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Original Research Article

Clinical disease activity index versus disease activity score (28 joints) for assessment of disease activity in obese patients of rheumatoid arthritis

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ABSTRACT

Background: Measurement of disease activity by Disease Activity Score 28 joints -Erythrocyte Sedimentation Rate (DAS28-ESR), Disease Activity Score (28 joints)-C-Reactive Protein (DAS28-CRP), and Clinical Disease Activity Index (CDAI) has become an integral part of management of Rheumatoid Arthritis (RA), by 'Treatment to Target' approach. With the exception of CDAI, the other two use inflammatory markers ESR and CRP to measure disease activity. Obesity is also known to increase inflammatory markers like CRP. We undertake this study to examine if obesity confounds the disease activity measurement in RA leading to overestimation of disease activity.
Methods: A cross-sectional observation study was conducted on one hundred patients of RA (40 obese and 60 non obese) in remission or low disease activity as defined by CDAI. They were divided into obese and non-obese groups based on Indian standards (BMI>25kg/m^2). ESR and CRP were measured in both the groups. DAS28-ESR and DAS28-CRP were calculated and compared using relevant statistical tests.
Results: DAS28-ESR and DAS-28-CRP scores were significantly higher in the obese subjects, despite both groups having comparable CDAI scores. Similar findings were also observed with inflammatory markers ESR and CRP, both being higher in obese patients.
Conclusions: We conclude that indices incorporating inflammatory markers, like DAS28 overestimate disease activity in obese RA patients. Treatment decisions regarding escalation or addition of DMARDs should be taken after considering the same. CDAI appears to be better suited for disease activity measurements in obese RA patients as compared to DAS 28.

Keywords: CDAI, DAS28, Disease activity assessment, Obesity, Rheumatoid arthritis

INTRODUCTION

Rheumatoid Arthritis (RA) is an inflammatory polyarthritis of autoimmune aetiology with a prevalence of 0.75% in the Indian population.[1] Recent advances have revolutionised the treatment of RA and the treatment armamentarium includes disease modifying anti rheumatic drugs (DMARD), biologics, and the new class of drugs called JAK inhibitors. Earlier diagnosis and initiation of treatment, escalation of dose and number, or change of DMARDs as required, based on the Treat to Target strategy has improved outcomes.[2] This strategy relies on measuring disease activity by different validated scores. The commonly used scores in the clinic are the Disease Activity Score- 28 joints (DAS28) and Clinical Disease Activity Index (CDAI). The former takes into account systemic inflammatory markers like Erythrocyte Sedimentation Rate (ESR) and C-Reactive protein (CRP), thus making it DAS28-ESR or DAS28-CRP, while the later does not incorporate these inflammatory markers. CDAI has been found more stringent in measurement of disease activity in RA.[3]

Measurements of systemic inflammation by ESR and CRP in RA can be confounded by obesity. Obesity in itself has been known to increase systemic inflammation through production of Interleukin-6 (IL-6) by adipose tissue.[4,5] CRP is increased even in obese patients without metabolic syndrome.[4] Thus, disease activity may be overestimated in obese RA patients when scores incorporating these inflammatory markers are used. The cut-off for values of obesity is lower in Indian patients and thus overestimation of disease activity on obese RA patients is more likely in our setting.[6] Besides, higher waist circumference signifying abdominal obesity as well as greater appendicular fat and lower lean body mass increases levels of CRP.[8] All these are likely to lead to inappropriate increase of doses or number of DMARDs, including biologics.

This study was designed to evaluate the appropriateness of using disease activity scores DAS28 and CDAI in obese vis-a-vis non-obese patients of RA.

METHODS

A cross-sectional observation study was conducted in the Department of Medicine, Atal Bihari Vajpayee Institute of Medical Sciences and Dr RML Hospital, a tertiary care hospital situated in New Delhi during the period from 1st January 2021 to 31st of May 2022. One hundred consecutive adult patients of RA who had achieved remission or were in low disease activity as per CDAI scores were screened for exclusion criteria which included pregnant females, patients with evidence of active infection or history of any infection in the last month, active smokers, patients undergoing surgery in past 3 months, uncontrolled hypothyroidism, acute coronary syndrome in the last 1 month, chronic steroid user or use of steroids in last 1 month, known case of diabetes mellitus, patients with overlap with other connective tissue disorders. Their clinical and laboratory parameters were evaluated. Clinical parameters included complete examination with measurements of height, weight, Body Mass Index (BMI) and abdominal circumference. Laboratory parameters included complete blood count (CBC), ESR by Westergren's method, CRP, liver and kidney function tests, anti-cyclic citrullinated peptide (Anti CCP), anti-nuclear antibody (ANA), and rheumatoid factor (RF). Disease activity scores DAS28-ESR, DAS28-CRP, and CDAI were recorded for each patient. The patients were then segregated into two groups based on BMI of Indian subjects, with the first consisting of those below 25Kg/m^2 (non-obese) and the second consisting of those with BMI equal or more than 25 Kg/m^2 (obese) and their parameters compared.

