ORIGINAL ARTICLE

HYPERTENSION, DIABETES AND OBESITY IN PATIENTS WITH RHEUMATOID ARTHRITIS AND THEIR ASSOCIATION WITH DISEASE ACTIVITY

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ABSTRACT

Background and Objective: Rheumatoid arthritis (RA) is a systemic autoimmune disease whish shows increased association with cardiovascular diseases, diabetes and obesity. The present study was designed to compare the frequency of modifiable CV risk factors (hypertension, diabetes and obesity) in patients with RA having high active disease (HDA) verses low disease activity (LDA).

Methods: This cross sec-tional analytical study was conducted at Division of Rheumatology, FMH College of Medicine, Lahore, Pakistan from Sep 2014 to Feb, 2015. RA patients with high HAD and low disease activity LDA as defined per Disease Activity Score on 28 joints (DAS 28) criteria, were enrolled through purposive sampling. Information regarding patient's demography and their CV risk factors was entered in a structured proforma. SPSS version 17 was used for statistical analysis.

Results: There were total of 120 patients in HDA and 118 in LDA group. There were 31% vs. 37% hypertensive, 30% vs. 19% diabetic [OR = 1.87, CI = 1.020 – 3.42 (p = 0.04)], 63% vs. 75% overweight and 80% vs. 84% centrally obese patients in HDA vs. LDA groups, respectively. After adjusting for confounders in a Multi-logistic regression model, association of diabetes with high disease activity was not found to be significant [OR = 0.378, CI = 0.150 – 0.98 (p = 0.03)].

Conclusion: This study has not shown any significant association of modifiable CV risk factors with RA disease activity. However high frequency of these risk factors in both the groups underscores the importance of aggressive screening of these risk factors in RA patients.

Key Words: Rheumatoid Arthritis, Hypertension, Diabetes, Obesity.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease manifesting mainly as polyarthritis leading to progressive disability and pre-mature death due to increased cardiovascular mortality.[1]

There is augmented risk of Myocardial Infarction (MI) and stroke[2] in patients with RA and its burden is considered to be equivalent to patients with diabetes.[3] The range of standardized mortality ratio in patients with RA is from 1.5 to 5.[4]

Multifactorial risk factors and enhanced danger of atherosclerosis is reported in many RA patients.[4] The high disease activity in Rheumatoid Arthritis leads to raised levels of Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Interleukin-1 (IL-1), IL-6 and Tumour Necrosing Factors (TNF α), which lead to accelerated atherosclerosis.[8] Moreover use of Non-Steroidal Anti-Inflammatory Drug (NSAID's) are also considered as risk factor for CVD.[5]It is evidenced based that use of steroids in RA can also increase risk of Diabetes Mellitus (DM), hypertension and Obesity.[5,6]

Hypertension in Rheumatoid Arthritis alone is considered as an independent risk factor of cardiovascular mortality and subclinical atherosclerosis.[6] The frequency of hypertension in Rheumatoid Arthritis patients is between 20% to 73%.[7] The Framingham Heart study in United States and National Health and Nutritional Examination Survey (NHANES) states that there is a strong evidence of association of uncontrolled blood pressure and development of ischemic heart disease and stroke in RA patients.[7]

The prevalence of obesity in RA patients vary from 18% to 35%.[9] Numerous studies have shown that that those who have Rheumatoid Arthritis patientsusually have deranged Body Mass Index (BMI) ranging from the Obesity to Cachexia.[8] The stated prevalence of rheumatoid cachexia is 10% to 67%.[8] It is interesting that some literature have indicated that obesity might have defensive effect against the joint damage[10] in the initial course of disease. But as the diseases duration advances, pro-inflammatory markers and the adipokines leads to destruction of the lean muscles, joint damage and sedentary life style become the fate of the patients

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which ultimately worsens the obesity and Waist to Hip Ratio (WHR).[11-14]

The reported prevalence of diabetes in RA patients has been controversial. In a study conducted in Karachi, the estimated prevalence was found to be 8.2%.[15] Inflammatory markers have been a contributing factor in the development of insulin resistance.[16] The Glucocorticoid use affects appetite, body metabolism, fat distribution and intensify insulin resistance.[17] The pathophysiology of deranged glycemic index, BMI and WHR all are influenced by steroids intake.[17] Moreover, even the patients taking medium to low dose steroid for a longer period of time lead to increased deposition of fats around the abdominal viscera.[18,19]

Despite the availability of data on high prevalence of modifiable CV risk factors in patients with RA, local data on the frequency of these factors in RA patients is scanty. Secondly it is still a matter of debate whether it's the disease activity itself or the increased frequency of these factors in RA population responsible for increased risk of CVD.[20,21] To address this gap we designed a comparative analytical study to compare the frequency of these factors in patients with highly active disease versus patients of low disease activity. We hypothesized that the frequency of these CV risk factors was higher in patients with high disease activity than patients with low disease activity.

