ORIGINAL ARTICLE

IS RHEUMATOID ARTHRITIS ASSOCIATED WITH OBESITY?

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ABSTRACT

Objective: To know the association of Rheumatoid arthritis with obesity.

Material and Methods: This study was conducted at Medical B Unit, Postgraduate Medical Institute, Lady Reading Hospital, Peshawar, from January 2014 to December 2014. Study design was cross sectional. Sample size was 166 cases and equal number of age and sex matched controls. Non probability consecutive sampling technique was used for sample collection.

Results: One hundred and sixty six patients of RA and equal number of age and sex matched controls were studied; Mean age was 35 years ± 2.12 SD, 69.87% were female, disease duration was 2 years ± 1.02 SD. In cases (RA) group, 60 patients (36.14%) patients were obese and 106(63.85%) patients were non-obese; where as in control group, 40(24%) controls were obese and 126(76%) controls were non-obese. Odds ratio (OR) of Obesity in Rheumatoid arthritis was 1.52, 95% CI (0.938-2.45) and the p-value was 0.023 which was significant. Out of 166 cases 116(69.87%) were females. Out of I66 female cases, 50(43.10%) were obese and OR of Obesity in female cases was 2.172, 95 CI (1.24-3.78); p-value was 0.008, which was significant. Male cases were 25. 12(24%) of male cases were obese and OR of obesity in male cases of RA was 1.231, 95% CI (0.503-3.016) and p-value was 0.82, which was not significant. Out of 116 RA patients (72.28%) were Rheumatoid factor (RF) positive and the remaining 46(27.71%) were RF negative. Odds Ratio (OR) of obesity in RF Positive cases was 1.47, 95% CI (0.80-2.71); p-value being 0.22, was not significant. For RF Negative cases the Odds Ratio of Obesity was 2.02 95% CI (1.10-3.72) and the p-vale was 0.03, which was significant.

Conclusion: Rheumatoid arthritis is associated with obesity in particular the association exists in female patients.

Key Words: Rheumatoid, Arthritis, Rheumatoid factor, Anti Cyclic Cittrulinated Peptide, Obesity.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that if uncontrolled may lead to destruction and deformity of joints due to erosion of cartilage and bone. The prevalence of RA in western countries is 0.3-0.8percent.[1] The exact prevalence of RA in Pakistan is not known. Several life style factors contributing to the etiology and severity of RA have been studied extensively in western counties.[2]

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Obesity is on rise in prevalence globally[3] and is a recognized cause of disabling morbidity.[4] Research in the past few decades has recognized adipose tissue as an active endocrine organ, playing a role not only on metabolism but also on immune and inflammatory processes by releasing a variety of adipocytokines and pro-inflammatory mediators, among which TNF-α, IL-6, adiponectin, leptin, resistin, visfatin, and C-reactive protein,[5] are of prime importance. The term 'adipokine' refers to bioactive molecules found in the adipocytes or at other sites other than adipose tissue and participate in functions unrelated to the adipose tissue.[6] A wider majority of adipokines is also implicated in regulation of inflammation.[7] As a general rule, increased adiposity associates with heightened production of pro-inflammatory molecules, whereas reduced adiposity associates with decreased concentration of pro-inflammatory, and increased concentration of anti-inflammatory molecules; for that reason obesity in now considered a pro-inflammatory state.[8]

All the above-mentioned adipokines are implicated in the production of several pro-inflammatory cytokines e.g, Tumour Necrosis Factor (TNF-α), IL-1, IL-6 and the acute-phase reactant CRP. TNF-α, IL-1 and IL-6 are central in the pathogenesis and progression of RA as they participate in several steps of the disease including T- and B-cell recruitment and activation, angiogenesis, chemotaxis, vessel permeability and Matrix Metalloproteinase (MMP) production.[9] TNF-α is mainly produced by macrophages and lymphocytes; however, it is also found in adipose tissue[10] its circulating levels increase in obesity[11] and especially in people with abdominal obesity.[12] IL-6 is also secreted from adipocytes[13] and its levels are increased in obesity.[14]

