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A Study of The Association of Impaired Glucose Metabolism in Patients with Newly Detected Rheumatoid Arthritis

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I. Introduction

Rheumatoid arthritis is a systemic, autoimmune disorder that primarily manifests as chronic synovial inflammation of multiple joints. As in the general population, both Diabetes Mellitus (DM) and Insulin Resistance (IR) appear to be independent risk factors for atherosclerotic CVD in patients with RA. Over the last few decades it has become increasingly apparent that chronic activation of the immune system, as observed in the pathogenesis of RA, is associated with corollary changes in intermediary metabolism, potentially leading to increased risk of cardiovascular disease. There is evidence of association of multiple immune regulatory components (including tumour necrosis factor and interleukin-6) in RA, IR, and type 2 diabetes mellitus. Disease associated reduction in lean muscle mass and sedentary lifestyle likely further contribute to IR in patients with RA (2).

Impaired glucose metabolism (pre-diabetes and overt diabetes) is seen around 40 – 45 % patients with RA. Hypertension is seen in more than 50 % of patients with RA and metabolic syndrome seen around 40% of patients. Central obesity is seen in >50 % of patients.

Both impaired beta cell function and insulin resistance is associated with impaired glucose handling in patients with rheumatoid arthritis. Abdominal obesity and RA disease activity are determinants of insulin resistance in patients with rheumatoid arthritis. Age and disease activity is associated with reduced beta cell function.

Tumour necrosis factor, a critical inflammatory cytokine in chronic active RA, has detrimental effects on lean muscle mass, resulting in sarcopenia and a relative increase in body adipose tissue, a condition known as rheumatoid cachexia. Levels of adiponectin, an adipocytokine, an inversely related to adiposity and IR, and adiponectin exerts favourable effects on insulin sensitivity and atherosclerosis. Adiponectin production by adipose cells is reduced by exposure to TNF-α, and low Adiponectin levels co-occur with characteristics of metabolic syndrome in patients with RA. Adipose tissue macrophages produce inflammatory cytokine, such as TNF-alpha and IL-6, thereby increasing inflammatory activity both locally and systemically. TNF-alpha can obstruct the bioactivity of the insulin by inhibiting tyrosine phosphorylation and subsequent activation of both the insulin receptor and insulin receptor substrate. This pivotal pro inflammatory cytokine also impedes insulin-glucose-mediated uptake in skeletal muscle.

As with TNF-alpha, IL-6 appears to affect insulin-signalling pathways by diminishing the effect of insulin. Human adipocytes releases IL-6, and IL-6 production is increased in obesity, with higher secretion in visceral than subcutaneous tissue. Reduction of IL-6 levels by the administration of anti-IL6 antibodies increased insulin sensitivity.

It is necessary to find out impaired glucose metabolism in early stage because

1) Patients with RA are likely to have increased risk of subclinical atherosclerosis and cardiovascular disease
2) Chronic inflammation in RA leads to impaired glucose metabolism due to insulin resistance and impaired beta cell function
3) Both pre-diabetes and overt diabetes aggravate atherosclerosis
4) Controlling of inflammation may improve glycaemic control through enhanced pancreatic insulin secretion and peripheral insulin sensitivity
5) Good glycaemic control reduce the risk of atherosclerosis and cardiovascular disease.

II. Aims And Objectives

- To assess the prevalence of Impaired glucose metabolism (pre-Diabetes and overt Diabetes) in newly detected Rheumatoid arthritis patients
- To improve the long term survival of Rheumatoid arthritis patients by early detection of Impaired glucose metabolism and timely institution of treatment

III. Review Of Literature

Rheumatoid arthritis

Most common form of chronic inflammatory arthritis is Rheumatoid arthritis which is idiopathic in nature. It commonly presents with peripheral polyarthritis which is symmetric in nature. Rheumatoid arthritis can present with extra articular manifestations because of systemic nature of disease. Rheumatoid arthritis cause significant mortality and morbidity. Compared with general population, patients with Rheumatoid arthritis has short life expectancy. Mortality rate is two times higher than general population. Leading cause of death in patients with Rheumatoid arthritis is cardio vascular disease. Infection is second most common cause of mortality.

Because of chronic activation of inflammation in Rheumatoid arthritis leads to changes in glucose metabolism. It can be due to increased peripheral resistance or impaired beta cell function. Altered glucose metabolism accelerates atherosclerosis which leads to increased cardiovascular mortality and morbidity in rheumatoid arthritis patients. Chronic inflammation also alters the lipid profile. Metabolic syndrome is also common in patients with rheumatoid arthritis because of insulin resistance.

Epidemiology

It affects 0.5 - 1% of adult population. In African and American countries it is around 0.2 - 0.4%. It has highest prevalence in Native Americans which is around 7%.

It affects adults between 25 to 55 years with increasing incidence. Incidence decreases after 75 years of age. Females are more commonly affected than males. Female to male ratio is 3:1. Highest female to male ratio is seen in Latin American and African. It is 6-8:1%.

Tumor necrosis factor production is enhanced by estrogen, which may be reason behind increased female prevalence.

Genetic Considerations

First-degree relative of a patient have risk of 2-10 times greater than general population. Most important alleles are located within the major histocompatibility complex. One-third of genetic risk resides ithin this locus. Most of this risk is associated with allelic variation in the HLA-DRB1 gene. HLA-DRB1*0401 is associated with high risk of disease. Alleles associated with moderate risk are *0101, *0404, *0901 and *1001. Most common alleles in Asians are *0405, and *0901. Several non-MHC- related genes also contribute.

Joint involvement

Joint stiffness is common presenting symptoms, which is more in early morning lasts around 1 hour and improves with physical activity. It affects small joints of hand and feet. It is symmetric in nature. Initially it can present as

1. Mono articular
2. Oligo articular or
3. Poly articular

Commonly affected joints are

1. Wrist
2. Metacarpo phalangeal joint
3. Proximal inter phalangeal joint
4. Metatarso phalangeal joint

Because of coexistent osteoarthritis distal inter phalangeal joint can be involved. Radiological evidence of temporo mandibular joint involvement is common. But it does not cause any functional significance. One of the dramatic complication of Rheumatoid arthritis atlanto-axial subluxation which leads to compressive myelopathy. Thoracic and lumbar spines are usually not involved in RA. Damage to joint and soft tissues leads to chronic irreversible deformity.

1. Swan neck deformity – Hyperextension of PIP Flexion of DIP
2. Boutonniere deformity – Flexion of PIP Hyperextension of DIP
3. Z line deformity – Subluxation of first MCP Hyperextension of first inter phalangeal joint
4. Ulnar deviation - Subluxation of MCP Subluxation of PIP to volar side of hand

5. Piano-key movement of Ulnar styloid – Subluxation of distal ulna
6. Flat foot – Pes planovalgus due to involvement of mid tarsal joints.

Constitutional symptoms:
Much more common than the joint symptoms. Rule out systemic vasculitis or infection if temperature > 101 F.

Subcutaneous nodules:
They are generally benign in nature. It occurs in the late course of disease. It affects 30 - 40 % of patients. It is firm and non-tender. Commonly occur over bony prominences which is adherent to periosteum and tendons.
Lung, pleura, peritoneum and pericardium are also affected by rheumatoid nodules.

Sjogren's syndrome:
Rheumatoid arthritis is important cause of secondary Sjogren's syndrome. It affects around 10% of patients with rheumatoid arthritis

Pulmonary Manifestation
1. pleural disease –Most common pulmonary manifestation. It presents as pleuritic chest pain, dyspnea and pleural effusion. Pleural effusions are exudative in nature. Pleural fluid sugar <30 mg%.
2. Interstial lung disease – carries poor prognosis.
Presents as dry cough and dyspnea.
3. Pulmonary Nodules –Solitary or multiple.
4. Respiratory bronchiolitis
5. Bronchiectasis
6. Caplan's Syndrome – Nodules and pneumoconiosis after exposure to silica.

Cardiac manifestations:
It can involve pericardium, myocardium and endocardium. Though pericardium is the most common site of involvement clinically manifests in less than 10 % of patients.
Cardiomyopathy can result from myocarditis or coronary artery disease. Commonest valvular abnormality is mitral regurgitation. Restrictive cardiomyopathy can result from deposition of amyloid.

Vasculitis:
It occurs in patients with long standing disease. Affects less than 1% of patients.
Cutaneous signs are petechiae, purpura, digital infarcts, gangrene, livedo reticularis and vasculitic ulcer.
It rarely presents as sensorimotor poly neuropathy.

Hematologic manifestations:
1. Normocytic normochromic anemia- severity of anemia correlate with degree of inflammation.
2. Platelet- usually elevated because of acute phase reaction. Rarely immune- mediated thrombocytopenia will be present.
3. Felty's syndrome – rare. Presents as triad of neutropenia, splenomegaly and nodular RA. It occurs in late stages of disease.
4. T cell large granular lymphocyte leukemia- due to indolent growth of LGL (Large granular lymphocyte) cells. It occurs in early stages of rheumatoid arthritis.
5. Lymphoma- fourfold risk of lymphoma. Diffuse large B-cell lymphoma is most common histologic type.

Osteoporosis- Inflammatory mediated activation of osteoclasts leads to generalized osteoporosis. Other factors contributing to osteoporosis are immobility and steroid abuse.
Hypoandrogenism - Testosterone, Dehydroepiandrosterone and Luteinizing hormone levels are lower in postmenopausal women and men with RA. Chronic inflammation leads to low testosterone level. Controlling of inflammation improves testosterone level.

Diagnosis
Acr-Eular 2010 classification criteria now is used to diagnose RA. Main aim of revising older 1987 ACR classification criteria is to diagnose RA patients at early stages and introduction of disease modifying therapy at early stages. Serum anti-cyclic citrullinated antibodies is included in newer criteria which is more specific for RA than RF. Rheumatoid nodules and radiographic joint damage is not included in newer criteria

because both of changes occurring in late stages of RA. This criteria is applicable to newly presenting patients. They must have at least one joint involvement with definite clinical synovitis.

Rheumatoid factor:

Seronegative patients have less extra-articular manifestations and better prognosis compared to seropositive patients. Three isoforms of RF is occurring in serum of RA patients IgM, IgG and IgA. Commonly measured in laboratories is IgM isotype. Sensitivity of RF is 75 – 80 %. RA can't be excluded by negative RF.