Sample size was calculated on basis of study by Ashish et al using the formula for sample size for difference in proportion, $(n)= [Z_{1-\alpha/2}\sqrt{\{2p(1-p)\}}+Z_{1-\beta}\sqrt{\{p_1(1-p_1)+p_2(1-p_2)\}}]^2/(p_1-p_2)^2$, where $Z_{1-\alpha/2}$ and $Z_{1-\beta}$ are the critical value of the given level of confidence at two sided test and power of study, and p_1 and p_2 are the proportions in two groups.[9] For a confidence interval of 95% and power of study of 80%, the sample size was derived to be 40 patients in each group. The screening of patients was continued till the sample size was attained.

All data were recorded in MS Excel worksheet, and analysed using Epi-Info, JASP and Statistical Package for Social Sciences (SPSS) version 23.0. Continuous variables were represented as mean ± SD or medians with interquartile range. Categorical variables were represented as number and percentage (%). The variables were tested for normality with the Kolmogorov-Smirnov test for normality, Q-Q plots, visual inspection of the histograms and the z-scores for the degree of skewness and kurtosis. Spearman Rank correlation test was used to assess correlation between continuous quantitative variables. All tests of significance were two-tailed and statistical significance was defined as P<0.05.

RESULTS

Forty patients were found to be obese and 60 patients were non obese. The majority of the patients in both the obese (n=23, 57.5%) as well as non-obese (n=37, 61.67%) were between the ages of 40 and 60. Females constituted the majority of cases (84 of 100, 84%), with 49 of 60 in the non-obese group (81.67%), and 35 of 40 (87.5%) in the obese group. Both the groups were matched with respect to mean age, age distribution, and gender. Since only those patients had been included in study who were in remission or low disease activity state as per CDAI, the two groups did not differ significantly in CDAI (P=0.056), tender joint count (TJC) (P=0.204), swollen joint count (SJC) (P=0.189), Patient Global Assessment (PtGA) (P=0.92), and Physician Global Assessment (PhGA) (P=0.374). Other clinical and laboratory parameters are tabulated and compared in Table 1.

Table 1: The clinical and laboratory parameters of both obese and non-obese groups.

		Obese (n=40)	Non obese (n=60)	P value
Age (years)	Mean±SD	49.32±12.21	45.83±11.46	0.149
	Median±IQR	46.5 (41-56.5	48 (38.5-53.0)	0.214
Gender	Male:Female	1:7	11:49	0.58
Height (cm)	Mean±SD	156.92±8.85	160±8.37	0.048
Weight (Kg)	Mean±SD	70.88±8.37	55.48±7.31	<0.001
BMI (Kg/cm^2)	Mean±SD	28.91±3.31	21.45±1.86	<0.001
Waist circumference (cm)	Mean±SD	96.45±12.47	87.53±13.29	<0.001

Continued.

		Obese (n=40)	Non obese (n=60)	P value
Waist/hip ratio	Mean±SD	0.92±0.05	0.89±0.05	0.001
ESR mm 1st hour	Median±IQR	37.5 (21.5-54)	24.5 (12-42)	0.007
CRP (mg/dL)	Median±IQR	5.6 (2.28-9.92)	2.3 (0.76-7.05)	0.017

Table 2: The difference in obesity parameters and levels of inflammatory markers among the genders.

Parameters	Female (n=84)	Male (n=16)	P value
ESR (mm 1st hour)	32.5 (IQR: 17.5-44)	25.5 (IQR:11.5-40)	0.236
CRP	4.15 (IQR: 1.2-8.48)	1.36 (IQR: 0.5-5.3)	0.036
CDAI	4 (IQR: 2-7)	5.5 (IQR: 2-6)	0.68
BMI	24.74±4.64	22.75±2.86	0.345
Waist circumference	91.3±12.69	90.06±18.28	0.621
Waist hip ratio	0.90±0.05	0.91±0.06	0.187

Gender differences of various parameters were studied and the results are tabulated in Table 2.

ESR and CRP were significantly higher in the obese group compared to the non-obese group, and so were the DAS28-ESR (3.05, IQR:2.6-3.7 vs 2.6, IQR:2.3-3.1; P=0.002), and DAS28-CRP (2.86, IQR:2.4-3.66 vs 2.64, IQR:2.3-2.94; P=0.031).

Correlation of BMI with other obesity parameters and inflammatory markers ESR and CRP are given in Table 3.

