Global Journal of Medical Research: I
Surgeries and Cardiovascular System
Volume 16 Issue 1 Version 1.0 Year 2016
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Metabolic Syndrome in Bangladeshi Patients of Rheumatoid Arthritis

By Aziza Sultana, Saimun Naher, Md. Abu Hanifa, Bimal Chandra Roy, Md. Shafiul Alam & Prosannajid Sarkar

Rangpur Medical College Hospital, Bangladesh

Abstract- *Background:* Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown etiology, characterized by systemic symptoms that particularly involve the joints and may lead to deformities during the course of the disease. It is the most common persistent inflammatory arthritis, occurring throughout the world and in all ethnic groups.

Objectives: To find out the association of metabolic syndrome in rheumatoid arthritis patients as compared to healthy individuals.

Methods: This case control study was carried out with 50 patients of rheumatoid arthritis (case) and 50 apparently healthy individual (controls) in Biochemistry Department, Dhaka Medical College, Dhaka from July 2014 to June 2015. After overnight fast (at least 8 hrs) venous sample was taken from each subject.

Keywords: *rheumatoid arthritis, metabolic syndrome, patients, biochemistry department, bangladesh.*

GJMR-I Classification: *NLMC Code: WE 346*

Strictly as per the compliance and regulations of:

Metabolic Syndrome in Bangladeshi Patients of Rheumatoid Arthritis

Aziza Sultana [α], Saimun Naher [σ], Md. Abu Hanifa [ρ], Bimal Chandra Roy [ω], Md. Shafiul Alam [¥] & Prosannajid Sarkar [§]

Abstract- Background: Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown etiology, characterized by systemic symptoms that particularly involve the joints and may lead to deformities during the course of the disease. It is the most common persistent inflammatory arthritis, occurring throughout the world and in all ethnic groups.

Objectives: To find out the association of metabolic syndrome in rheumatoid arthritis patients as compared to healthy individuals.

Methods: This case control study was carried out with 50 patients of rheumatoid arthritis (case) and 50 apparently healthy individual (controls) in Biochemistry Department, Dhaka Medical College, Dhaka from July 2014 to June 2015. After overnight fast (at least 8 hrs) venous sample was taken from each subject. Plasma glucose, serum total cholesterol, serum triglycerides, high density lipoprotein-cholesterol was measured by enzymatic procedure and serum low density lipoprotein-cholesterol was calculated. Metabolic syndrome was diagnosed according to NCEP ATP III 2004 criteria.

Results: In this age and sex matched study metabolic syndrome was significantly more common (p =0.002) in rheumatoid arthritis patients (44%) than in controls (16%). The components of NCEP ATP III 2004 criteria for metabolic syndrome were also significantly more in rheumatoid arthritis patients than in controls-impaired fasting plasma glucose levels (66% vs 4%), central obesity (28% vs 12%), high blood pressure (68% vs 22%), high triglyceride (36% vs 6%), and low HDL-C (96% vs 66%).

Conclusion: The association of metabolic syndrome is significantly higher in patients with rheumatoid arthritis as compared to healthy controls. These findings suggest that screening for metabolic syndrome in patients with RA may reduce the risk of cardiovascular diseases in these patients.

Keywords: rheumatoid arthritis, metabolic syndrome, patients, biochemistry department, bangladesh.

Author α: Department of Biochemistry, Sir Solimulla Medical College, Dhaka, Bangladesh. e-mail: drazizasultana@gmail.com
Author σ: Consultant of Surgery, Rangpur, Bangladesh. e-mail: saimunssmc26@gmail.com
Author ρ: Registrar, Department of Surgery, Rangpur Medical College Hospital, Rangpur, Bangladesh. e-mail: drpavel135@gmail.com
Author ω: Associate Professor, Department of Surgery, Rangpur Medical College Hospital, Rangpur, Bangladesh. e-mail: drbimalroy@gmail.com
Author ¥: Assistant Professor, Department of Medicine, Rangpur Medical College Hospital, Rangpur, Bangladesh. e-mail: shafiulssmc23@gmail.com
Author §: Researcher, Dr. Wazed Research Institute, Begum Rokeya University, Rangpur, Rangpur-5400, Bangladesh. e-mail: drpsarkarbrur@yahoo.com

I. Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disorder of unknown etiology, characterized by systemic symptoms that particularly involve the joints and may lead to deformities during the course of the disease[1]. It is the most common persistent inflammatory arthritis, occurring throughout the world and in all ethnic groups. The prevalence is lowest in Black Africans and Chinese and highest in Pima Indians. In Caucasians, approximately 0.8-1.0% is affected, with a female to male ration of 3:1. The clinical course is prolonged, with intermittent exacerbations and remissions[2].