About 1-5 % of health population is positive for RF. RF is also positive in other connective tissue diseases and chronic infections like

1. Primary Sjogren's disease,
2. SLE (systemic lupus erythematosus),
3. Type II mixed essential cryoglobulinemia
4. Subacute bacterial endocarditis,
5. Chronic hepatitis B and C.

Classification Criteria For Rheumatoid Arthritis

			SCORE
JOINT INVOLVEMENT		1 large joint	0
		2-10 large joints	1
		1-3 small joints	2
		4-10 small joints	3
		>10 joints (at least 1 small joint)	5
SEROLOGY		Negative RF and negative Anti-CCP	0
		Low positive RF or anti-CCP (≤3 times)	2
		High positive RF or anti-CCP (>3times)	3
ACUTE-PHASE		Normal CRP and ESR	0
RECTANTS		Abnormal CRP and ESR	1
DURATION	OF	<6 Weeks	0
SYMPTOMS		≥6 Weeks	1
		21	

Anti-ccp:

It is more specific than RF.
Sensitivity is 75-80%
Specificity is 95%.

It is helpful to differentiate RA from other inflammatory arthritis in early stages. Patient who are positive for Anti-CCP have poor prognosis. Patients who are negative for one test (RF or Anti-CCP) may be positive for other test so it is complementary to go with both tests.

Synovial fluid analysis

It is inflammatory in nature with WBC count between 5000 to 50000 per cubic micro liter. Predominant cell type is neutrophil. RF, anti-CCP antibodies and immune complexes are also found in synovial fluid.

Joint imaging:

Plain x-ray is commonly used but MRI is sensitive than Pain X-ray in early stages. Common X-ray findings are

1. Juxta articular osteopenia,
2. Soft tissue swelling ,
3. Symmetric joint space loss
4. Subchondral bone erosions
5. Joint subluxation.

Periarticular osteopenia is earliest radiographic finding.

MRI- has greater sensitivity to early bone and bone marrow changes as well as synovitis and joint effusions. One of the early sign of inflammatory joint disease is bone marrow edema which can be easily picked up by MRI. Limiting factors are availability and cost.
USG can be used to detect bony erosions in accessible joints. Synovitis is also reliably detected by USG. It has advantages of lack of radiation, portability and low cost.
DAS28 (Disease Activity Scoring – 28):

DAS28 to assess improvement and progression of RA. It is a composite measure. It includes four parameters
1. Number of joints showing tenderness
2. Number of joints showing swelling
3. ESR or CRP
4. Subjective assessment of disease activity

Joints to be assessed
1. MCP
2. PIP
3. Wrist
4. Elbow
5. Shoulder
6. Knee

Ankle and MTP is not included. Values range from 2.0 to 10.0

SOCRE	DISEASE ACTIVITY
>5.1	High disease activity
5.1 to 3.2	Moderate disease activity
3.2 to 2.6	Low disease activity
<2.6	Remission

Pathoegenesis of impaired glucose metabolism in patients with rheumatoid arthritis:
Rheumatoid cachexia:

Increasing in central obesity is important risk factor for insulin resistance and metabolic syndrome. Elevation of TNF-alpha due to chronic activation of inflammation leads to decrease in lean body mass resulting in sarcopenia (1). There is redistribution of adipose tissue resulting central obesity. There is little or no weight loss. In spite of central obesity and sarcopenia, Body mass index calculated by BMI may be normal. It affects more than 50% patients of RA. Women are more prone to Rheumatoid Cachexia than men (2). Controlling of inflammation leads to decrease in obesity and increasing lean body mass.

Adipose tissue:

Adipose tissue is one of the important organ to store excess energy. Now it is recognized that adipose tissue is not a passive organ which can produce many important adipocytokines and inflammatory mediators. Adipose tissue regulate metabolism in other tissues by production of this adipocytokines and play an important role in propagation and initiation IR (3). Major adipocytokines and inflammatory mediators are
1. Adiponectin,
2. Leptin,
3. Resistin
4. visfatin
5. IL6
6. TNF-α

Low grade inflammation is induced by excess accumulation of lipid in adipose tissue. This leads to macrophage infiltration in adipose tissue. Inflammatory cytokines produced by this macrophages augment the inflammation both systemically and locally. Pro inflammatory cytokines is produced by liver also in response to cytokines from adipose tissue.

tnf- (tumor necrosis factor):
Major cytokine in RA is TNF-α. It plays major role in induction of insulin resistance in the following ways
1. Induction of rheumatoid cachexia
2. By inhibiting tyrosine phosphorylation of insulin receptors block the effects of insulin (4).
3. In skeletal muscles block the insulin mediated glucose uptake (5).
4. Decrease adiponectin production (6).
5. Increase resistin production

IL- 6 another important cytokine in RA. Insulin resistance is induced in the same way as TNF-α (7).
Other cytokines elevated in RA is IL-2 and IL-17 (8).

Leptin:
Leptin produced by adipocytes. It plays role in glucose metabolism by 1. Decreasing insulin secretion,

2. Improving insulin sensitivity.
In chronic inflammatory conditions like RA, There is elevation of CRP. CRP induce leptin resistance by blocking receptor binding.
It also has atherogenic effects by
1. Induction of endothelial dysfunction,
2. Stimulation of inflammatory reaction,
3. Oxidative stress,
4. Reduction of Paraxonase activity,
5. Platelet aggregation,
6. Smooth muscle cells modification (9).

Adiponectin:
It has following favourable effects
1. Anti inflammatory,
2. Anti atherogenic,
3. Antidiabetic properties (10).

Production of adiponectin by adipocytes is decreased by TNF-αand other inflammatory cytokines which leads to insulin resistance, dyslipidemia and metabolic syndrome.

Resistin:
In contrast to other adipokines which are mainly produced by adipocytes, macrophages and monocytes of peripheral blood produce Resistin (11). TNF-α induce expression of Resistin gene in mononuclear cells. It has
1. Pro inflammatory properties – up-regulate the TNF-α and IL-6 of mononuclear cells of peripheral blood (12).
2. Induce hepatic IR by increased hepatocellular production of TNF-α and IL-6. VISFATIN (colony enhancing factor of pre-B-cell):

TNF- α and interleukin-6 increase visfatin production. High
levels of visfatin is associated with hyperglycemia and insulin resistance (13).

Lipotoxicity:
Beta cell function is impaired by adipokines and excess non esterified fatty acids which released by enlarged adipose cells. Steroids in high dose also impair beta cell activity (19).

Vitamin d:
Vitamin D deficiency in patients with RA is associated with hyperlipidemia and metabolic syndrome. Supplementation of vitamin D improves dyslipidemia and decrease metabolic syndrome (14).
Finally it is concluded that patient with RA has high risk of impaired beta cell function and insulin function which potentially leads to impaired glucose metabolism and acceleration of atherosclerosis.

Diabetes Mellitus: Diagnosis of impaired glucose tolerance and diabetes mellitus done with ADA-2014 guidelines

		Normal glucose tolerance	Pre-diabetes	Diabetes mellitus
Fasting glucose	plasma	<100 mg/dl	100-125 mg/dl	≥126 mg/dl
2-hour glucose	plasma	<140 mg/dl	140-199 mg/dl	≥200 mg/dl
HbA1C		<5.6 %	5.7 – 6.4 %	≥6.5%

Etiological classification of Diabetes mellitus:

1. Type 1 diabetes (Immune mediated / idiopathic),
2. Type 2 diabetes (Insulin resistance/ Insulin deficiency),
3. Other specific types of diabetes- Genetic defects of beta cell development or function, genetic defects in insulin action, disease of exocrine pancreas, Endocrinopathies, Drug or chemical induced, infections and other genetic syndromes.
4. Gestational diabetes mellitus.

Diabetes related complications:

Microvascular:

1. Eye disease Retinopathy, Macular edema.
2. Neuropathy
   Sensory and motor (mono- and polyneuropathy), Autonomic.

Nephropathy
Albuminuria,
Declining renal function.

Macrovascular:

1. Coronary heart disease,
2. Peripheral arterial disease,
3. Cerebrovascular disease.

Other

1. Gastrointestinal (gastroparesis, diarrhea)
2. Dermatologic
3. Genitourinary (uropathy/sexual dysfunction)
4. Infectious,
5. Cataracts,
6. Cherioarthropathy.
7. Glaucoma,
8. Hearing loss,
9. Periodontal disease,
10. Obstructive sleep apnea,
11. Fatty liver disease,
12. Osteoporosis,
13. Depression.

Acute complications of diabetes mellitus:

1. DKA
Relative or absolute insulin deficiency, Counter regulatory hormone xcess.
2. Hyperglycemic Hyperosmolar state (HHS) Relative insulin deficiency, Inadequate fluid intake.
Compared with DKA, patients with HHS has lower levels of counter regulatory hormones.

