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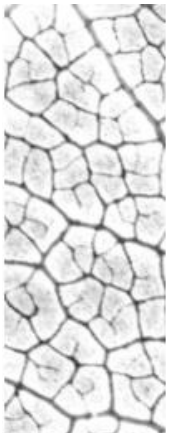

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An exploration of the relationship between interleukin 37, 8-ohdg and a number of anthropometric measurements in iraqi rheumatoid arthritis patients

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Abstract

Background: Anti-inflammatory intermediaries like interleukin-37 (IL-37) have a central function in the disease regulation of rheumatoid arthritis (RA). This study was designed to explore the relationship between IL-37, 8-hydroxydeoxyguanosine (8-OHDG) and certain anthropometric measurements in RA patients, and to investigate whether there are any correlations between IL-37 and 8-OHDG. **Materials and Methods:** The study comprised 60 patients with RA and 24 age- and sex-matched healthy control subjects (HCs). IL-37 and 8-OHDG serum concentrations were estimated by ELISA. The width of waist (W.W), hip (W.H), thorax (W.T) and neck (W.N) were calculated, along with body mass index (BMI) for all subjects. **Results:** IL-37 and 8-OHDG serum concentrations were significantly greater in patients with RA. Nevertheless, RA patients showed lower levels of high-density lipoprotein (HDL) and hemoglobin (Hb). Elevated serum concentrations of IL-37 were found to be positively associated with waist to hip ratio (W/H), waist to thoracic ratio (W/T), waist to neck ratio (W/N), ESR and Hb, while raised serum concentrations of 8-OHDG were positively related with W/H, W/T, SBP, DBP, creatinine and total cholesterol (TC). IL-37 exhibited the highest ROC curve value in comparison to other studied markers. **Conclusion:** Both anti-inflammatory cytokine (IL-37) and the marker of DNA impairment (8-OHDG) form part of RA's pathogenesis. IL-37 and 8-OHDG may be used as possible biomarkers of active RA.

Keywords: interleukin-37, 8-OHDG, rheumatoid arthritis, anthropometric measurements

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INTRODUCTION

Rheumatoid arthritis (RA) is a prolonged universal autoimmune infection characterized by synovial cell proliferation and lymphocyte incursion, connecting to advanced devastation of articular gristle and bone destruction (Yuan et al. 2019). IL-17 has been revealed to play an essential role in the manifestation and development of RA, and the regulated use of IL-17 thus provides a possible cure for it (Wei and Duan 2016). IL-37, previously known as IL-1 family participant-7 (IL-1F7), is an anti-inflammatory interleukin that destroys innate inflammatory and immune replies (Xu et al. 2015, Ye and Huang 2015). Animal studies have found that IL-37 has a defensive function in inflammatory diseases and Alzheimer's disease (AD), through frustrating the production of proinflammatory interleukins and stimulating macrophage and dendritic cells (DCs) (McNamee et al. 2011). Numerous recent papers have publicized the finding that IL-37 has an abnormal expression in RA and many other diseases (Yang et al. 2015, Wu et al. 2016, Fawzy et al. 2016). Moreover, research by Akdis et al. has shown that presence of IL-37 decreases as these diseases progress growth and pathogenesis of these autoimmune illnesses (Akdis et al. 2011).

Reactive oxygen species (ROS) have also received increasing research interest as a result of their pivotal function in the development of numerous inflammatory infections (Mittal et al. 2014). ROS's include oxygen free radicals, as well as further non-radical oxygen products that participate in oxygen radical manufacture (Lushchak 2014). They are involved in normal cellular metabolism and are continually being produced via the cells in the many tissues.

8-hydroxydeoxyguanosine (8-OHdG) is thought to be one of the most common DNA injuries, and results from free radical prompted oxidative stress in nuclear and mitochondrial DNA. It is frequently used as a delicate biomarker of DNA oxidative injury (Pilger et al. 2006,

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Valavanidis et al. 2009).