The established RA can be distinguished from other forms of arthritis by multiple criteria; and those agreed by the American Rheumatism Association. The median prevalence estimate the RA for the total population in South European Countries is 3.3 cases per 1000, and for developing countries 3.5 cases per 1000[3]. RA affects 0.5-1.0% of adults in developed countries and is 2-3 times more frequent in women than men[4]. The onset is most frequent during the fourth and fifth decades of life with 80% of all patients developing the disease between the ages of 35-50 years[5]. The overall prevalence of RA in Bangladesh is 0.7% in rural population and 0.4% in urban population[6].

RA is considered an autoimmune disease[7] and the overall systemic and articular inflammatory load drives the destructive progression of the disease. In addition, the extent of inflammation has been linked to an increased risk of cardiovascular mortality in patients with RA as compared to general population[8]. This is because the patients with RA are more prone for accelerated atherosclerosis which in turn is a risk factor for cardiovascular disease and thus there decreased survival in them[9].

The metabolic syndrome is considered as one of the best known risk factors to the development of CVD. The autoimmune systemic inflammatory response, along with the presence of metabolic syndrome doubles the risk for fatal or non fatal CVD and coronary atherosclerosis, regardless of age and sex[10]. Rheumatoid arthritis has been associated with increased prevalence of metabolic syndrome, but its role in the different characteristics of the disease, such as disease duration, activity and treatment with

glucocorticoids, is not well defined from a clinical point of view, the relevance of metabolic syndrome derives from its strong association with the occurrence of subclinical atherosclerosis, major adverse cardiovascular events and death. Atherosclerosis, the main determinant of CV morbidity, and mortality occurs prematurely in RA. Patients with RA have an increased risk for CVD. Metabolic syndrome occurs up to 45% of RA patients[11,12].

Metabolic syndrome previously known as syndrome X constitutes a cluster of abnormalities including abdominal obesity, insulin resistance, hypertension, hypertriglyceridemia and decreased high density lipoprotein cholesterol[13] and recognized it as multiplex of risk factors for cardiovascular diseases[14]. Syndrome X has now been re-designated as metabolic syndrome after WHO named it so in 1999. WHO included several parameters as the diagnostic criteria for metabolic syndrome such as presence of diabetes mellitus, hypertension, hypertriglyceridemia and low serum HDL-cholesterol and high BMI. The National Cholesterol Education programmes adult treatment panel III (NCEP-ATP III) report identified the metabolic syndrome as a multiplex of risk factors for cardiovascular diseases that deserve more clinical attention[15]. Modified NCEP-ATP III for metabolic syndrome includes raised fasting plasma glucose, hypertension, hypertriglyceridemia low serum HDL-Cholesterol and increased waist circumference[13].

Proinflammatory cytokines, tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6) seen in patients with RA contribute to insulin resistance which is the basic metabolic disorder seen in metabolic syndrome. Insulin resistance leads to other metabolic disturbances, like hyperglycaemia, dyslipidemia[16] which independently contribute to atherosclerosis and cardiovascular risk.

The basic pathology in RA is inflammation which in turn is the basis of atherosclerosis and this has led to study the relationship between systemic inflammatory conditions such as RA and the risk for CVD. It was seen that even in the absence of traditional coronary risk factors, women with RA have a 2-3 fold higher risk of CVD[17]. Also another study showed that patients with RA are 50% more likely to suffer a cardiovascular event than subjects from the general population[18].

Present study was designed in a small group of Bangladeshi population to observe the association of metabolic syndrome in patients of Rheumatoid Arthritis.

II. Objective of the Study

The main objective of this study was to find out the association of metabolic syndrome in rheumatoid arthritis patients as compared to healthy individuals.