METHODOLOGY

Patients diagnosed as RA according to American College of Rheumatology (ACR) 1987 criteria[1] with age above 16 years and both gender were enrolled through purposive sampling from Division of Rheumatology, Fatima Memorial Hospital from Sep 2014 to Feb, 2015. The study was approved by the Institutional review board (IRB) of Fatima Memorial College of Medicine and Dentistry with issuance of certificate with IRB# FMS-4-2014-IRB-M-160.

Patients disease activity was assessed by the same rheumatologist (MAS) with a help of Disease Activity Score on 28 joint counts (DAS 28 score).[22] Patients were categorized into two groups, high disease activity (DAS 28 score ≥ 5.1) and Low disease activity (DAS 28 score ≤ 3.2) groups.[22] Patients with moderate disease activity were excluded as per study protocol to highlight the relationship of disease activity with the frequency of CV risk factors. Patient having overlap with other autoimmune diseases like Systemic Lupus Erythematosis (SLE), any patient not willing to participate, not willing to give blood sample and any Rheumatoid Arthritis patient who was currently and/or during the last 8 weeks on prednisolone ≥ 10 mg/day or any patient who was currently and/or during the last 8 weeks on Hakeem medications was excluded from the study. Information regarding patient's demography was obtained and entered in a structured proforma.

Sample size was calculated using software developed by Lwanga and Lemeshow[23], entering the following information Z^2 at 95% Confidence level = 3.84. Hypertension was defined as BP ≥ 140/90mm of Hg, either of the systolic or diastolic blood pressure or current use of anti-hypertensive drugs.[7] Diabetes Mellitus was established as Blood Sugar Fasting (BSF) ≥ 126 mg/dl, Blood Sugar Random (BSR) ≥ 200 mg/dl or already diagnosed as diabetic by a physician on the basis of above criteria.[24] Obesity was defined as Body Mass Index (BMI) ≥ 23 kg/m^2 as over-weight and ≥ 27 kg/m^2 as obese using Asian cut offs.[18] Formula for BMI calculation = weight (kg)/height (m^2).[14] Waist to Hip Ratio (WHR) was used as a measure to determine central obesity. Hip circumference was measured at the point of greatest circumference around hips and buttocks to the nearest 0.5 cm. The high risk WHR was defined as equal to or more than 0.80 and 0.95 for the females and males respectively.[27]

For statistical analysis data was entered in SPSS version 17. For the computation of continuous variables, means and standard deviations (± SD) and for categorical variables frequencies and percentages was done. Rates of the cardiovascular risk factors (hypertension, diabetes, overweight, obesity and central obesity) of patients with low (DAS 28 ≤ 3.2) and high disease activity group (DAS 28 ≥ 5.1) were compared as dichotomous variables (yes/no). The student t-test was applied to assess the difference between the distribution of continuous variables and chi-square test to appraise the association between the categorical variables. P value equal to and less than 0.05 (2 tailed) was considered statistically significant and power of the study was kept at 80%. To define the correlation between the variables like BMI and the disease activity linear regression was applied. In order to remove the effect of confounders like age and use of steroids, multivariate logistic regression was used .Moreover, the frequency of the cardiovascular risk factors enhances with age, disease duration and steroid intake, so in this study these were adjusted.

RESULTS

Out of total of 238 patients enrolled in this study, 120 patients were with high disease and 118 were with low disease activity with female predominance. Patient's demography and disease characteristics have been shown in Table 1. The mean age of patients was 44.6 ± 14 SD and 43 ± 12 SD in high and low disease activity grouprespectively. The mean disease duration in months was 79 ± 67 SD and 64 ± 55 SD in the high and low disease activity groups respectively.

Out of these 238 patients 34% were detected to have high blood pressure, among these 37% were with low disease and 31% [OR = 1.33, CI = 0.78 – 2.28 (p = 0.293)] (Table 2) were with high disease activity.