The best public anthropometric calculation for assessing obesity is the BMI scale (which measures weight health by dividing weight by height squared). The World Health Organization (WHO) (World Health Organisation 2000) notes that Anthropometric measures (AMs) of central adiposity, such as waist width and the waist to hip ratio, have been suggested as substitutes for BMI (Janssen et al. 2004, Dalton et al. 2003), and it is suggested that central adiposity is the reason why metabolic disorders are connected to measurements of waist width in the standards for metabolic disorders (Alberti et al. 2005). Furthermore, some researchers have contended that obesity should be redefined in relation to waist to hip ratio, as this standard for evaluating it is related to many risk factors, such as RA (Yusuf et al. 2005). Nevertheless, the prognostic strength of this measurement may be undermined in relation to sex differences and total body mass measurements as pear-shaped or heavy persons might have good waist to hip ratios, but augmented total body masses (Li et al. 2006, Shyam et al. 2019).

The aim of the present study was to carefully measure the concentrations of IL-37 and 8-OHDG and evaluate the link between them and general and specific anthropometric parameters in healthy individuals and patient subjects, and to determine if any of these parameters have a close enough association to enable a precise prognosis of RA.

METHODS

Sixty RA patients who were present at the Unit of Rheumatology at the Heet General Hospital between July 2018 and July 2019 were enrolled on the study, using the American Rheumatism Association's 1987 revised principles for the classification of RA (Arnett et al. 1988). Twenty-four age and sex matched healthy control subjects (HCs) with no history of any rheumatic or autoimmune disease were also enrolled in the study, which was given ethical clearance by the ethics board of the University of Anbar. Written informed consent was provided by all of the contributors.

A blood serum sample was elicited from 60 patients with RA (20 males and 40 females, age 26-66-years old, mean 46.10 years old) at the Heet General Hospital, Anbar, Iraq. Serum was also taken from the 24 healthy volunteers (8 males and 16 females, age 28-66-years old, mean 44.79 years old).

Demographic data and AMs were collected from the patients with RA and the HCs. Weight was estimated to the nearest 0.1 kg, sans shoes, socks, large clothing, and extra accessories. Height was estimated to the nearest 0.01 m, sans shoes and socks by a stadiometer. BMI (kg/m2) was calculated by weight (kg) divided by height (m) squared. AMs, such as width of neck, width of hip, width of waist and width of thorax (cm) were also measured.

To determine the concentrations of IL-37 and 8-OHDG in the subjects, we used ELISA kits manufactured by the Elabscience Company (USA) with a Thermo Scientific Varioskan microplate reader system. Other biochemical parameters in the study were determined using commercially available kits.

Statistical Analysis

Statistical analyses were conducted using SPSS version 24 and GraphPad prism version7. The statistical importance level was set at a P value of less than 0.05. Descriptive statistics consisting of mean, standard deviation (SD), and standard error (SE) were calculated for each parameter. Comparisons among RA cases and HCs were computed using the Student's t-test. The associations between AMs and the IL-37 and 8-OHDG characteristics of both RA cases and HCs was studied via Pearson's correlation (r=−1 to 1). A receiver operating characteristic (ROC) curve was created to examine the levels IL-37 and 8-OHDG among healthy individuals and patients with RA.

RESULTS

In this study, the mean ages of RA patients and HCs were 46.10 (SD. 11.83) and 44.79 (SD. 8.46) years (p=0.6235) respectively. AMs and other characteristics of all subjects are presented in (**Table 1**). Among AMs, Weight, Height, W/H, W/T and W/N were significantly higher in patients than in HCs (P for all except height <0·001) [83.95 (SD .11.74) v. 74.80 (SD. 8.65) kg], [164.98 (SD. 7.66) v. 162.70 (SD 5.74) cm], [0.99 (SD. 0.12) v. 0.86 (SD. 0.03)], [1.09 (SD 0.12) v. 0.95 (SD. 0.04)] and [2.89 (SD 0.40) v2.48 (SD. 0.15)].