III. Materials and Methods

This is a case control study and conducted from July 2014-June 2015 in the Department of Biochemistry, Dhaka Medical College, Dhaka, Bangladesh. Study population included 50 adult diagnosed cases of rheumatoid arthritis attending in Department of Medicine of Dhaka Medical College Hospital, Dhaka and 50 apparently healthy individuals (attendants of patients and stuff members of the hospital) as control. Sample Size was one hundred and purposive sampling was done. Rheumatoid arthritis patients were selected as per inclusion and exclusion criteria. Diagnoses were done on the basis of revised criteria of ACR 2010 including:

1. Compatible clinical history.
2. Physical examination of the patients.
3. Laboratory investigation in selected cases (ESR, CRP, RF, X-ray, Anti-CCPA).

Controls were selected by age and sex matched apparently healthy men and women. After selection of the subjects, the objectives, natures, purpose and potential risk of all procedures used for the study were explained in details and informed written consent were taken from both the patients or attendants and the control. Particulars, detail history, clinical examination, physical and anthropometric measurements were taken in a predesigned data collection form, from all the cases and controls .All data were recorded in a predesigned data collection sheet. Continuous variables were expressed as mean ± SD and were compared between groups of patients by student's 't' test. Categorical variables were compared using a chi-square test or Fischer's exact test as appropriate, and were presented as absolute frequencies with percentages. All p values were two-tailed with significance defined as $p < 0.05$ at the level of 95% confidence interval. All analysis was done using the SPSS version 21 package for windows.

IV. Results

Out of total 100 study subjects, 50 were RA cases and 50 were apparently healthy controls. Following results were found in this study-

Mean age was 41.94 (SD±8.57) years in case and 39.62 (SD±9.26) years in control. The case and control groups were age matched. In both groups maximum study subjects were in age group 41-50 years. In case maximum 22 (44.0%) patients were in age group 41-50 years and similarly in control group maximum 20 (40.0) patients were in same group. Difference between two group was not statistically significant ($p>0.05$). In both groups female was predominant than male. The case and control groups were sex matched.

In case group, 22 (44.0%) patients had metabolic syndrome and in control group only 8 (16.0%) subjects had metabolic syndrome. The difference between these two groups was statistically significant ($p<0.05$).

Table I : Distribution of metabolic syndrome in case and control groups

Metabolic syndrome	Group		*p* value
	Case n (%)	Control n (%)	
Yes	22 (44.0)	8 (16.0)	
No	28 (56.0)	42 (84.0)	0.002
Total	50 (100.0)	50 (100.0)	

Chi-square test was done to measure the level of significance, $p < 0.05$ was significant

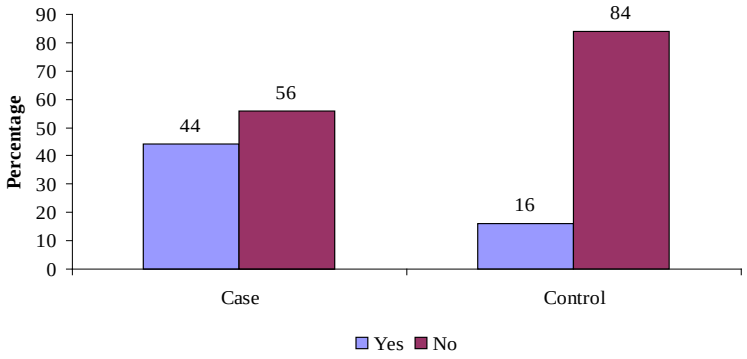

Figure 3 : Bar diagram of distribution of metabolic syndrome in case and control groups.

When comparison of different anthropometric components of metabolic syndrome (BP & WC) in case and control according to NCEP-ATPIII 2004. There were statistical significant difference in BP and WC between case and control. Mean of systolic BP, Diastolic BP, WC and BMI were significantly higher in case group than control group.

Mean fasting plasma glucose and Triglyceride were significantly higher in case group than control group and HDL-C was significantly lower in case group than control group. Mean of total cholesterol and LDL-C were almost same in both groups.