Aside from a potential causative role, obesity has the potential to affect functional disability in RA in a number of ways. Increasing BMI has been associated with more bodily pain and greater disablement for the same amount of pain.[15] Obese patients may have increased inflammatory burden due to metabolic activity of adipose tissue.[16] Obesity has also been associated with impaired health-related quality of life and disability in established RA.[17] Obesity has also been shown to be associated with worse disease outcomes.[18] Interestingly, the adipokines described above are directly related to RA activity.[19]

The leading cause of mortality in RA is related to cardiovascular disease (CVD).[20] To date, the exact pathophysiologic mechanism by which this relation between CVD and rheumatoid arthritis can be explained is not completely clear. Obesity itself is modifiable risk factor of cardiovascular disease.[21] Metabolic Syndrome, of which obesity is an important component, has also been shown to be associated with RA.[22]

MATERIAL AND METHODS

This cross sectional study was conducted at Medical B Unit, Postgraduate Medical Institute, Lady Reading Hospital, Peshawar. Study duration was one years and the Sample size was 166 cases and equal number of age and sex matched controls. Consecutive patients who met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for the classification of RA[23] were taken as cases. The control group consisted of patients who had inflammatory polyarthritis not fitting into RA according to 2010 ACR/EULAR classification criteria of RA, those presenting with acute infections (e.g. Upper respiratory tract infections) of less than 3 days duration, and healthy hospital staff. Among cases and controls, subjects having already diagnosed malignancy, tuberculosis, malabsorption, thyrotoxicosis, untreated diabetes mellitus, HIV, other chronic co-morbidities like Chronic Renal Failure, Congestive Cardiac failure, Chronic Liver Disease, Hypothyroidism, or having clinical features of Cushing's syndrome other than obesity(or already diagnosed), were taken in the exclusion criteria. Out of the total 200 cases and 180 controls, the subjects meeting the exclusion criteria were excluded, and the remaining 166 cases and 166 controls were studied further The Ethics Committee of PGMI Lady Reading Hospital approved the study and written consent was taken from all participants.

All the patients and controls were interviewed. The demographic data (age, gender) and clinical data (disease duration, previous therapies) was gathered from patients' history and documents. Height and weight were measured using a same weight machine and height scale. Body mass index (calculated as weight in kilograms divided by the square of height in meters) was categorized into underweight (<18.5 kg/m2), normal (18.5-22.9 kg/m^2), overweight (23-27.4 kg/m^2), and obese (≥27.5 kg/m^2).24 All patients were referred to hospital laboratory for measurement of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). RA factor with dilution agglutination titers was measured at hospital laboratory, where as anti CCP titers were not done due to cost issues and were seen only in the previously diagnosed patients already having this investigation.

Data was analyzed using SPSS software version 21.Binary logistics were applied and analytical statistics were used to calculate Odds Ratio (OR) of Obesity in Rheumatoid arthritis, and in other subgroups. Fisher's Exact t test was used to calculate the p-values. Frequencies and percentage were used for qualitative variables like gender. Mean, ±SD was calculated for quantitative or numerical variables like age, BMI, ESR, CRP and duration of illness.

RESULTS

The demographic and clinical variables of cases and controls are shown depicted in Table 1. Out of 116 RA patients 120(72.28%) were Rheumatoid factor (RF) positive and the remaining 46(27.71%) were RF negative. In the 120 RF positive RA patients 42 (35%) were obese, whereas 40(24%) subjects were obese in 166 controls. In 46 RF negative RA patients 18(39.13%) were