RA patients had significantly higher BMIs in comparison with HCs (P <0·01) [30.8545 (SD. 14.54938) v. 28.3240 (SD. 3.60523) kg/m^2]. The SBP, DBP, ESR, RF, CRP and Creatinine levels of RA patients were significantly higher than those of HCs (P for all <0·001) [142.33 (SD. 17.30) v. 125.00 (SD. 17.19) mmHg], [97.83 (SD. 13.03) v. 84.57 (SD. 7.49) mmHg], [56.76 (SD. 18.27) v. 19.71 (SD. 4.36) mm/H],[18.56 (SD. 5.95) v. 10.00 (SD. 1.91) IU/mL], [23.96 (SD. 10.90) v. 8.99 (SD 2.66) mg/L] and [1.72 (SD. 0.610) v. 1.15 (SD. 0.36) mg/dL], respectively.

The Urea, TC and TG levels of RA patients were moderately higher than those of HCs (P for all <0·05) [34.25 (SD. 14.64) v. 27.45 (SD. 5.23) mg/dL], [189.36 (SD. 30.66) v. 172.02 (SD. 29.21) mg/dL] and [142.46 (SD 52.91) v. 109.25 (SD. 27.19) mg/dL], while levels of HDL and Hb were slightly lower in patients with RA than in the HCs (p for all < 0.05) [41.56 (SD 9.19) v. 47.46 (SD. 5.99) mg/dL] and [12.27 (SD. 1.31) v. 13.18 (SD. 1.08) g/dL], respectively. Moreover, the count of WBCs, Neut. cells and mono. cells were significantly higher in RA patients than in HCs (p for all < 0.05) [8.12 (SD. 2.19)

Table 1. Clinical and Anthropometric Characteristics of Rheumatoid Arthritis Patients and Controls

			Healthy controls			Patients		
Parameter		**Mean**	**SE**	**SD**	**Mean**	**SE**	**SD**	**p-value**
Age	years	44.7917	2.06461	8.46465	46.1000	1.52765	11.83316	0.6235
Wt.	kg	74.8000	1.76589	8.65106	83.9500	1.51580	11.74137	0.0009
height	cm	162.7000	1.17282	5.74562	164.985	0.98906	7.66126	0.1910
W.N	cm	32.18	0.5138	2.517	34.39	0.3667	2.841	0.0013
W/H		0.8668	0.00565	0.02767	0.9960	0.00431	0.11946	<0.0001
W/T		0.9503	0.00778	0.03812	1.0876	0.00234	0.12329	<0.0001
W/N		2.4766	0.03133	0.15347	2.8889	0.01505	0.40105	<0.0001
BMI	Kg/M^2	28.3240	0.73591	3.60523	30.8545	1.87832	14.54938	0.0079
SPB	mmHg	125.0000	3.50982	17.19454	142.3333	2.23438	17.30746	<0.0001
DBP	mmHg	84.5750	1.52908	7.49094	97.8333	1.68227	13.03082	<0.0001
ESR	mm/H	19.7117	0.89175	4.36865	56.7667	2.35882	18.27137	<0.0001
RF	IU/mL	10.0000	0.39009	1.91107	18.5667	0.76869	5.95425	<0.0001
CRP	mg/L	8.9917	0.54500	2.66995	23.9667	1.40804	10.90664	<0.0001
Creatinine	mg/dL	1.1500	0.07518	0.36831	1.7217	0.07876	0.61011	<0.0001
UA	mg/dL	5.2583	0.18610	0.91172	6.0983	0.28828	2.23300	0.0819
Urea	mg/dL	27. 457	1.06913	5.23765	34.2500	1.89060	14.64452	0.0310
TC	mg/dL	172.0167	5.96242	29.20976	189.3667	5.08204	30.65940	0.0210
TG	mg/dL	109.2500	5.55057	27.19215	142.4667	6.83086	52.91165	0.0070
HDL	mg/dL	47.4633	1.22277	5.99033	41.5667	1.18640	9.18984	0.0038
LDL	mg/dL	105.8417	3.24064	15.87582	113.6833	4.56521	29.23458	0.2187
VLDL	mg/dL	23.0817	1.16171	5.69118	24.7167	0.92195	5.85732	0.2396
Hb	g/dL	13.1850	0.22020	1.07875	12.2767	0.16903	1.30934	0.0033
WBCs	$10^3/\mu L$	7.2385	0.29793	1.45955	8.1200	0.28260	2.18902	0.0706
Neut.	$10^3/\mu L$	4.3275	0.23742	1.16313	5.0533	0.22830	1.76841	0.0783
Lymph.	$10^3/\mu L$	2.5045	0.17082	0.83682	2.4933	0.08813	0.68268	0.9505
Mono.	$10^3/\mu L$	0.4375	0.03798	0.18606	0.5667	0.03359	0.26016	0.0293
IL-37	pg/mL	6.2755	0.64740	3.17159	29.8442	0.50673	3.92513	<0.0001
8-OHDG	ng/mL	7.6472	0.45105	2.20969	12.4831	0.65677	5.08728	0.0002