Table II : Comparison of Fasting Plasma Glucose and Lipid Profile between case and control

FPG and Lipid Profile	Group		*p* value
	Case (Mean ± SD)	Control (Mean ± SD)	
Fasting Plasma Glucose (mmol/l)	6.52 ± 1.93	4.66 ± 0.95	0.001
Total Cholesterol (mg/dl)	181.06 ± 30.38	177.40 ± 27.77	0.531
HDL-C (mg/dl)	34.88 ± 7.02	42.72 ± 7.02	0.001
LDL-C (mg/dl)	118.34 ± 30.53	110.40 ± 26.78	0.170
Triglyceride (mg/dl)	137.02 ± 40.74	112.72 ± 37.76	0.003

Unpaired t-test was done to measure the level of significance, $p < 0.05$ was significant

In comparison to different biochemical components of metabolic syndrome (FPG, HDL-C & TG) in case and control according to NCEP-ATP III 2004, there were statistical significant difference in FPG, HDL-C and TG between case and control.

Table III : NCEP-ATP III 2004 based comparison to biochemical components of metabolic syndrome in case and control

Biochemical components of metabolic syndrome		Group		*p* value	OR (95% CI)
		Case n (%)	Control n (%)		
FPG	≥ 5.6 mmol/L	33 (66)	2 (4)	0.001	46.58 (10.08-215.31)
	< 5.6 mmol/L	17 (34)	48 (96)		
HDL-C	Male ≤ 40 mg/dl / Female ≤ 50 mg/dl	48 (96)	33 (66)	0.001	12.36 (2.67 – 57.13)

TG	Male > 40 mg/dl / Female > 50 mg/dl	2 (4)	17 (34)	0.001	8.81 (2.39 – 32.04)
	≥ 150 mg/dl	18 (36)	3 (6)		
	< 150 mg/dl	32 (64)	47 (94)		

Chi square test was done to measure the level of significance. $p < 0.05$ was significant

V. Discussions

Rheumatoid Arthritis is a systemic inflammatory disorder characterized by chronic symmetric and erosive synovitis that preferentially affects peripheral joints, with a prevalence of 0.5-1% in the population[19]. Emerging epidemiological evidence suggests that CVDs account for approximately 50% of all RA associated deaths[20]. Metabolic Syndrome is a cluster of cardiovascular risk factors including central obesity, atherogenic dyslipidemia, hypertension and glucose intolerance, and is a strong predictor of cardiovascular diseases, diabetes and stroke[21]. Overlapping inflammatory pathways and genetic susceptibility may be potential biologic links underlying this association[22].

The age of the study participants ranged from (20-60) years. The mean age was found 41.91±8.57 years in cases and 39.62 ±9.26 years in control group. The mean age difference was not found statistically significant (p=0.197).

In the case group 17(34.0%) cases were males and 33 (66.0%) cases were females. In the control group there were 23 (46.0%) were males and 27(54.0%) were females the difference of male female ration was not found statistically significant (p=0.221) between two groups. This observation was consistent with the result of the study[23]. They observed that age and sex are not important risk factors for metabolic syndrome.

Increased waist circumference (Abdominal obesity) was a notable feature in our study which was found 84.5±10.3 cm in cases and 80.0±9.1 cm in controls, which showed significant difference between two groups (p=0.025) statistically. This result is in agreement with that of other previous study[24,25].

In our study, it is observed a higher prevalence of metabolic syndrome among RA patients than the controls (44% Vs 16%, p=0.002), which was similar to the results of well designed studies[24,26].

These findings tend to support that, there is an association between RA and Metabolic syndrome in hospital based RA patients in Bangladesh, which gives an insight into the pattern of co-morbidities of RA in our country.

In our study, the prevalence of high blood pressure was significantly high in cases than in controls. The mean systolic Blood pressure was 132.7±12.46 mm of Hg in cases and 120.3±8.33 mm of Hg in controls (p=0.001) and the mean diastolic BP was 83.9±8.8 mm of Hg in cases and 74.9±6.7 mm of Hg in controls (p=0.001). The difference was statistically significant. These observation were consistent with the results of the others studies[26,27]. Possible explanation may be, insulin resistance or obesity activates sympathetic nervous system and renin-angiotensin aldosteron system which subsequently results in hypertension.

Increased fasting plasma glucose was the most predominant feature (66%) contributing to increased prevalence of metabolic syndrome in RA group in our study and it was significantly higher in cases than controls (66% Vs 4%). This result is supported by several previous studies.