Table 1: Demographics and Clinical Characteristics of Cases (RA) and Controls

Parameter	Cases	Controls
Age in years		
20-30	58(35%)	58(35%)
31-40	54(32%)	54(32%)
41-50	38(23%)	38(23%)
51-60	16(10%)	16(10%)
Total	166(100%)	166(100%)
Mean and SD	35 years ± 2.12	35 years ± 2.12
Gender		
Male	50(30%)	50(30%)
Female	116(70%)	116(70%)
Total	116(100%)	116(100%)
Duration of illness in years		
0	0	10 (12%)
< 1	50(30%)	126 (76%)
1-3	84(51%)	20 (12%)
4-7	24(14%)	0
> 7	8(5%)	0
Total	166(100%)	166(100%)
Mean and SD	3 years ± 1.86	2 years ± 1.02
	P-value=0.209	
ESR (mm in 1st hour		
0-10	4	14
11-20	8	6
21-30	28	112
31-40	90	28
41-50	24	6
51-60	6	0
61-70	4	0
71-80	2	0
Mean and SD	35±7mm	17±3mm
	P-value =>0.005	
CRP		
Positive	122	34
Negative	44	136
	P-value=>0.005	

ESR: Erythrocyte Sedimentation Rate

CRP: C reactive protein

Table 2: BMI and association of RA with Obesity

Obesity Status	Cases	Controls
Non-Obese < 27.5 Kg/m^2	106(63.85%)	126(76%)
Obese ≥ 27.5 Kg/m^2	60(36.14%)	40(24%)
Total	166(100%)	166(100%)

obese and whereas 40(24.09%) out of 166 controls were obese. OR of obesity in RF positive cases was 1.47, 95% CI (0.80-2.71) with a p-value of 0.22 which was not significant. For RF Negative cases the Odds Ratio of Obesity was 2.02 95% CI (1.10-3.72) with a p- value of 0.03. Thus Obesity was associated with RF negative Rheumatoid arthritis. Anti CCP were done only for a total of 16 patients due to financial issues. Twelve out of 16(75%) patients were anti CCP positive and the remaining 4 out of 8(25%) were anti CCP negative. Due to the small size of sample, no conclusion could be drawn as regarding association of obesity with AntiCCP+ and AntiCCP- patients.

Out of 116 RA female patients 50(43.10%) were obese and 66(56.89%) were non-obese where as in 116 control group females 30(25.86%) were obese and 66(56.89%) were non-obese. Odds ratio (OR) of Obesity in female cases was 2.172, 95 CI (1.24-3.78) and p-value was 0.008 which was highly significant. In 25 male patients 14(28%) were obese and 36(72%) were non-obese, whereas in 50 control male group 12(24%) were obese and 38(76%) were non obese. OR of Obesity in Male cases of RA was 1.231, 95% CI (0.503-3.016); p- value determined was 0.82 which was non-significant.

DISCUSSION

Rheumatoid, Arthritis is associated with obesity, previous studies have found a similar association. Obesity was associated with RA risk in three population based case – control studies [OR for BMI ≥30 vs <25 = 3.74 (1.14, 12.27) in the NOAR study, for the highest vs lowest quartile of BMI 1.4 (1.0, 2.0) in an American case – control study, and for BMI ≥30 vs 18.5 to <25 = 3.45 (1.73, 6.87) for ACPA– RA in the CACORA study.[25,26,27] Specifically, the newer studies have demonstrated an association of Anti CPP- RA but not Anti-CCP+ RA, with obesity. In a large case-control study Body mass index 10 years before interview was strongly and selectively associated with anti-CCP-negative RA (p-trend < 0.001), with obese (body mass index ≥30 kg/m2) individuals at more than threefold increased risk compared with normal-weight (body mass index

18.5 to <25 kg/m2) individuals (OR = 3.45; 95% CI: 1.73 to 6.87).[25]