Table 2. Bivariate correlation between IL-37 and 8-OHDG with and other parameters in the study

Parameter		**IL-37 pg/mL**	**Wt. kg**	**height cm**	**W/H**	**W/T**	**W/N**	**Age years**
IL-37 pg/mL	r	1	0.181	0.046	0.366**	0.386**	0.410**	-0.093
	p		0.682	0.099	0.001	0.000	0.000	0.402
Parameter		**BMI Kg/M2**	**SPB mmHg**	**DBP mmHg**	**ESR mm/H**	**RF IU/mL**	**CRP mg/L**	**Creatinine mg/dL**
IL-37 pg/mL	r	0.150	0.136	0.127	0.560**	0.132	0.260*	-0.136
	p	0.174	0.216	0.254	0.000	0.230	0.017	0.216
Parameter		**UA mg/dL**	**Urea mg/dL**	**TC mg/dL**	**TG mg/dL**	**HDL mg/dL**	**LDL mg/dL**	**VLDL mg/dL**
IL-37 pg/mL	r	-0.064	0.020	0.253*	0.095	0.017	0.149	0.110
	p	0.563	0.854	0.020	0.391	0.875	0.177	0.319
Parameter		**Hb g/dL**	**WBC 10^3 /µL**	**Neut. 10^3/µL**	**Lymph 10^3/µL**	**Mono. 10^3 /µL**	**8-OHDG ng/mL**	
IL-37 pg/mL	r	-0.297**	0.160	0.154	-0.044	0.401**	0.155	
	p	0.006	0.147	0.163	0.692	0.000	0.159	
Parameter		**8-OHDG ng/mL**	**Wt. kg**	**height cm**	**W/H**	**W/T**	**W/N**	**Age years**
8-OHDG ng/mL	r	1	0.134	0.024	0.233*	0.239*	0.201	0.162
	p		0.225	0.831	0.033	0.029	0.067	0.141
Parameter		**BMI Kg/M2**	**SPB mmHg**	**DBP mmHg**	**ESR mm/H**	**RF IU/mL**	**CRP mg/L**	**Creatinine mg/dL**
8-OHDG ng/mL	r	0.122	0.299**	0.318**	0.136	0.195	0.141	0.278*
	p	0.269	0.006	0.003	0.218	0.076	0.202	0.010
Parameter		**UA mg/dL**	**Urea mg/dL**	**TC mg/dL**	**TG mg/dL**	**HDL mg/dL**	**LDL mg/dL**	**VLDL mg/dL**
8-OHDG ng/mL	r	0.024	0.256*	0.168	0.334**	-0.183	0.028	0.075
	p	0.831	0.019	0.127	0.002	0.096	0.803	0.499
Parameter		**Hb g/dL**	**WBC 10^3 /µL**	**Neut. 10^3/µL**	**Lymph 10^3/µL**	**Mono. 10^3 /µL**	**IL-37 pg/mL**	
8-OHDG ng/mL	r	-0.022	0.026	-0.057	0.112	0.239*	0.155	
	p	0.843	0.814	0.610	0.313	0.028	0.159	

v. 7.24 (SD. 1.46) $10^3/\mu L$], [5.05 (SD. 1.77) v. 4.33 (SD 1.16) $10^3/\mu L$] and [0.57 (SD. 0.26) v. 0.44 (SD 0.19) $10^3/\mu L$], respectively. The present study also showed that the levels of LDL and VLDL were non-significantly higher in RA cases than in HCs (P>0·05) (**Table 1**) [113.68 (SD. 29.23) v. 105.84 (SD. 15.87) mg/dL] and [24.71 (SD. 5.86) v. 23.08 (SD. 5.69) mg/dL], respectively.