Metabolic syndrome:

(Syndrome X / insulin resistance syndrome)
Main underlying pathology of metabolic syndrome is insulin resistance. Metabolic syndrome is clustering of risk factors of cardiovascular disease including

1. Central obesity,
2. Hypertension,
3. High triglycerides,
4. Low HDL levels.

Metabolic syndrome affects around 25 % of adult population. They have two fold higher risk of death from cardiovascular disease and three fold from stroke. Risk of developing type 2 DM is fivefold compared to general population. They are also increased risk of

1. Fatty liver disease,
2. Hepatocellular carcinoma,
3. Intrahepatic cholangiocarcinoma,
4. Chronic kidney disease,
5. Polycystic ovary syndrome,
6. Obstructive sleep apnea,
7. Hyperuricemia and gout

There are five definitions for the MS. Most commonly used are

1. National cholesterol education program (NCEP/ATPIII),
2. International Diabetes Federation (IDF). NCEP:ATPIII 2001 Three or more of the following

1.	Central	obesity:	waist	>102 cm (Male)
	circumference			>88cm (Female)
2.	Triglyceride level			≥150 mg/dl
	Or specific medication			
3.	HDL			<40 mg/dl (Male)
	Or specific medication			<50 mg/dl (Female)
4.	Hypertension			SBP ≥ 130 mmHg
	Or specific medication			DBP ≥ 85 mmHg
5.	Fasting plasma glucose			≥ 100 mg/dl
	Or specific medication Or			
previously diagnosed type 2 DM				
			34	

1. A study was conducted by Karin L.G. Svenson et al., at 1988 in 14 untreated active rheumatoid arthritis patients. Compared with healthy controls, the patients had impaired glucose handling and enhanced insulin response ($p< 0.01$). Impaired glucose handling is found to be due to insulin resistance. Normalization of inflammatory activity with treatment improved insulin resistance and normalized glucose metabolism (15).
2. A study was conducted in Sweden at 1987 in the department of general medicine by Karin L.G. Svenson in 45 untreated rheumatoid arthritis patients. In the patient group, the basal serum insulin concentration ($p< 0.001$) and the maximum insulin response to glucose loading ($p<.01$) were significantly higher. The rine output of cortisol and catecholamines was normal. So stress reaction can't be reason for impaired glucose metabolism (16).
3. A study was conducted by Lundqvist at 1987 in 42 patients with RA. Changes in glucose metabolism was monitored after institution of antirheumatic therapies. A reversal of glucose handling to normal was observed in patients treated with prednisolone 20 mg daily ($n=16$, $p<.001$), chloroquine ($n=7$), penicillamine ($n=4$), Azathioprine and cyclophosphamide ($n=7$) (17).
4. A study was conducted in South Africa at 2005 by Patrick H. Dessein et al., to identify factors that regulate glucose metabolism in RA patients. Insulin resistance and beta cell function is assessed in 94 RA patients. More insulin resistance is seen in patients with high grade inflammation (hsCRP > 1.92 mg/ liter) than low grade inflammation. Predictors of insulin resistance are abdominal obesity and disease activity. Disease activity and age is associated with impaired beta cell function. The cumulative use of glucocorticoids and ACE inhibitors or ARB was associated with enhanced beta cell function (18).
5. A study was conducted in 2002 by Sharma et al., effect of ACE inhibitors / ARBs in the prevention of Type 2 DM. Differentiation of adipocytes may be promoted by blockade of renin-angiotensin system which may be result in improved insulin activity. Decreased storage of excess calories in the pancreas reduce lipotoxicity which improves insulin secretion (20).

6. A study was conducted by V. R. Da Cunha et al., in 2012 which includes 283 patients and 226 controls. Metabolic syndrome is seen in 39% of RA patients (p<.001). Metabolic syndrome is seen only in 19% of controls.
   When compared with controls increased prevalence of elevated blood sugar, waist circumference, and fasting blood sugar is seen in RA patients. RA
   patients with MS has significantly high DAS-28 score (3.59±1.27 versus
   3.14±1.53 p=.01) than those without MS (21).
7. A study was conducted in 2011 by C. S. Crowson et al., which includes 1214 non RA patients without CV disease and 232 RA patients without overt CV disease. MS, elevated blood pressure and waist circumference is significantly higher in RA patients (22).
8. In 2009 study was conducted in 400 RA patients by T. E. Toms et al., controlling of inflammation with methotrexate therapy was independently associated with reduced with risk to suffer MS. Prevalence of MS in 398 RA patients is 40.1% (23).
9. A study conducted by Chung et al., in 154 RA patients and 85 controls, increased risk of having higher coronary artery calcification score is seen in RA patients with MS (24).
10. Seriolo et al., conducted a study in 38 RA patients during follow up 24 of week improvement in HOMA / QUICKI seen in patients treated with Etanercept / Infliximab (25).
11. A study conducted by Tam et al., in 2007 in 19 RA patients treatment with Infliximab improves insulin sensitivity and lipid profile (26).

Treatment of rheumatoid arthritis:
Drugs used in the treatment of RA are
1. NSAIDs,
2. Glucocorticoids,
3. Conventional DMARDs
4. Biological DMARDs.

Anti-tnf agents:
1. The benefits of treatment with TNFα antagonists as a class appear to extend beyond control of joint disease activity.
2. With prolonged anti-TNF treatment the partial restoration of metabolic function and alleviation of IR are becoming increasingly evident (27) (28).

Classical drugs are infliximab, Etanercept, Adalimumab.
Anti-TNF therapy carries risk of reactivation of latent TB, bacterial and fungal infections.

Anakinra:
The recombinant form of the naturally occurring IL-1 receptor antagonist. Due to high rate of serious infections it should not be combined with an anti-TNF drug.

Abatacept:
- It inhibits the co-stimulation of T cells by blocking CD28-CD80/86 interactions.
- It also inhibit the function of antigen-presenting cells by reverse signaling through CD80 and CD86.

Rituximab:
- Chimeric monoclonal antibody directed against CD20.
- It carries risk of progressive multifocal leukoencephalopathy.

Tocilizumab:
- Humanized monoclonal antibody directed against soluble and membrane forms of IL-6 receptor.

Tofacitinib:
- Small-molecule inhibitor that primarily inhibits JAK1 AND JAK3.

Materials and methods:
Study population:
This study is to be conducted in 50 newly detected Rheumatoid arthritis patients
attending Rheumatology CLINIC at Govt Rajaji hospital, Madurai.

Inclusion criteria:
Newly detected Rheumatoid arthritis patients according to ACR-EULAR criteria 2010 not on treatment.

Exclusion criteria:
Patients with
1. Previously known Diabetic patients
2. Family H/o DM
3. Patients on drugs impairing glucose metabolism
4. Conditions associated with impaired glucose tolerance such as

- Endocrinopathies
- Disease of exocrine pancreas
- Infections
- Genetics syndromes like Down's syndrome, Turner's syndrome

Increased prevalence of Impaired Glucose metabolism in patients with newly detected Rheumatoid arthritis.

The following information collected from patients who attended the Rheumatologic clinic for Rheumatoid arthritis in the form of Age, Sex, H/O Diabetes, Family H/O Diabetes, Duration of symptoms, Anthropometry measurements, Biochemical parameters [Rheumatoid factor, ESR, CRP], Complication of Rheumatoid arthritis.

I excluded the patient with Family H/O diabetes, H/O overt diabetes, those on drugs impairing glucose metabolism, those on treatment for Rheumatoid arthritis and conditions associated with impaired glucose metabolism.

Random blood glucose, fasting plasma glucose, 2-hours plasma glucose in OGTT, urine sugar and fasting lipid profile is done in all patients.
NCEP:ATPIII 2001 criteria is used to define metabolic syndrome.
ADA, 2014 guidelines is used to define pre-diabetes and diabetes. Impaired glucose metabolism includes both pre-diabetic and diabetic.

Laboratory investigations Random blood glucose Fasting plasma glucose Two-hours plasma glucose in ogtt rine sugar Fasting lipid profile Erythrocyte sedimentation rate C- reactive protein Rheumatoid factor Design of study:
Observational study.

Period of study:
4 months (june 2015 to september 2015)

Collaborating departments:
Department of Pathology
Department of Biochemistry
Department of Microbiology
Ethical clearance: obtained
Consent: individual written and informed consent.
Analysis: statistical analysis.- chi square
Conflict of interest: nil
Financial support: nil
Participants:
50 newly detected Rheumatoid arthritis patients attending Rheumatology clinic at Govt Rajaji hospital, Madurai.

IV. Statistical metthods:

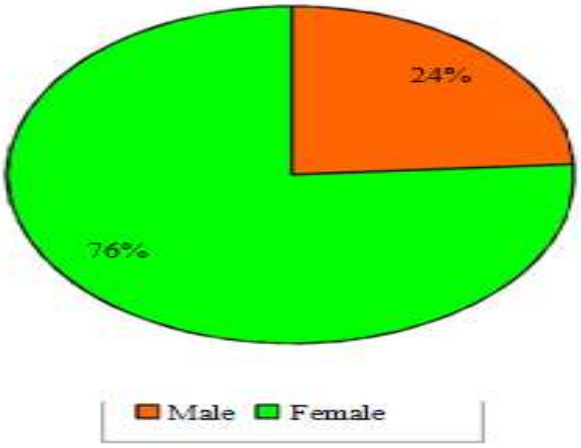
The data collected during the study was formulated into a master chart in Microsoft office excel and statistical analysis was done with help of computer using statistical software package SPSS V.17 for windows.
Using this software, frequencies, range, mean, standard deviation and 'p 'were calculated through Student 't' test, One way ANOVA, Pearson Correlation and Chi square test . P value of < 0.05 was taken as significant.

V. Results

Gender Distribution Of Ra

Gender	No of cases	Percentage
Male	12	24
Female	38	76
Total	50	100

Gender Distribution Of Ra



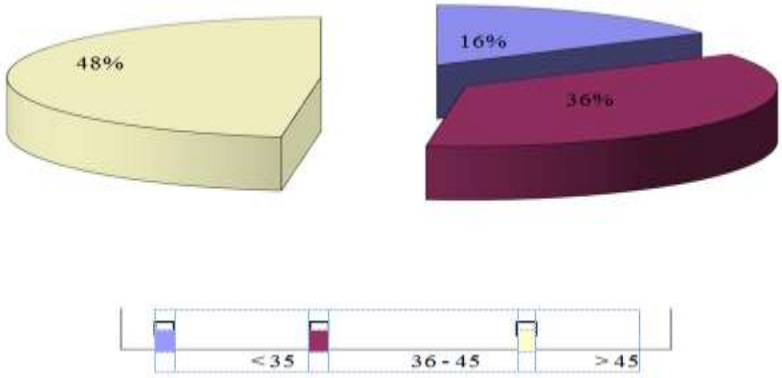
In our study, male constituted nearly 24% (n=12) and female 76% (n=38).

This study shows RA is more common in female than in male ($p<0.001$) which is statistically significant. Female to male ratio is 3:1.