However out of total of 58 (24%) diabetic RA pati-

ents, 30% [OR = 1.87, CI = 1.020 – 3.42 (p = 0.04)] with high disease had diabetes and 19% with low disease activity group were diabetic (Table 2). The results did not support our hypothesis [OR = 0.378, CI = 0.150 – 0.98 (p = 0.03)] in the adjusted model (table 3).

It is noteworthy that the combined frequency of overweight and obese patients was 69%,out of which 75% with low disease activity group were either overweight and obese while 63% were with high disease activity {OR = 0.56, CI = 0.32 – 0.985 (p = 0.04)} (Table 2). Higher rate of obesity with BMI ≥ 27 kg/m^2

Table 1: *Comparison of Patients demography and disease characteristics in High and Low disease activity groups.*

Variables	*High Disease (DAS ≥ 5.1) n = 120*	*Low Disease (DAS ≤ 3.2) n = 118*	*p-value*
Female n (%)	95 (79)	102 (86)	0.14
Age Mean ± SD years	44.6 ± 14.08	43.1 ± 12.3	0.387
Disease duration Mean ± SD months	79.2 ± 67.3	64.52 ± 55.8	0.060
Duration of DMARDs* Mean ± SD months	40.43 ± 43.3	33.26 ± 41.6	0.067
RA Factor Positive n (%)	89 (74)	98 (83)	0.18
Anti-CCP * Positive n (%)	23 (19)	25 (21)	0.137
Steroid intake n (%)	51 (42)	40 (34)	0.694

*DMARDs (Disease Modifying Anti- Rheumatic Drugs)
*Anti CCP (Anti Cyclic Citrullinated Peptide) antibody test was available in 59 (24%)

Table 2: *Comparison of frequencies of CV risk factors in patients between low and high disease activity.*

Variables	*Total No. of RA Patients n = 238*	*High Disease (DAS ≥ 5.1) n = 120*	*Low Disease (DAS ≤ 3.2) n=118*	*p-value*
Hypertension n (%)	81 (34)	37 (31)	44 (37)	0.293
Diabetes n (%)	58 (24)	36 (30)	22 (19)	0.041
Overweight and obese n (%)	165 (69)	76 (63)	89 (75)	0.04
Central obesity n (%)	196 (82)	97 (80)	99 (84)	0.535

Table 3: *Regression model with unadjusted and adjusted values.*

Sr. No.	*Variables*	*Unadjusted*			*Adjusted*		
		Odds Ratio	*95% CI*	*p-value*	*Odds Ratio*	*95% CI*	*p-value*
1.	Age	1.04	0.62 – 1.755	0.873	0.84	0.375 – 1.97	0.69
2.	Gender	0.59	0.30 – 1.185	0.137	0.396	0.129 – 1.21	0.10
3.	RA factor	0.649	0.342 – 1.232	0.184	0.25	0.09 – 0.66	0.006
4.	Steroid	0.69	0.410 – 1.174	0.172	0.711	0.32 – 1.55	0.394
5.	Disease duration	2.51	0.85 – 7.36	0.08	2.3	0.45 – 12.17	0.30
6.	Hypertension	1.104	0.779 – 2.28	0.293	0.42	0.168 – 1.07	0.06
7.	Diabetes	1.87	1.020 – 3.42	0.04	0.378	0.150 – 0.98	0.04
8.	BMI(overweight and obese)	0.56	0.32 – 0.98	0.04	0.64	0.25 – 1.67	0.37
9.	WHR	0.809	0.415 – 1.58	0.535	0.63	0.21 – 1.85	0.408

(57%) (p = 0.886) were observed in female population in low disease activity group. However the male with overweight (BMI ≥ 23 kg/m²) and obese (BMI ≥ 27 kg/m²) were 24% and 29% (p = 0.73) respectively. Although the percentage of males with BMI ≤ 18 kg/m² with high disease activity was 16%.

The total percentage of centrally obese patients (both males and females) was 82% with almost comparable percentage of patients in both low (84%) and high disease (80%) activity group (p-value ≥ 0.05) (Table 2). There were 87% females were centrally obese out of which 75% had low disease verses 70% had high disease activity (p-value ≥ 0.05) were centrally obese. However, the proportion of centrally obese males was 52% (p = 0.288) in high disease activity group verses 68% in low disease activity group.

Moreover there exists a negative correlation between BMI and high disease in both males and female population with r = -0.212 and -0.044 respectively (Figure 1 and 2). However, this study gives us a positive correlation between BMI and low diseases activity in females with r = 0.104 (figure 3).