CDAI showed a positive and statistically significant correlation with both DAS28-ESR and DAS28-CRP as shown in Table 4.

80 of the 100 patients (80%) were on methotrexate as DMARD therapy. In the non-obese group, it was 53 out of 60 (88.33%), while among the rest 7 patients, 5 were on leflunomide (8.33%) and 2 on combined methotrexate and leflunomide (3.33%). In the obese group, 27 out of 40 (67.5%) were on methotrexate, while 5 patients were on leflunomide (12.5%) and 8 were on combined methotrexate and leflunomide (20%). All patients were taking hydroxychloroquine (HCQ) concurrently. Thus, proportion of patients taking methotrexate in the non-obese group was significantly higher than the obese group (P=0.03, Chi Square).

Table 3: The correlation of obesity parameters with levels of inflammatory markers.

BMI (Kg/m^2)	24.42±4.46	22.9 (IQR: 21.3- 27.35)	Correlation coefficient	P value
WC (cm)	91.1±13.63		0.498	<0.001
WHR	0.9±0.05		0.336	<0.001
ESR (mm)		31 (IQR: 16-44)	0.318	<0.001
CRP (mg/dL)		1.06 (IQR: 0.4-4.1)	0.384	<0.001

Table 4: The correlation between disease activity scores.

Disease activity	Mean±SD	Median (IQR 25-75)	Correlation coefficient	P value
CDAI	4.62±2.84	4.0 (IQR: 2.0-6.25)		
DAS28-ESR	2.88±0.72	2.8 (IQR: 2.38-3.2)	0.593	<0.001
DAS28-CRP	2.81±0.72	2.35 (IQR: 1.61-3.12)	0.657	<0.001

DISCUSSION

In our study, both the obese as well as the non-obese patients were well matched with respect to age, and gender distribution, though there was a predominance of female patients. As most of the cases were less than 60 years of age, with the mean of both groups below 50 years, this is consistent with the gender prevalence of young females being 4-5 times those in males.[10] The two groups however differed in WC and WHR, which were significantly higher in the obese group, thereby indicating that the obesity in our sample was mostly central obesity. The levels of ESR and CRP were also significantly higher in the obese group. That central obesity has been associated with higher levels of CRP has been mentioned before.[7] Besides, the BMI across groups showed significantly positive correlation with WC, WHR, ESR, and CRP. Thus, central obesity was the main determinant of increased BMI in our cases, and as BMI increased, so did the levels of inflammatory markers.

This shows that while CDAI, which does not use levels of inflammatory markers to calculate disease activity scores did not differ significantly between the obese and non-obese groups, ESR and CRP, and by extension DAS28-ESR and DAS28-CRP were significantly higher in the obese group.

We also studied the gender difference of the parameters. While BMI, WC, WHR, and ESR did not differ

significantly between males and females, CRP was significantly higher in the females compared to males. Though there were two outliers in the CRP in female cases of 32 mg/dL and 36 mg/dL which could have skewed the distribution, recalculating after discarding them did not yield any different results. Thus, CRP could be related to gender with females having higher levels than men independent of demographic or cardiometabolic risk factors[11]. However, this gender related difference cannot explain the difference between obese and non-obese patients as the gender distribution of both groups was similar.

The treatment protocol followed in our clinic for treatment of RA is to start Methotrexate at 0.3 mg/Kg body weight, and evaluate for its effect in reaching the desired disease activity score after 8-12 weeks. In case of the disease activity improves but does not reach the target, leflunomide is added to methotrexate. But if methotrexate fails to show any effect, it is stopped and replaced by leflunomide. In our study, a significantly higher proportion of obese patients were on leflunomide compared to the non-obese cases, thus suggesting that more obese patients of RA failed initial therapy with methotrexate. Studies have shown that increased BMI was associated with lesser remissions in RA across different treatments.[12,13]

The strength of our studies lies in the two groups of obese and non-obese being matched for age and gender distribution, additional parameters of WC, and WHR were measured in addition to BMI, and the DMARDS treatment was correlated with obesity.

The limitations of this study include a smaller number of male RA patients which is due to the increased prevalence of RA in the female population and lack of a control group of age and sex matched obese subjects without RA who could have been compared with the obese patients of RA with respect to inflammatory parameters.

CONCLUSION

We conclude by stating that elevated levels of ESR and CRP in obese patients of RA may be due to obesity itself and not due to increased disease activity and thus change DAS 28 scores, thereby leading to escalation of dose or number of DMARDs. Thus, a holistic approach and not just laboratory parameters should be the basis of treatment decisions in patients of RA. We also recommend that CDAI be preferred for measuring the disease activity in obese patients of RA.

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