Age Distribution Of Ra

Age in years		Frequency	Percentage
<	35	8	16
36 - 45		18	36
>	45	24	48
Total		50	100

Age Distribution Of Ra



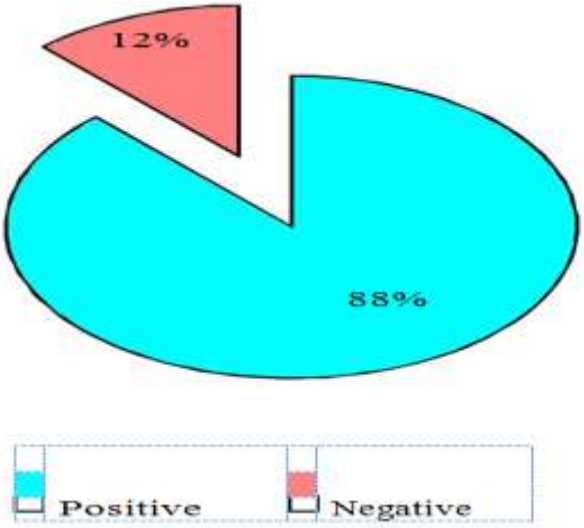
In our study among 50 patients, 16% (n=8) of patients were less than 35 years, 36 % (n=18) of patients are between 36-45 years and 48% (n=24) of patients are >45 years. It shows that incidence of RA increasing with age. Majority of patients were above 45 years.

Age (years)

Rheumatoid Factor

Rheumatoid factor	Frequency	Percentage
Positive	44	88
Negative	6	12
Total	50	100

Rheumatoid Factor

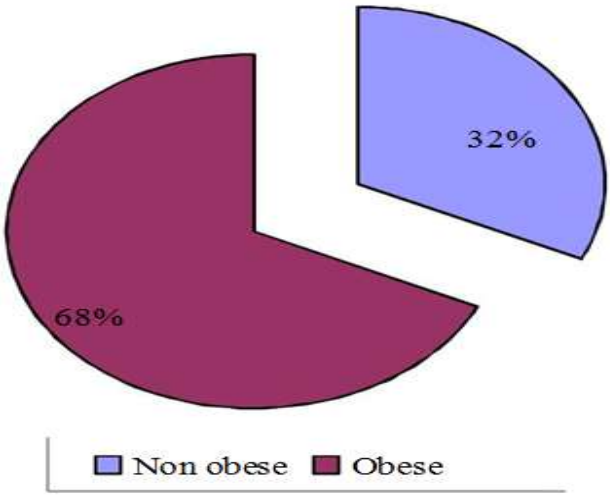


In our study among 50 patients, 88% (n=44) of patients were Rheumatoid factor positive and 12 % (n=6) of patients were Rheumatoid factor negative. So sensitivity of Rheumatoid factor in our study is 88%. Most patients were RF positive which is statistically significant (p<0.001).

Obesity In Ra Patients

Obesity	Frequency	Percentage
Non obese	16	32
Obese	34	68
Total	50	100

Obesity

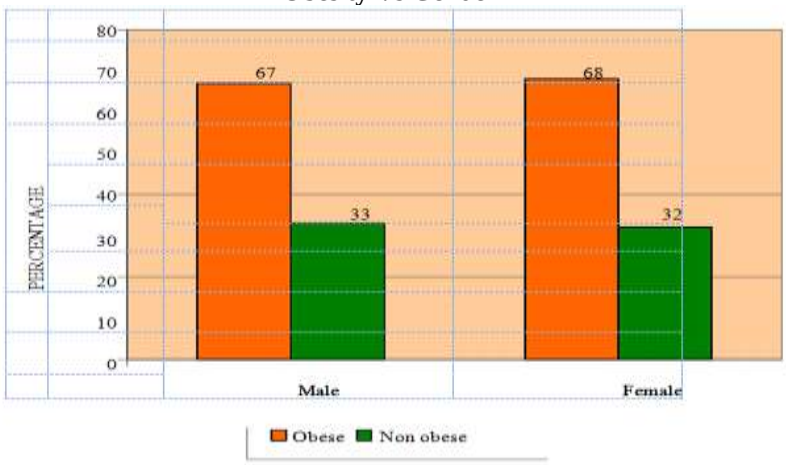


In our study, 68 % (n=34) of patients were obese (p<0.005) and 32 % (n=16) of patients were non obese. Hence statistically significant number of RA patients had central obesity.

Gender Distribution Of Obesity

BESITY VS				
GENDER	FREQUENCY		PERCENTAGE	
	MALE	FEMALE	MALE	FEMALE
OBESE	8	26	67	68
NON OBESE	4	12	33	32
TOTAL	12	38	100	100

Obesity Vs Gender



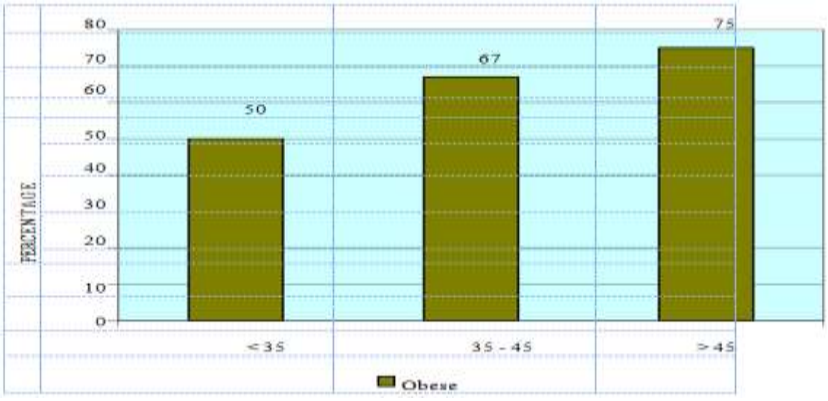
In our study among 12 male patients, 67 % (n=8) male were obese and among 38 female patients, 68 % (n=26) were obese. Both male (p<0.008) and female (p<0.005) RA patients had significant obesity. Female Patients had slightly high prevalence of obesity.

Age Distribution Of Obesity

OBESITY VS							
AGE		FREQUENCY				PERCENTAGE	
						35-45	
	< 35	35 – 45	> 45	< 35		YERAS	>45
	YEARS	YEARS	YEARS	YEARS			YEARS
OBESE	4	12	18	50		67	75
NON OBESE	4	6	6	50		33	25
TOTAL	8	18	24	100		100	100

In our study among 8 patients less than 35 years, 50 % (n=4) of patients were obese and among 18 patients between 35-45 years, 67 % (n=12) of patients were obese. Among 24 patients greater than 45 years, 75 % (n=18) of patients were obese. Patients in the age group of 35-45 years (p<0.008) and >45 years (p<0.001) had significant obesity. Prevalence of obesity is increasing with age

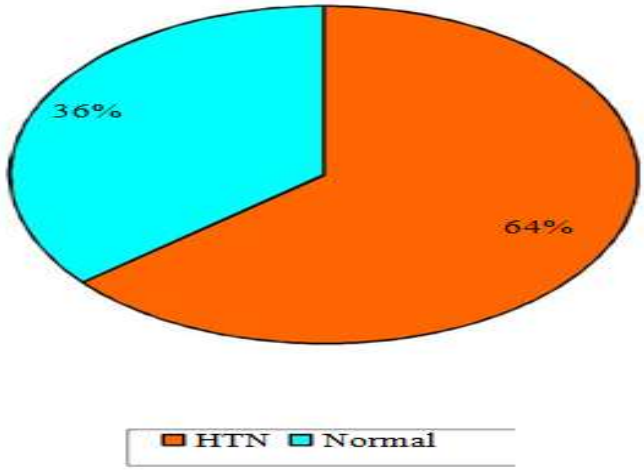
Obesity Vs Age



Hypertension In Ra

HYPERTENSION	FREQUENCY	PERCENTAGE
YES	32	64
NO	18	36
Total	50	100

Hypertension



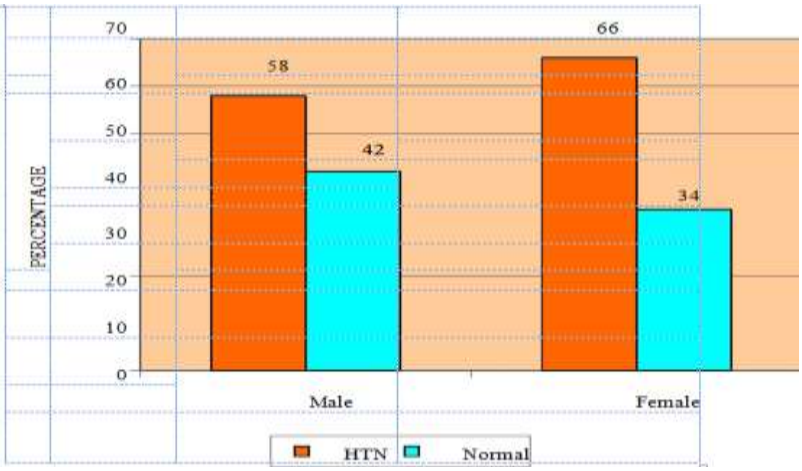
In our study among 50 patients, 64 % (n=32) of patients were hypertensive and 36 % (n=18) of patients were normotensive. Significant number of RA patients were hypertensive (p<0.030).

Gender Distribution Of Hypertension

HYPERTENSION	FREQUENCY		PERCENTAGE	
			Male	Female
	Male	Female		
YES	7	25	58	66
NO	5	13	42	34
Total	12	38	100	100

In our study among 12 males, 58 % (n=7) of males were hypertensive and among 38 females, 66 % (n=25) were hypertensive. More number of female patients (p<0.030) were hypertensive compared to male patients.