Multi-logistic regression has been applied in this table. After adjusting for age, gender, RA factor, steroid intake and disease duration only association of diabetes and RA factor in high disease activity group have been found to be significant. Overweight/ obesity, hypertension and diabetes are independent risk factor for the cardiovascular event in RA patients and they act as confounders but they are used in this study as variable.

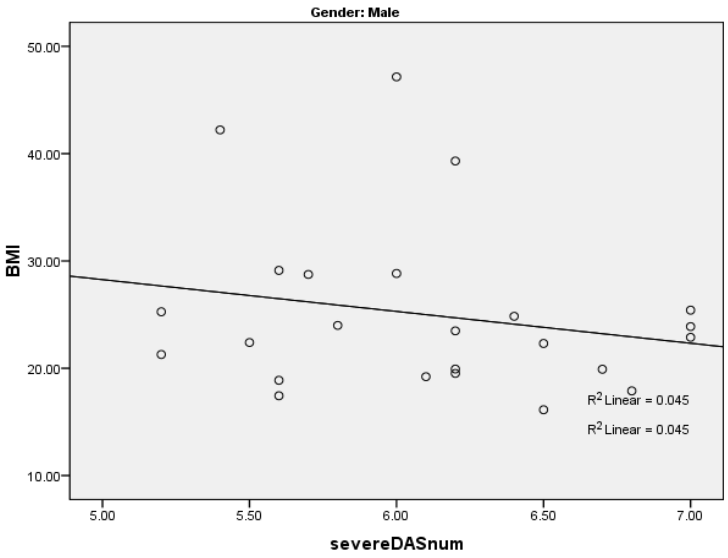

Fig. 1: *Correlation of change of BMI with high disease activity in males.*

The figure showed a negative correlation (significant at 5% level) with the BMI. The Pearson's correlation coefficient r = -0.212.

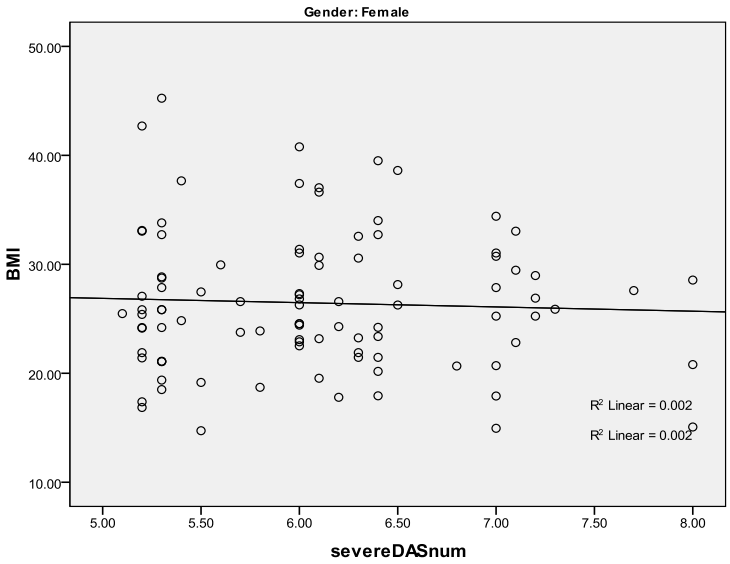

Fig. 2: *Correlation of change of BMI with high disease activity in females.*

The figure showed a negative correlation (significant at 5% level) with the BMI. The Pearson's correlation coefficient r= - 0.044.

DISCUSSION

Rheumatoid arthritis is a multi-system disease linked with increase morbidity and mortality due to early progress of cardiovascular co-morbidities.[5] The health care providers should be focusing on health education, promotion of healthy life style and diet to decrease CV mortality and morbidity.[2]

This study has been premeditated in line with EULAR recommendations[3] to highlight the importance of screening rheumatoid arthritis patients for cardiovascular risks. This study had been done in the outpatient Rheumatology department of Fatima Memorial Hospital, which is one of the few academic units, where Rheumatoid arthritis patients are referred from all over Punjab. Total 238 patients were enrolled out of which 50% were with the high disease (DAS 28 score ≥ 5.1)[22] and 50% were with low disease (DAS 28 score ≤ 3.2)[22] activity. In this observational study, we used purposive sampling so majority enrolled patients were females as RA is a female predominant disease. In order to delineate the association of gender with the frequency of these traditional CV risk factors, we need to conduct a study with more controlled sampling technique.

