES
						SMOKING	DM	HT	OBESITY	DYSLIPIDEMIA	FAMILY H/O IHD		
51	41	M	210599	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
52	29	F	198890	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
53	60	F	196067	YES	LT	NO	YES	YES	YES	NO	NO	YES	YES
54	52	M	176202	YES	HT	NO	YES	NO	NO	NO	NO	NO	NO
55	49	F	167365	YES	LT	NO	NO	YES	NO	NO	NO	NO	NO
56	52	F	150308	YES	LT	NO	NO	YES	NO	YES	NO	NO	NO
57	23	M	147204	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
58	36	F	141846	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
59	29	F	140283	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
60	29	F	134536	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
61	35	F	132368	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
62	35	F	132368	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
63	36	F	116051	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
64	47	M	106804	YES	HT	NO	NO	YES	NO	NO	NO	YES	YES
65	50	F	103918	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
66	30	F	96287	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
67	26	F	95245	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
68	30	F	86694	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
69	49	F	68551	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
70	47	M	65949	YES	HT	NO	YES	NO	YES	NO	YES	YES	YES
71	48	F	59866	YES	HT	NO	NO	YES	YES	NO	NO	YES	YES
72	48	F	59866	YES	LT	NO	YES	NO	NO	NO	NO	NO	NO
73	48	F	54196	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
74	60	F	39021	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
75	60	M	32594	YES	LT	YES	NO	YES	NO	NO	NO	YES	YES

SL NO	AGE	SEX	OP NO	RA	RF	TRADITIONAL RISK FACTORS						ECG CHANGES	ECHO CHANGES
						SMOKING	DM	HT	OBESITY	DYSLIPIDEMIA	FAMILY H/O IHD		
76	24	M	31734	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
77	30	F	29529	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
78	43	M	29328	YES	HT	NO	NO	NO	NO	NO	NO	YES	YES
79	49	F	29224	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
80	57	M	25869	YES	LT	NO	YES	YES	NO	NO	NO	YES	YES
81	58	M	25310	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
82	40	F	24420	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
83	39	F	24142	YES	LT	NO	YES	NO	NO	NO	NO	NO	NO
84	41	M	23897	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
85	39	F	21389	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
86	41	F	19242	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
87	32	F	18293	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
88	45	F	16539	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
89	51	F	16510	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
90	50	F	15237	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
91	21	F	14261	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
92	60	F	10984	YES	LT	NO	YES	YES	NO	NO	NO	NO	NO
93	36	F	9081	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
94	55	M	7429	YES	HT	NO	NO	NO	NO	NO	NO	YES	YES
95	35	F	7423	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
96	33	F	2549	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
97	39	F	2338	YES	LT	NO	NO	NO	NO	NO	NO	NO	NO
98	41	M	1642	YES	HT	NO	NO	NO	NO	NO	YES	NO	NO
99	55	F	1540	YES	HT	NO	NO	NO	NO	NO	NO	NO	NO
100	33	M	1416	YES	HT	NO	YES	YES	NO	NO	NO	YES	YES