Htn Vs Gender

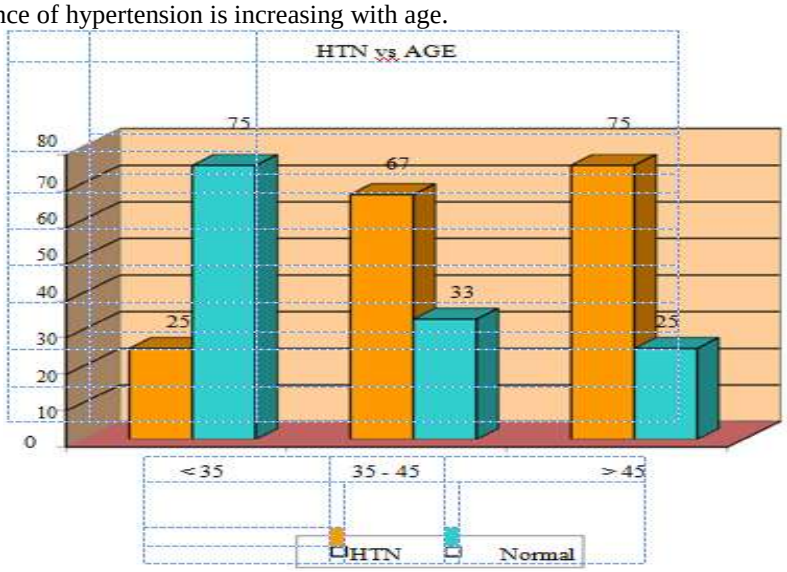


Age Distribution Of Hypertension In Ra

HTN vs Age		FREQUENCY				PERCENTAGE	
	< 35	35 - 45	> 45	<35	35-45	>45	
HTN	2	12	18	25	67	75	
Normal	6	6	6	75	33	25	
Total	8	18	24	100	100	100	

In our study among 18 patients who were aged between 35-45 years, 67 % (n=12) were hypertensive (p<0.008) and among 24 patients who were aged >45 years, 75% (n=18) were hypertensive. Both were

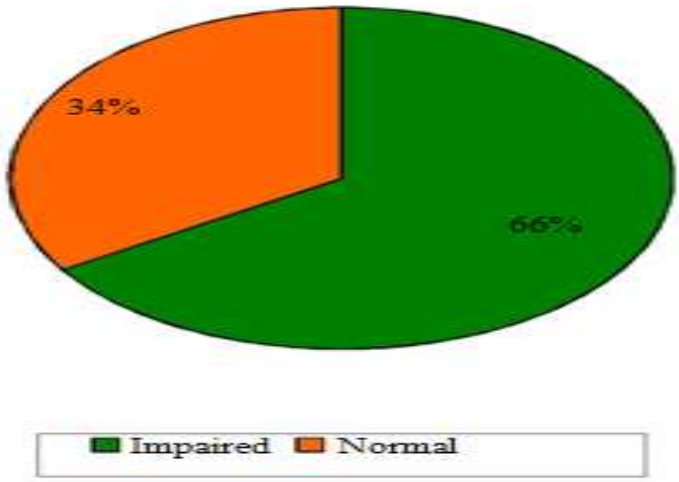
significant. Compared with patients < 35 years, hypertension was more prevalent in patients aged >45 years (p<0.001). Prevalence of hypertension is increasing with age.



Impaired Glucose Metabolism (Pre-Diabetes And Diabetes) In Ra

Glucose metabolism	FREQUCENCY	PERCENTAGE
Normal	17	34
Impaired	33	66
Total	50	100

Glucose Metabolism



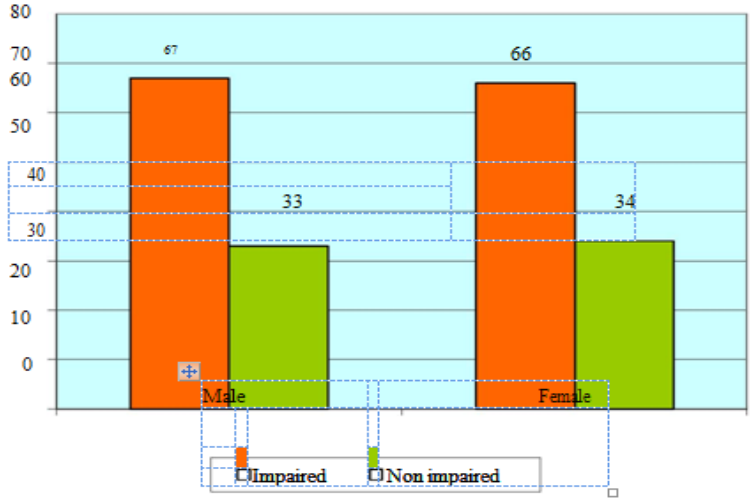
In our study 66 % (n=33) of patients had impaired glucose metabolism and 34 % (n=17) of patients had normal glucose metabolism. Impaired glucose metabolism is statistically significant (p<0.012).

Gender Distribution Of Impaired Glucose Metabolism In Ra

IMPAIRED				
GLUCOSE				
METABOLISM VS				
GENDER	FREQUENCY		PERCENTAGE	
	Male	Female	Male	Female
Impaired	8	25	67	66
Normal	4	13	33	34
Total	12	38	100	100

In our study out of 12 males, 8 (67%) had impaired glucose metabolism and out of 38 females, 25 (66%) had impaired glucose metabolism. Both male ($p<0.008$) and female ($p<0.012$) patients had significant impaired glucose metabolism.

Impaired Glucose Metabolism Vs Gender

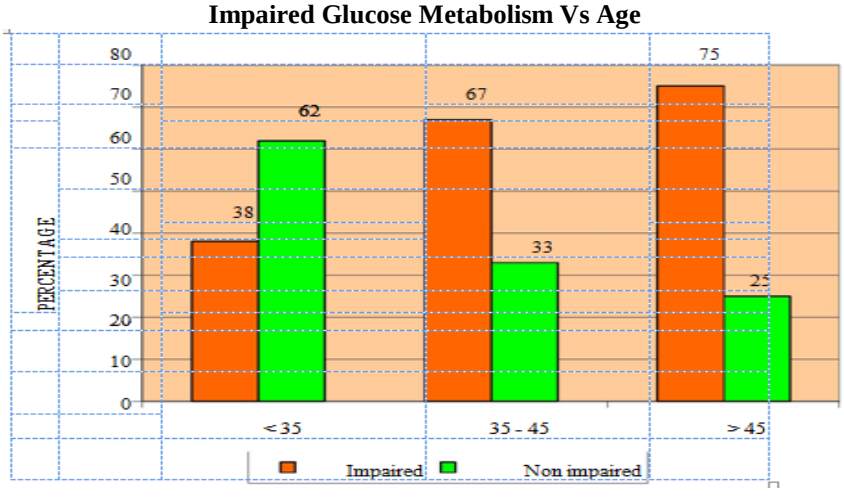


Age Distribution Of Impaired Glucose Metabolism In Ra

IMPAIRED GLUCOSE METABOLISM VS AGE	FREQUENCY			PERCENTAGE		
	< 35	35 - 45	> 45	<35	35-45	>45
Impaired	3	12	18	38	67	75
Normal	5	6	6	62	33	25
Total	8	18	24	100	100	100

In our study out of 8 males aged < 35 years, 3 (38%) had impaired glucose metabolism and out of 18 males aged 35-45 years, 12 (67%) had significant impaired glucose metabolism ($p<0.008$). Out 24 patients (age >45 years), 18 (75%) had impaired glucose metabolism which is statistically significant ($p<0.001$). Compared with patients aged <35 (38%), patients with age >45 years had significant impaired glucose metabolism ($p<0.008$) which shows that prevalence of impaired glucose metabolism increasing with age.

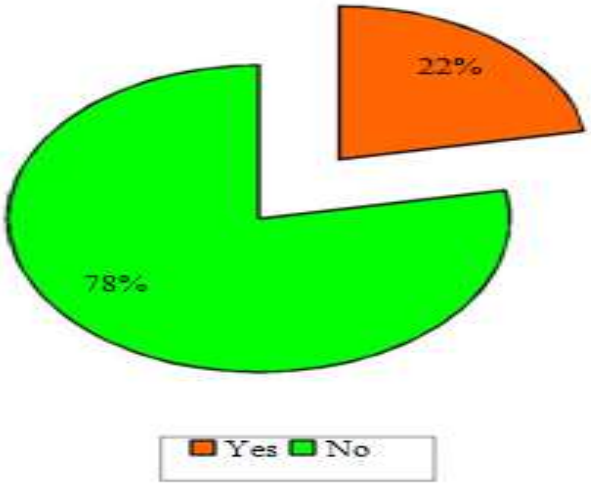
Impaired Glucose Metabolism Vs Age



Frank Diabetes In Ra

Diabetes	FREQUENCY	PERCENTAGE
Yes	11	22
No	39	78
Total	50	100

Diabetes

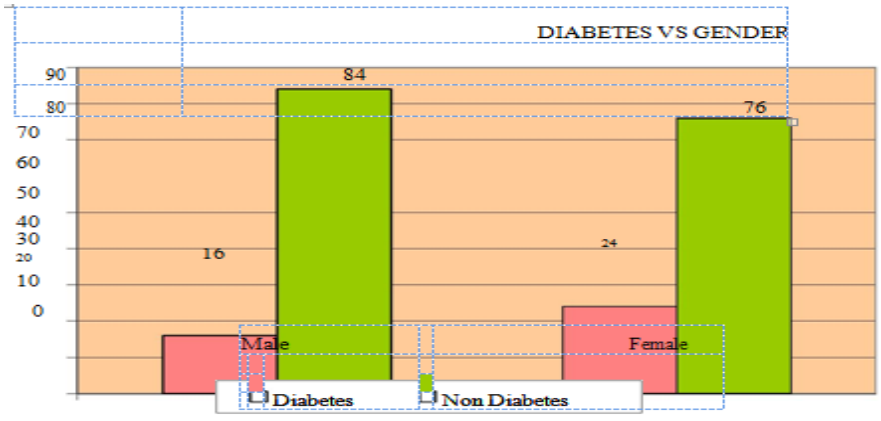


In our study 11(22%) had diabetes out of 50 patients. Among 66% of patients with impaired glucose metabolism (pre-diabetes and diabetes), frank diabetes contributed 22%. Statistically it is not significant.