The prevalence of hypertension in general populations is between 20–30%[28] and 35%-73% in RA pati-

ents according to different epidemiological studies[8]. In this study the total 34% RA patients were having hypertension, out of which 31% with high disease had hypertension while the figure among low disease activity was 37% [odd ratio (OR = 1.33) 95% CI = 0.779 – 2.284 (p = 0.293)] (Table 2). Which is supported by a study conducted by Labitighan M et al,[21] to be of 40% which is much higher than prevalence of 13.7% in a study conducted by Alam S M et al[15] in Karachi through a retrospective chart review. This study did not show any correlation of hypertension with high diseases activity despite the fact that overall Frequency of HT in this study 34% much higher than the prevalence reported in general population. RA patient with low disease activity logically should have less frequency of hypertension as compared to patients with high disease activity but this cross-sectional study had not been able to establish the relation of high disease activity and the blood pressure status in RA patients. As this is a cross-sectional study, we were able to determine only two readings of blood pressure but were not able to follow these patients further. So in future a longitudinal study should be designed to follow the blood pressure of these patients in order to have better understanding of burden of hypertension in RA patients and its effect in causation of cardiovascular diseases.

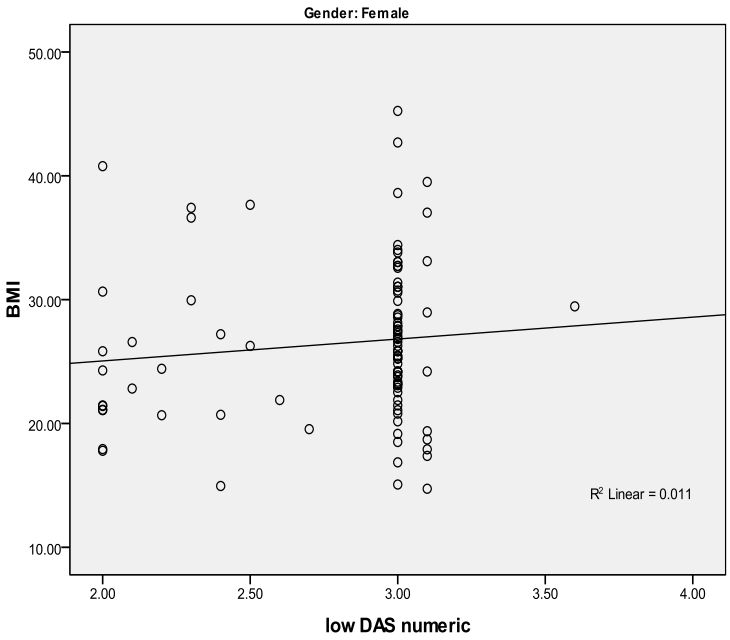

Fig. 3: *Correlation of change of BMI with low disease activity in females.*

The figure 3 showed a positive correlation between BMI and low disease activity at 5% confidence interval with Pearson's correlation coefficient r = 0.104.

So it is worth to emphasize that the clinicians taking care of these RA patients should make efforts for early diagnosis of these co-morbidities by early screening and appropriate long term control irrespective of their RA disease activity.

In this study 24.3% patients had diabetes (Table-2) based on history of diabetes and screening random blood sugar level, which is much higher than prevalence of diabetes in Pakistani general population[18] and also from figure of 8.2% in a retrospective study conducted few years back in Karachi.[15] As most of the patients were walk in, hence we could not determine the fasting blood sugar levels and had to rely on random levels.

This cross sectional study a much higher proportion of diabetic patients were found in high disease than low disease activity group [odd ratio (OR = 1.87) 95% CI = 1.02 – 3.42 (p = 0.04)]. These finding are also supported by the Labitigan M et al, 2014 that the metabolic syndrome like hypertension, diabetes, dyslipidemia and obesity are more prevalent in patients with RA.[2]

Although unadjusted estimate indicates higher odds for high disease activity group with somewhat precise estimate for population .However, when adjusted for age, gender, disease duration and steroid intake to address confounding effect, this was no more supporting our hypothesis (Table 3).

So to control chronic inflammation in RA patients is an important step which should be taken to prevent joint damage and long term functional impairment and development of insulin resistance.[16] It is noteworthy that in this cross sectional study there was higher prevalence of diabetes in patients with high disease, so early screening and health education should be main goal of our preventive strategies.