In our study, it was observed that 36% patients had presented with hypertriglceridemia in case group and 6% in control group which was statistically significant (p=0.001). In some studies[24,26] found insignificant difference of triglyceride level between case and control and another study[23] found triglyceride is significantly higher in control group in their study.

Regarding HDL-C, which is one of the biochemical components of metabolic Syndrome, it was found that 96% of cases had reduced HDL-C in case group whereas it was 66% in control group which was statistically significant (p=0.001), which was consistent with the findings of other studies[24,28].

VI. Limitations

We have some limitations of this study like-

- Small sample size, which may reduce the strength of the study.
- The sample was taken purposively, so there may be a chance of bias which can influence the result.

VII. Conclusion

Although a broad and evolving literature supports that RA is associated with metabolic syndrome, the association as well as their causal relationship is still unsettled. Exploration of these associations has practical consequence in the management of both the disorders. In conclusion this study revealed that metabolic syndrome is associated with RA. Therefore, in addition to the evaluation of RA, metabolic syndrome should be sort out in all RA patients to reduce impending cardiovascular events.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

VIII. Acknowledgement

It is a great pleasure to acknowledge our profound gratitude and honor to Dr. Mohammad

Hafizur Rahman, Associate Professor, Department of Biochemistry, Dhaka Medical College, Dhaka, Prof. Dr. Nasima Sultana, Professor & Head, Biochemistry Department, Dhaka Medical College, Dhaka and Prof. Dr. H. A. M. Nazmul Ahsan, Professor & Head, Department of Medicine, Dhaka Medical College, Dhaka for their guidance, support and encouragement throughout the study period.