Gender Distribution Of Diabetes In Ra

DIABETES VS			PERCENTAGE	
GENDER	FREQUENCY			
	Male	Female	Male	Female
Diabetic	2	9	16	24
Non Diabetic	10	29	84	76
Total	12	38	100	100

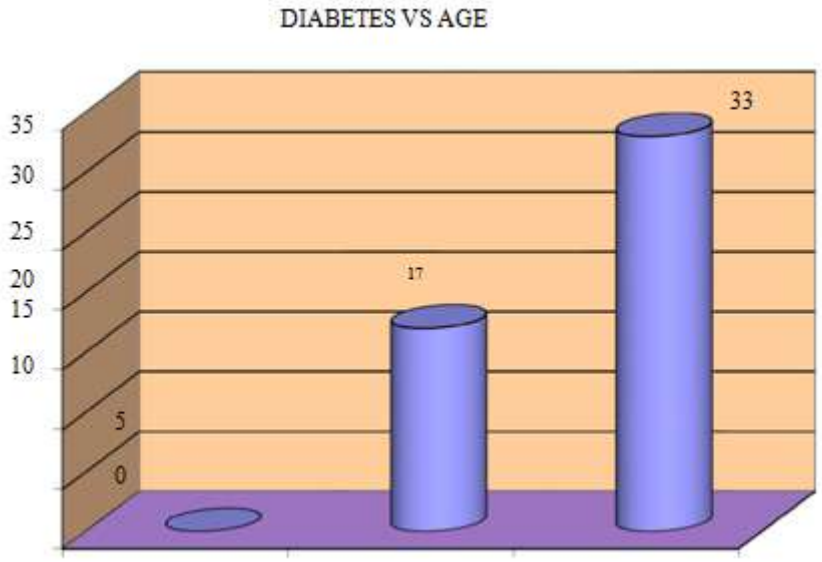
In our study 2 (16%) males had diabetes out of 12 and 12 (24%) females had diabetes out of 38. Prevalence of diabetes is higher in female RA patients.



Age Distribution Of Diabetes In Ra

DIABETES VS										
AGE		FREQUENCY				PERCENTAGE				
	< 35		35 - 45		> 45	<35		35-45		>45
Diabetic	0		3		8	0		17		33
Non Diabetic	8		15		16	100		83		67
Total	8		18		24	100		100		100

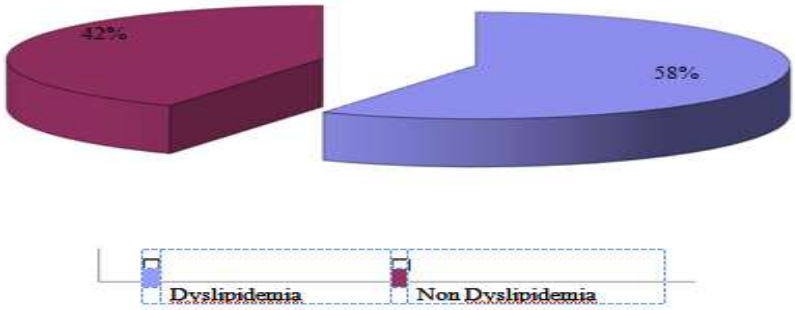
In our study 3 (17%) out of 18 had diabetes in the age group of 35-45 years and 8 (33%) out 24 had diabetes in the age group >45 years. Prevalence of diabetes is higher in the patients aged >45 years but it is not statistically significant.



Dyslipidemia In Ra Patients

DYSLIPIDEMIA	FREQUENCY	PERCENTAGE
YES	29	58
NO	21	42
Total	50	100

Dyslipidemia

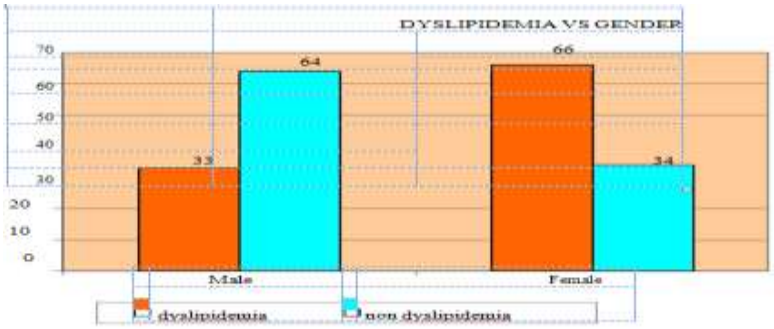


In our study 29 (58%) out of 50 patients had dyslipidemia. Though significant number of patients had dyslipidemia P value is <0.236 (statistically not significant).

Gender distribution of dyslipidemia in ra patients.

DYSLIPIDEMIA VS				
GENDER	FREQUENCY		PERCENTAGE	
	Male	Female	Male	Female
Dyslipidemia	4	25	33	66
Non Dyslipidemia	8	13	67	34
Total	12	38	100	100

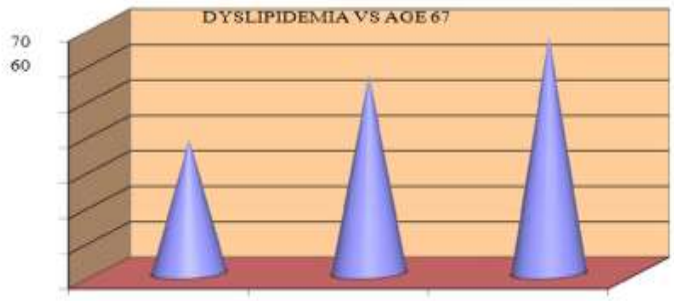
In our study 4 (33%) out of 12 male patients had dyslipidemia and 25 (66%) out of 38 female patients had dyslipidemia. Compared with male, prevalence of dyslipidemia is higher in female patients (p<0.012 significant).



Age distribution of dyslipidemia in ra patients.

DYSLIPIDEMIA VS AGE	FREQUENCY			PERCENTAGE		
	< 35	35 - 45	> 45	<35	35-45	>45
Yes	3	10	16	38	56	67
No	5	8	8	62	44	33
Total	8	18	24	100	100	100

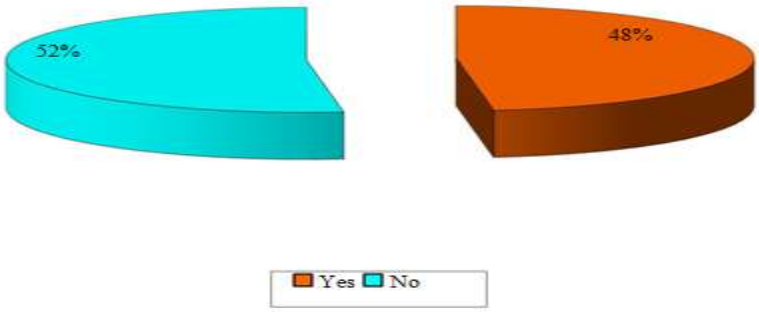
In our study 3 (38%) out of 8 patients in the age group of <35 years had dyslipidemia and 10 (56%) out of 18 patients in the age group of 35-45 years had dyslipidemia. In the age group of > 45 years 16 (67%) out of 24 patients had dyslipidemia. Prevalence of dyslipidemia is increasing with age with maximum incidence in patients >45 years (p<0.047 significant).



Metabolic Syndrome In Ra

Metabolic syndrome	Frequency	Percentage
Yes	24	48
No	26	52
Total	50	100

Metabolic Syndrome



In our study 24 (48%) out of 50 patients had metabolic syndrome according to NCEP:ATP III 2001 but P value is <0.838 (not significant).

Gender Distribution Of Metabolic Syndrome

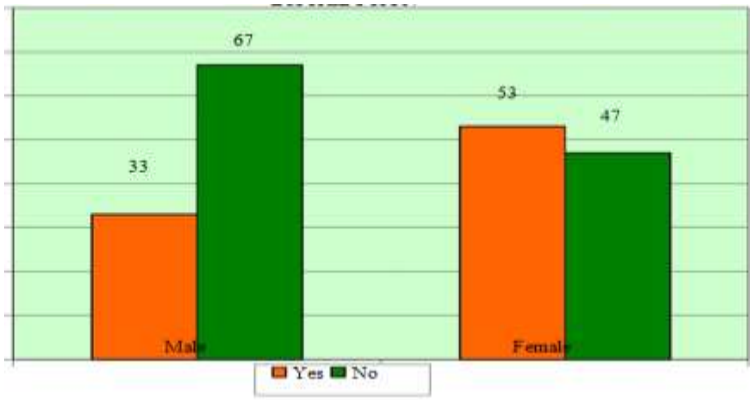
METABOLIC SYNDROME VS GENDER	FREQUENCY		PERCENTAGE	

	Male	Female	Male	Female
Yes	4	20	33	53
No	8	18	67	47
Total	12	38	100	100

In our study 4 (33%) out of 12 male patients full filled the criteria for metabolic syndrome and in female patients 20 (53%) out of 38 full filled the criteria for metabolic syndrome. Female patients had higher prevalence of metabolic syndrome but it is not significant statistically.

Metabolic Syndrome Vs Gender

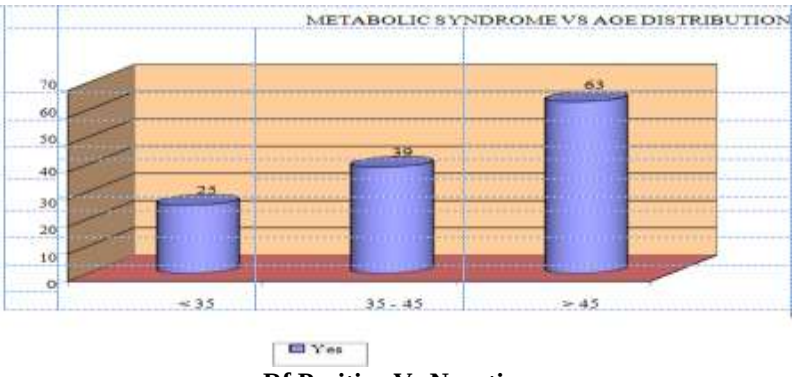
Distribution



Age Distribution Of Metabolic Syndrome In Ra

METABOLIC SYNDROME VS AGE		FREQUENCY			PERCENTAGE		
	< 35	35 - 45	> 45	<35	35-45	>45
Yes	2	7	15	25	39	63
No	6	11	9	75	61	37
Total	8	18	24	100	100	100

In our study 7 (39%) out of 18 patients full filled the criteria for metabolic syndrome in the age group of 35-45 years and 15 (63%) out of 24 patients full filled the criteria for metabolic syndrome in the age group of >45 years (p<0.045 significant). Increasing age is found to be risk factor for metabolic syndrome.