In general population, obesity is an integral part of metabolic syndrome and a well-established independent risk factor of CVD.[21] According to recent figures, the overall prevalence of obesity in RA is 33% which is equal to the prevalence in general population [14]. In this study, proportion of patients with obesity (BMI ≥ 27 kg/m^2) and overweight (BMI ≥ 23 kg/m^2)[18] were 42% and 27% respectively (Table 2) as we have used lower cutoff values for obesity and overweight suggested for Asian population.[18]

It is noteworthy that the combined frequency of overweight and obese patients was 69% (Table 2), out of which 75% were with low disease activity group and 63% were in high disease activity group [odd ratio (OR = 0.56) CI = 0.32 – 0.985 (p = 0.04)]. Higher rate

of obesity with BMI ≥ 27 kg/m² showed a percentage of 47% (p = 0.886) in female population in low disease activity group. The percentage of the male with overweight (BMI ≥ 23 kg/m²) and obesity (BMI ≥ 27 kg/m²) were 24% and 29% (p = 0.73) respectively. However, 16% of the male who had high disease were underweight (BMI ≤ 18 kg/m²).

The total percentage of centrally obese patients (both males and females) was 82% with equal percentage of patients in both low (84%) and high disease (80%) activity group (Table 2). There were 87% females who were centrally obese out of which 75% with low disease verses 70% had highdisease activity. However, 52% of males with high disease were centrally obese (p = 0.288) versus 68%% with low disease activity.

One possible reason of this observation might be that, mostly our females in general population as well as RA patients have deranged BMI because of sedentary life style.[13] Stavropoulos-Kalinoglou et al in 2010 publication has reported higher proportion of subcutaneous adiposity in female RA population. So RA female patients are more prone to get obese and overweight due to inflammation, pain and disability which further restrict their mobility.[11-13] Which in the initial course of disease provide protective action against the joint damage but as the duration of disease increases, the inflammatory markers cause reduction in the lean muscle mass i.e., Rheumatoid cachexia masked by adiposity.[11-13] Calculation of deranged BMI by anthropometry alone is not a reliable tool to assess the adiposity in RA patients. So in order to have a clear picture of extent of subcutaneous adiposity and the reduction in lean muscles mass needs assessment by more sophisticated tests like CT scan and whole body MRI.[14,19]

In our cross-sectional study, there was female predominance so we are unable to decipher effect of gender on obesity.[29] However male and female RA patients with high disease activity showed a negative correlation (significant at 5% level) with the BMI, the Pearson's correlation coefficient r = -0.212 and -0.044 (figure 1, 2) respectively. Which might be due to the inflammation in high disease activity group leading to reduction in the lean muscle mass in both male and female population.[30] Many series of studies have shown that two third of the RA patients have muscles wasting with significant correlation between depletion of lean body mass and the number of swollen joints, ESR, CRP and the presence of extra-articular disease.[31] For the better understanding of the underlying cause more sophisticated tools like MRI and CT scan can be used.[14] However there exist a positive correlation between the low disease activity and the BMI especially in females with Pearson's correlation coefficient r = 0.104 (figure 3), which is explaining the fact that in patients with low disease activity due to low grade inflammatory processes and sedentary life style especially in females can be responsible for the increasing obesity.[13]

There was an interesting finding that in this study, male population was only 12% and majority (61%) of them had high disease and were underweight. These finding can be explained on the basis of concept rheumatoid cachexia which in the clinical practice is often unrecognized and associated with un-controlled long standing disease.[9,10]

To further explore the relationship of modifiable CV risk factors in RA patients with disease activity and their correlation with the CV outcome like myocardial infarction, heart failure and cardiovascular deaths a longitudinal prospective study with larger sample size should be conducted.

It is ***concluded*** that this cross sectional study has highlighted the increased burden of traditional CVD risk factors in Pakistani RA patients. It is noteworthy that that this study has not been to establish association of modifiable CV risk factors with RA disease activity, but our finding highlights the importance of aggressive screening of these traditional cardiovascular risk factors in RA patients. There is an unmet need to conduct further longitudinal studies to determine whether by modifying these risk factors we can actually reduce the CV morbidity and mortality in our RA patients.

Authors' Contribution

HA: Developed concept of this project; Literature search; Data collection; Data compilation and analysis; discussion and conclusion. MAS: Helped in literature search; Data collection; discussion and conclusion. FK: Data analysis and interpretation; discussion and conclusion writing.

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