Finally, the current study demonstrated that patients with RA have significantly higher levels of IL-37 and 8-OHDG than those seen in HCs (P<0·001) (**Table 1**).

[29.84 (SD. 3.92) v. 6.27 (SD. 3.17) pg/mL] and [12.48 (SD. 5.09) v. 7.65 (SD. 2.21) ng/mL], respectively.

Table 2 shows the correlations of IL-37 and 8-OHDG with the studied parameters of both patients and control groups. From this table we can see that there is a significant association between IL-37 and W/H, W/T,

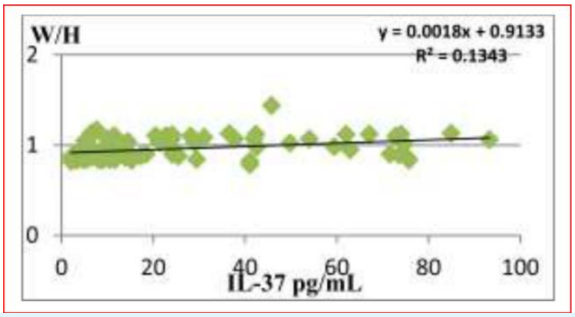

Fig. 1. Correlation of IL-37 with W/H

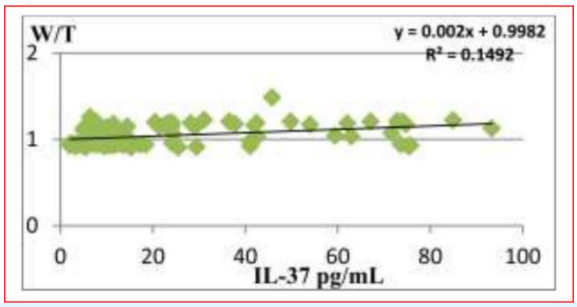

Fig. 2. Correlation of IL-37 with W/T

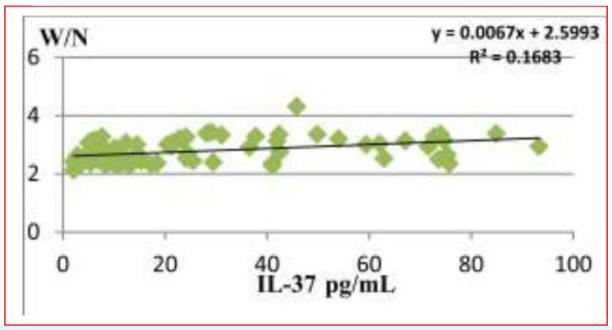

Fig. 3. Correlation of IL-37 with W/N

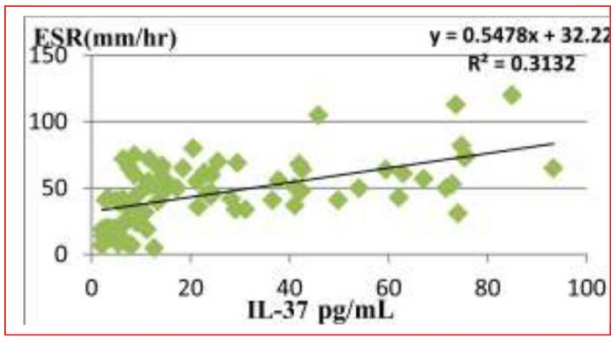

Fig. 4. Correlation of IL-37 with ESR

W/N, ESR and monocyte cells (r=0.366; P<0·001; **Fig. 1**), (r=0.386; P<0·001; **Fig. 2**), (r=0.410l; P<0·001; **Fig. 3**), (r=0.560; P<0·001; **Fig. 4**) and (r=0.401; P<0·001; **Fig. 5**), respectively. However, we don't observe any significant association between IL-37 and other studied variables. While a significant association was found between 8-OHDG and W/H, W/T, SBP, DBP and TG (r=0.233; P<0.05; **Fig. 6**), (r=0.239; P<0.05; **Fig. 7**), (r=0.299; P<0.01; **Fig. 8**), (r=0.318; P<0.01; **Fig. 9**), and