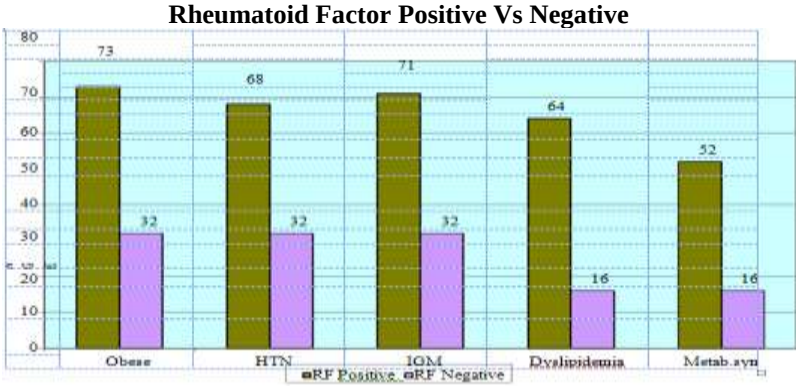
Rf Positive Vs Negative

	Obese	HTN	IGM	Dyslipidemia	Metab.syn	TOTAL
RF			31			
Positive	32 (73%)	30 (68%)	(71%)	28 (64%)	23 (52%)	44
RF						
Negative	2 (32%)	2 (32%)	2 (32%)	1 (16%)	1 (16%)	6

In our study 73 % of RF positive patients had obesity and 32 % of RF negative patients had obesity (P<0.002 significant). 68 % of RF positive patients were hypertensive (P<0.005 significant) and 32 % of RF negative patients were hypertensive. 71 % of RF positive patients had impaired glucose metabolism (P<0.002 significant) and 32 % of RF negative patients had impaired glucose metabolism. Dyslipidemia was seen 64 % of RF positive (P<0.001 significant) and 16% of RF negative patients. Criteria for metabolic syndrome was full

filled by 52 % of RF positive (P<0.001) and 16 % RF negative patients. Patients with RF positive had higher prevalence of obesity, hypertension, impaired glucose metabolism, dyslipidemia and metabolic syndrome and carries poor prognosis.

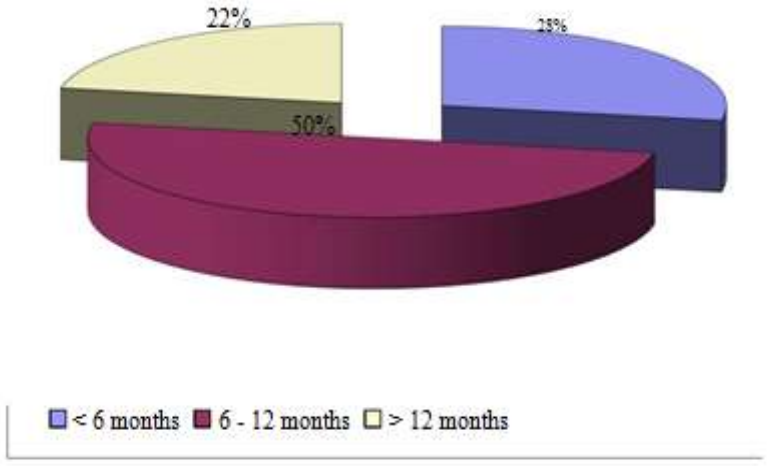
Rheumatoid Factor Positive Vs Negative



Duration Of Symptoms In Ra

Duration of Symptoms		Frequency	Percentage
< 6 months		14	28
6 - 12 months		25	50
> 12 months		11	22
Total		50	100

Duration Of Symptoms



In our study group 28 % (n=14) of patients had duration of symptoms < 6 months and 50 % (n=25) of patients had duration of symptoms 6 -12 months. 22 % (n=11) of patients were symptomatic > 12 months. Majority of patients were symptomatic for 6 to 12 months.

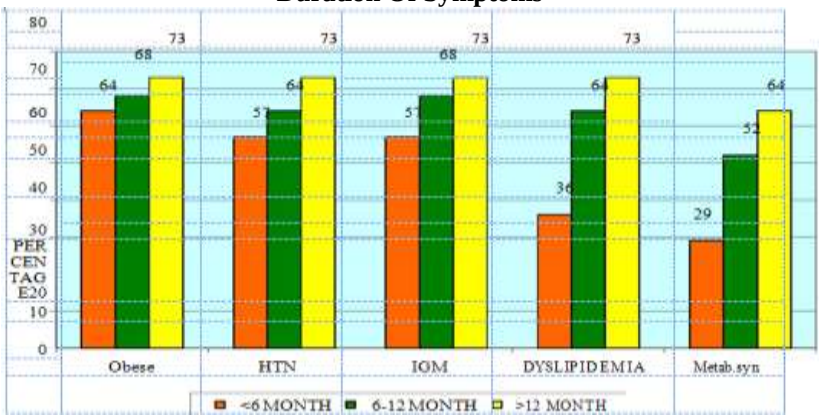
Distribution Of Duration Symprtoms

Duration of Symptoms	Obese	HTN		IGM	Dyslipidemia		Metab.syn	Total
< 6 month	9 (64%)	8 (57%)	8	(57%)	5	(36%)	4 (29%)	14
6 - 12 month	17 (68%)	16 (64%)	17 (68%)		16 (64%)		13 (52%)	25
> 12 month	8 (73%)	8 (73%)	8	(73%)	8	(73%)	7 (64%)	11
Total	34 (100%)	32 (100%)	24	(100%)	22	(100%)	20 (100%)	50

In our study patients who were symptomatic for less than 6 months had prevalence of obesity- 64% (P<0.045 significant), hypertension-57%, impaired glucose metabolism-57%, dyslipidemia-36% and metabolic syndrome-29%. Patients with symptoms 6-12 month had prevalence of obesity-68% (P<0.008 significant),

hypertension-64% (p<0.045), impaired glucose metabolism-68% (P<0.008), dyslipidemia-64% (P<0.045) and metabolic syndrome-52%. Patients with symptoms >12 months had prevalence of statistically significant obesity-73% (p<0.002 significant), hypertension-73% (p<0.002), impaired glucose metabolism-73% (p<0.002), dyslipidemia-73% (P<0.002) and metabolic syndrome-64% (P<0.045 significant). Patient with long standing symptoms have more co-morbid illness.

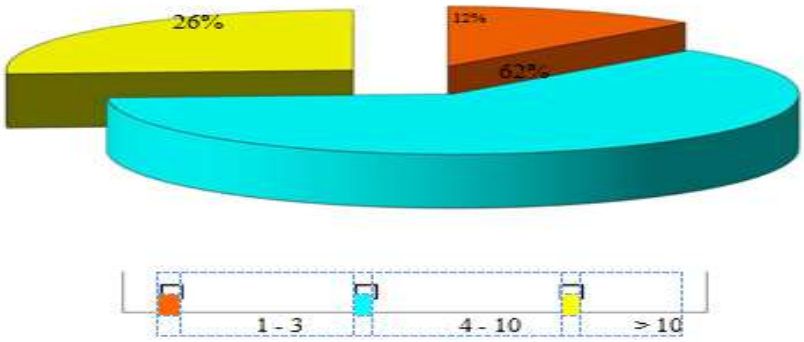
Duration Of Symptoms



Small Joint Involvemant In Ra

SMALL JOINT INVOLVEMENT	FREQUENCY	Percentage
1 - 3	6	12
4 - 10	31	62
> 10	13	26
Total	50	100

Joint Involvement



In our study 26 % (n=13) patients had involvement of 1-3 small joints, 62% (n=31) of patients had 4-10 and 12 % (n=6) have > 10 small joint involvement.

Joint Involvement Vs Co-Morbid Illness

JOINT INVOLVEMENT	Obese	HTN	IGM	Dyslipidemia		Metab.syn		Total
1 - 3	3 (50%)	2 (33%)	3 (50%)	2	(33%)	1	(17%)	6
4 - 10	21 (68%)	20 (65%)	20 (65%)	18 (58%)		14 (45%)		31
> 10	10 (77%)	10 (77%)	10 (77%)	9	(69%)	9	(69%)	13
Total	34 (100%)	32 (100%)	33 (100%)	29	(100%)	24	(100%)	50

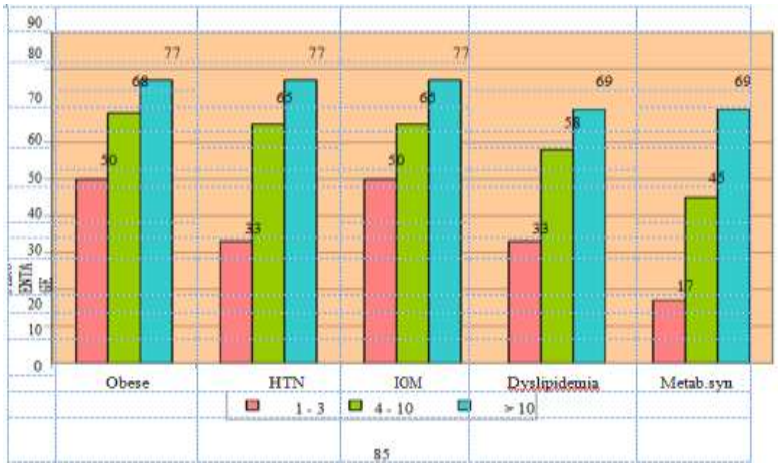
In our study out of 6 patients with involvement of 1-3 small joint involvement, obesity and impaired glucose metabolism were seen in 3 patients. 2 patients had hypertension and dyslipidemia. Metabolic syndrome was seen in one patients.

In patients with involvement of 4-10 small joint out (n=31), 65% of patients had impaired glucose metabolism and hypertensive (p<0.023 significant). Obesity was seen 68% of patients (p<0.008 significant). Dyslipidemia and metabolic syndrome was seen 58%, 45% of patients respectively.

Out of 13 patients with involvement of >10 small joint, 77 % of patients had hypertension, impaired glucose metabolism and obesity (p<0.001 significant). 69% of patients have dyslipidemia and metabolic syndrome (p<0.08 significant).

So patients with more number of joint involvement and increasing disease activity are prone to impaired glucose metabolism, hypertension and metabolic syndrome. Hence it is important to treat the disease in early stage.

Joint Involvement



IV. IV. Discussion

The study was conducted in the patients who attended Rheumatologic clinic, Govt Rajaji hospital, Madurai. Diagnosis of Rheumatoid arthritis was made according to ACR-EULAR 2010 criteria. Only new diagnosed treatment naïve patients were included in this study. After applying exclusion criteria 50 patients were selected for study.