Due to non-availability of the Anti-CCP assay in the institutional setting and financial restrains, only 16 patients had their Anti-CCP done. Therefore no meaningful conclusion could be drawn as regards the anti-CCP status. RA factor was done, however, for all patients. In the diagnosis of RA, the sensitivity, specificity, Positive Predictive Value and Negative Predictive Value of the RF test have been shown to be 67%, 79%, 37% and 93%, respectively. The corresponding data for the anti-CCP test were 79%, 98%, 86% and 96%, respectively. The presence of either anti-CCP or RF increased the sensitivity to 85%, and when they both were present, the specificity increased to 98%.[28] Clearly AntiCCP+ RA and Anti CCP- RA, and RF+ RAand RF- RA, are different in the disease phenotype as well as their associations. It was recently demonstrated that smoking is selectively associated with rheumatoid factor (RF)-positive RA[29] or with RA positive for anti-cyclic citrullinated peptide (CCP) antibodies.[30] Also, coffee consumption has been found to be selectively associated with RF-positive RA, although the association diminished considerably after adjustment for tobacco smoking.[31] Further supporting the existence of etiologically distinct subtypes of RA, recent case-control studies have shown that measures of low socioeconomic status are predominantly associated with risk of RF-positive RA.[32] In one study, patients of normal weight differed significantly in joint damage by RF serology, while this difference did not exist in obese patients. The mean radiological joint damage in the RF-positive obese patients therefore was lower than that of the RF-negative patients of normal weight. In RF-positive patients, the BMI was negatively correlated with radiographic joint damage (0.160, P 0.001); a similar correlation did not exist in RF-negative patients (0.001, P 0.991).[33] Metabolic syndrome, of which, obesity is an important component is shown to be associated with higher RF positivity (P = 0.049).[34] In the study by Giles et al,[35] RF seropositivity was inversely associated with Visceral Fat Adiposity (β= 1.287, P=0.039). Yet another study revealed that Increased BMI was associated with the activity of disease (DAS28) (r = 0.426), structural damage (Sharp total score) (r = 0.297), the rate of rheumatoid factor (r = 0.311).[36] Our study revealed that RF- RA, but not RF+ RA, is associated with obesity (OR=2.02, P=.03 and OR 1.47, P=0.22 respectively. To our knowledge this finding has not been seen or present in all previous studies.

In one of the studies association of RA with obesity was more pronounced in women than men.[27] A previously quoted study found that abdominal visceral adiposity was 51% higher in men with RA compared to men without RA, whereas there was no difference between women with and without RA.[34] In a study by Crowson et. al,[37] the association between history of obesity and development of RA was similar for both sexes.

There has been no local study to see the association of RA with obesity in Pakistan. The purpose of this study was, therefore, to see an association between RA and obesity in Pakistani patients of RA. As the afore-mentioned association is found here in our study, this should generalize the outcomes of the above cited western studies to our population. This in turn has many impacts. First, the public awareness, that among so many adverse outcomes, obesity is also related to chronic debilitating illnesses like RA. Of importance is the fact that Cardiovascular disease (CVD) is considered an extra-articular manifestation (EAM) of RA[38] and a major predictor of poor prognosis.[20] Several studies have documented a high prevalence of CVD in many autoimmune diseases.[39] Various traditional risk factors such as obesity, dyslipidemia, type 2 diabetes mellitus, metabolic syndrome, hypertension, physical inactivity, advanced age, male gender, family history of CVD, hyperhomocysteinemia, and tobacco have been associated with CVD in RA patients.[40] In fact, seropositive RA may, like diabetes, act as an independent risk factor for CVD.[20] So, the second impact would be–dealing with obesity by lifestyle measures and pharmacotherapy would decrease the incidence and severity of RA and a reduction in mortality attributable to CVD, firstly by decreasing the incidence and severity of RA and thus decreasing the associated CVD, and secondly by reduced occurrence of CVD due to eliminating its established risk factor i.e. Obesity.[21]

CONCLUSION

There is strong association of Rheumatoid Arthritis (RA) with obesity especially in female population.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Wazir N: Concept and design, acquisition of data.

Waqas M: Critical review, drafting of manuscript.

Zeb S: Manuscript writing.

Taqweem A: Data analysis and interpretation.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.