References Références Referencias

1. Kojima M., Kojima, T., Ishiguro, N., Oguchi, T., Oba, M., Tsuchiya, H., Sugiura, F. (2009), 'Phychosocial factors, disease status, and quality of life in patients with rheumatoid arthritis. *J Psychosom Res*. 67(5), pp. 425-431. [pubMed]
2. Ralston, S.H., McInnes I.B., (2014) 'Rheumatology and Bone disease in: Walker B.R., Colledge N.R., Ralston S.H., Penman I.D., (Editors). Davidson's principle & practice of medicine 22nd edition; Edinburgh: Churchill Livingstone (Elservier); 2014: pp 1096-1102
3. Alamanos, Y., Voulgari, P.V., Drosos, A.A., (2006) 'Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review.' *Semin Arthritis Rheum*, 36, pp. 182-8.
4. Scott, D.L., Wolfe, F., Huizinga, T.W., (2010) 'Rheumatoid arthritis.' *Lancet*, 376, pp. 1094-108.
5. Lipsky P.E., Vender Heigde D.M., ST Clain E.W., Furst D.E., Breedveld F.C., Kalden J.R., (2000), 'Inflaximab and methtroxate in the treatment of rheumatoid arthritis'. *N Engl J Med*, 343, pp. 1594-602
6. Haq S.A, Darmawan J., Islam M.N., Uddin M.Z., Das B.B., Rahman F, et al., (2005), 'Prevalence of rheumatic disease and associated outcomes in rural and urban communities in Bangladesh: a COPCORD study' J. Rheumatil, 32, pp. 348-53
7. Smolen, J.S., Aletaha, D., Koeller M., Weisman M., Emery P. (2007) 'New therapies for the treatment of rheumatoid arthritis'. *Lancet*, 370, pp. 1861-74.
8. Meune, C., Touze, E., Trinquart, L., Allanore, Y., (2009) 'Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-annalysis of cohort studies'. *Rheumatology (Oxford)*, 48, pp. 1309-13.
9. Manzi, S., Wasko, M. C., (2000) 'Inflammation-medicated diseases and atherosclerosis. *Ann Rheum Dis*, 59, pp. 321-5.
10. Cojocaru, M., Cojocaru, I.M., Silosi, I., Vrabie, C.D., (2012) 'Metabolic syndrome in rheumatoid arthritis'. *Maedica (Buchar)* 7, pp.148-52.
11. Van Doornum, S., McColl, G., Wicks, I. P. (2002). 'Accelerated atherosclerosis: an extraarticular feature of rheumatoid arthritis? *Arthritis Rheum*. 46, pp. 862-73 [PubMed].
12. Stevens, R. J., Douglas, K. M., Saeatzis, A. N. (2005) 'Inflammation and atherosclerosis in rheumatoid arthritis'. *Expert Rev Mol Med.* 7, pp 1-24 [PubMed].
13. Dhanraj E., Bhansali A., Jaggi S., Dutta P., Jain S., Tiwari P. (2005), 'Prevalence and predictors of metabolic syndrome in nonobese Asian Indians with mewly detected type 2 diabetes mellitus'. *J ind Med Assoc*; 106, pp. 366-72
14. Reaven, G.M. (1988). Banting lecture 1988. 'Role of insulin resistance in human disease'. *Diabetes*, 37, pp. 1595-607.
15. Grundy, S.M., Brewer, H.B., Cleeman, J.I., Smith, S.C. Jr., Lenfant, C. et al., (2004) 'Definition of metabolic syndrome: Report of the National Heart, Lungh, and Blood Institute'. *Circulation* 109(3), pp. 433-438.
16. Mittelman, S.D., van Citters, G.W., Kirkman, E.L., Bergman, R.N., (2002) 'Extreme insulin resistance of the central adipose depot in vivo'. *Diabetes* 5, pp. 755-61.
17. Fischer, L.M., Schlienger, R.G., Matter, C., Jick, H., Meier. C.R., (2004) 'Effect of rheumatoid arthritis or systemic lupus erythematosus on the risk of first-time acute myo-cardial infarction'. *Am J Cardiol* 93 pp. 198-200.
18. Avina-Zubieta, J.A., Choi, H.K., Sadatsafavi M., Etminan, M., Esdaile, J.M., Lacaille, D. (2008) 'Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies'. *Arthritis Rheum,* 59, pp. 1690-7
19. Gabriel, S.E., (2001). 'The epidemiology of rheumatoid arthritis'. *Rheum Dis Clin North Am,* 27, pp. 269-281.
20. Goshayeshi, L., Saber, H.R., Sahebari, M., Rezaieyazdi, Z., Rafatpanah, H. et al., (2012). 'Association between metabolic syndrome, BMI, and serum Vitamin D concentrations in rheumatoid arthritis'. *Clin Rheumatol*, 31, pp. 1-7.
21. Wilson, P.W., D' Agostino, R.B., Parise, H. et al., (2005). 'Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus'. *Circulation*, 112, pp. 3066-3072.
22. Gelfand, J.M., Shin, D.B., Neimann, A.L., Wang, X., Margolis, D.J., Troxel, A.B. (2006). 'The risk of lymphoma in patients with psoriasis'. *Journal of Investigative Dermatoogy,* 126, pp. 2194-2201.
23. M. Sahebari, L. Goshayeshi, Z., Mirfeizi (2011), 'Investigation of the association between metabolic syndrome and disease activity in rheumatiod arthritis.' The Scientific World Journal, 11, pp. 1195-1205, View at publisher. View at google Scholar. View at Scopus.
24. Samira Rostom, Mariam Mengat, Racha Lahlou, Asmaa Hari, Rachid Bahiri and Najia Hajjaj-

Hassouni (2013). 'Metabolic syndrome in rheumatoid arthritis: case control study'.
25. Crowson, C.S., Myasoedova, E. Davis, J.M. III, Matteson, E.L., Roger, V.L. et al., (2011). 'Increased prevalence of metabolic syndrome associated with rheumatoid arthritis in patients without clinical cardiovascular disease'. *J Rheumatol*, 38, pp. 29-35.
26. Karakok, M., Batmaz, I., Sariyildiz, M.A., Tantasiz, M., Cevik, R. (2012) 'The relationship of metabolic syndrome with disease activity and the functional status in patients with Rheumatoid Arthritis'. *Clin Med Res*, 4, pp. 279-285.
27. Da Chunha, V.R., Brenol, C.V., Brenol, J.C., Fuchs, S.C., Arlindo, E.M. (2012) 'Metabolic syndrome prevalance is increased in rheumatoid arthritis patients and is associated with disease activity'. *Scand J Rheumatol*, 41, pp. 186-191
28. Karvounaris, S.A., Sidiropoulos, P.I., Papadakis, J.A., Spanakis, E.K., Bertsias, G.., Kritikos, H.D. (2007) 'Metabolic syndrome is common among rniddle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study'. *Ann Rheum Dis.* 66(1), pp. 28-33.