Out of 50 patients 38 patients were female and 12 patients were male (3:1). It is consistent with previous studies because autoimmune nature of disease RA is more common female.

Rheumatoid factor was positive in 44 patients and negative in 6 patients. Sensitivity of Rheumatoid factor was 88% (p<0.001 significant). Negative test for Rheumatoid factor doesn't rule out diagnosis of Rheumatoid arthritis because diagnostic sensitivity of RF is around 80% only.

Out of 50 patients 8 patients were <35 years, 18 patients 35-45 years and 24 patients >45 years. Mean age of patient in this study was 42.06 years. With increasing age prevalence of RA was increasing.

As like previous studies conducted by Roubenoff and colleagues, central obesity was seen in 68% of patients which statistically significant (p<0.005 significant). In our study women were more prone for central obesity (Rheumatoid cachexia). It is consistent with previous studies like conducted by Giles et al., . Prevalence of obesity was increasing with increasing age, long duration of symptoms, more number of joint involvement and high degree of inflammation. Because central obesity one of the key factor responsible for insulin resistance early diagnosis of RA and introduction of treatment is important to control inflammation. Controlling of inflammation improves obesity.

In our study 66% of patients had impaired glucose metabolism which was statistically significant (p<0.012). Out of 66% of patients with impaired glucose metabolism (pre-diabetes and diabetes), 22 % of patients had frank diabetes. As we knew from previous studies like conducted by Patrick H. Dessein et al., age, high grade inflammation and long duration of disease are important risk factor for impaired glucose metabolism. In our study also impaired glucose metabolism was more prevalent with increasing age (>45 years 75%), long duration of disease (>12 months 73%) and high grade of inflammation (>10 small joint involvement 77%) which is consistent with previous studies. By controlling inflammation with early diagnosis and introduction of treatment we can improve impaired glucose metabolism.

In our study hypertension was seen 64 % of patients (p<0.030 significant) which is consistent with previous studies like conducted by Dessein et al., . In previous studies like conducted by chung et al., reported presence of metabolic syndrome in

42 % patients with long standing disease. In our study also dyslipidemia and metabolic syndrome was seen in 58 % and 48 % of patients respectively which is consistent with previous studies.. All these risk factors for cardiovascular disease was seen in patients with long standing disease and high grade inflammation.

In our study compared with Rheumatoid factor negative patients, patients with Rheumatoid factor positive were more prone to impaired glucose metabolism, hypertension and metabolic syndrome. Hence patients with Rheumatoid factor positive were more prone to cardiovascular disease.

V. Limitation

- Sample size is small.
- The study population involved patients seeking medical care in our hospital which is a tertiary care center and hence they may not represent the general population.

VI. Conclusion

In our study obesity, impaired glucose metabolism, hypertension, dyslipidemia and metabolic syndrome were seen in 68 %, 66 %, 64 %, 58 % and 48 % of patients respectively.

- Long duration of disease and disease activity is important risk of factor impaired glucose metabolism, obesity, dyslipidemia, hypertension and metabolic syndrome.
- Impaired glucose metabolism and metabolic syndrome carries high risk of cardiovascular disease.
- Early diagnosis and early introduction of treatment will reduce disease activity and control inflammation.
- By controlling inflammation we can reduce risk of impaired glucose metabolism and metabolic syndrome.
- We can improve long term survival of Rheumatoid arthritis patients.

VII. Summary

This prospective observational study was conducted to identify the prevalence of impaired glucose metabolism and other to cardiovascular risk factors in Rheumatoid arthritis patients.

With 50 patients were selected carefully and were evaluated on clinical and laboratory aspects after institutional ethical clearance with an informed consent. The data were entered in Microsoft Excel spread sheet and analysed statistically.

Prevalence of central obesity, impaired glucose metabolism, hypertension, dyslipidemia and metabolic syndrome is seen 68 %, 66 %, 64 %, 58 % and 48% of newly detected treatment naive Rheumatoid arthritis patients.

Age, disease activity and duration of disease is found to be important key factor in induction of impaired glucose metabolism and other cardiovascular risk factors.

In our study many of the patients are diagnosed after one year of symptoms. Hence early diagnosis is important to prevent this cardiovascular risk factors. Because disease activity correlate with cardiovascular risk factors early control of disease activity is important. atient with obesity shows poor response to Anti- TNF agents. So measures to reduce to obesity like exercise should be considered along with DMARDs.

So with early diagnosis and early introduction of treatment we can reduce the prevalence of impaired glucose metabolism, hypertension, obesity, dyslipidemia and metabolic syndrome in Rheumatoid arthritis patient. With all these measures we can reduce the risk of cardiovascular disease and improve long term survival of Rheumatoid arthritis patients.

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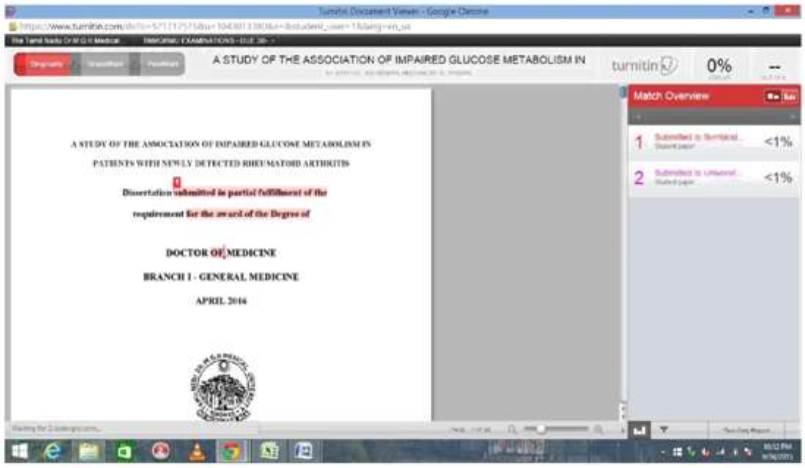
Contents

Master Chart

S.No	Sex	Age	Rf	S.Joint	Duration	Obesity	Igm	Htn	Dyslipidemia	Ms
1	Female	48	Negative	8	14	Yes	Yes	Yes	No	Yes
2	Female	48	Negative	8	15	Yes	No	Yes	No	No
3	Female	47	Negative	7	5	No	Yes	No	No	No
4	Female	47	Negative	8	16	No	No	No	Yes	No
5	Male	39	Negative	14	10	No	No	No	No	No
6	Male	48	Negative	12	10	No	No	No	No	No
7	Male	37	Positive	14	5	Yes	Yes	Yes	Yes	Yes
8	Male	38	Positive	15	14	Yes	Yes	Yes	Yes	Yes
9	Male	49	Positive	8	14	Yes	Diabetic	Yes	Yes	Yes
10	Male	49	Positive	12	8	Yes	Diabetic	Yes	Yes	Yes
11	Male	48	Positive	2	8	Yes	Yes	No	No	No
12	Male	47	Positive	8	9	Yes	Yes	No	No	No
13	Male	32	Positive	8	10	Yes	No	No	No	No
14	Male	39	Positive	9	4	Yes	No	Yes	No	No
15	Male	38	Positive	10	10	No	Yes	Yes	No	No
16	Male	39	Positive	8	11	No	Yes	Yes	No	No
17	Female	38	Positive	8	5	Yes	Yes	No	No	No
18	Female	39	Positive	9	4	Yes	Yes	No	No	No
19	Female	31	Positive	2	5	Yes	No	No	No	No
20	Female	40	Positive	2	14	No	No	No	Yes	No
21	Female	38	Positive	14	5	Yes	No	Yes	No	No
22	Female	30	Positive	8	9	No	No	No	No	No
23	Female	31	Positive	9	9	No	No	No	No	No
24	Female	47	Positive	9	4	No	No	Yes	No	No
25	Female	33	Positive	13	8	Yes	Yes	Yes	Yes	Yes
26	Female	32	Positive	14	9	Yes	Yes	Yes	Yes	Yes
27	Female	41	Positive	11	8	Yes	Diabetic	Yes	Yes	Yes
28	Female	38	Positive	13	4	Yes	Yes	Yes	Yes	Yes
29	Female	38	Positive	7	10	Yes	Yes	Yes	Yes	Yes
30	Female	37	Positive	2	11	Yes	Diabetic	Yes	Yes	Yes
31	Female	38	Positive	8	12	Yes	Diabetic	Yes	Yes	Yes
32	Female	46	Positive	9	5	Yes	Diabetic	Yes	Yes	Yes
					102					

33	FEMALE	48	POSITIVE	14	4	YES	YES	YES	YES	YES
34	FEMALE	48	POSITIVE	15	13	YES	YES	YES	YES	YES
35	FEMALE	47	POSITIVE	9	14	YES	DIABETIC	YES	YES	YES
36	FEMALE	49	POSITIVE	8	16	YES	DIABETIC	YES	YES	YES
37	FEMALE	48	POSITIVE	9	15	YES	DIABETIC	YES	YES	YES
38	FEMALE	51	POSITIVE	7	8	YES	YES	YES	YES	YES
39	FEMALE	49	POSITIVE	8	9	YES	YES	YES	YES	YES
40	FEMALE	48	POSITIVE	9	10	YES	YES	YES	YES	YES
41	FEMALE	47	POSITIVE	10	8	YES	DIABETIC	YES	YES	YES
42	FEMALE	48	POSITIVE	9	9	YES	DIABETIC	YES	YES	YES
43	FEMALE	47	POSITIVE	9	10	YES	YES	YES	YES	YES
44	FEMALE	32	POSITIVE	8	5	NO	NO	NO	YES	NO
45	FEMALE	39	POSITIVE	8	8	NO	NO	YES	YES	NO
46	FEMALE	41	POSITIVE	8	8	YES	NO	NO	YES	NO
47	FEMALE	49	POSITIVE	7	9	NO	NO	NO	YES	NO
48	FEMALE	48	POSITIVE	2	5	NO	NO	YES	NO	NO
49	FEMALE	33	POSITIVE	14	5	NO	YES	NO	NO	NO
50	FEMALE	41	POSITIVE	3	14	NO	YES	NO	NO	NO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