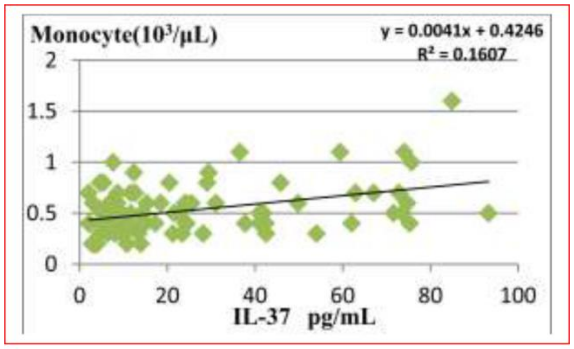

Fig. 5. Correlation of IL-37 with W/H

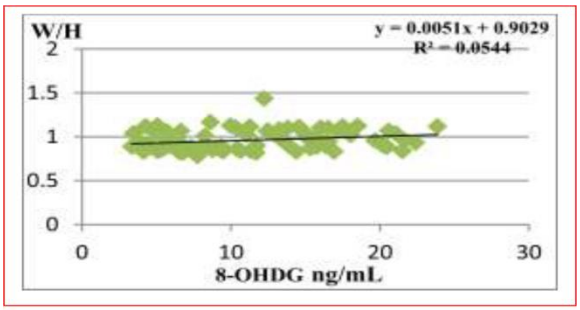

Fig. 6. Correlation of 8-OHDG with W/H

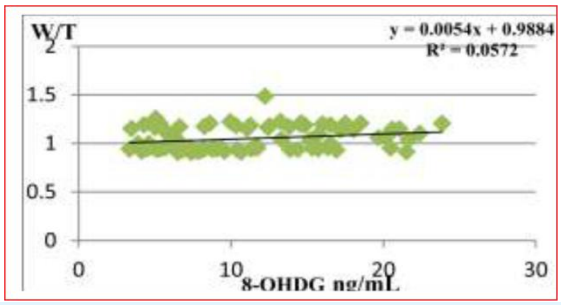

Fig. 7. Correlation of 8-OHDG with W/T

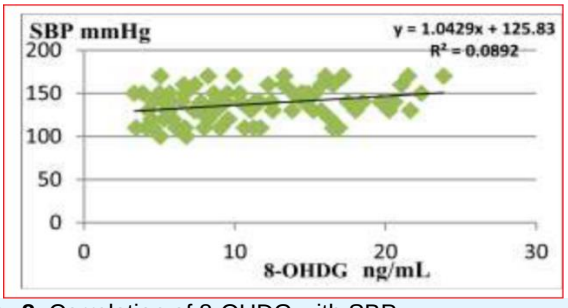

Fig. 8. Correlation of 8-OHDG with SBP

(r=0.334; P<0.01; **Fig. 10**), respectively, the other studied variables showed no significant association with 8-OHDG.

As **Table 3** shows, the ROC curve established that serum IL-37 levels exhibited a good method for discriminating' between healthy individuals and patients with RA [AUC = 0.9875; P < 0.0001; 95% Confidence Interval (CI): 0.9713 to 1.004 and SE: 0.0082] (**Fig. 11**). IL-37 was found to be a better predicator for RA than 8-OHDG [AUC = 0.7451; P = 0.0005; 95% CI: 0.6424 to

Table 3. Area under the ROC curve for all analyzed Biomarkers

Parameter		AUC	Std. Error	95% confidence interval	P-value
Weight	kg	0.7188	0.05481	0.6113 to 0.8262	0.0018
height	cm	0.5861	0.06357	0.4615 to 0.7107	0.2195
Age	years	0.5378	0.06348	0.4134 to 0.6623	0.5895
SBP	mmHg	0.7642	0.05721	0.6521 to 0.8764	0.0002
DBP	mmHg	0.7753	0.05552	0.6665 to 0.8842	<0.0001
ESR	mm/H	0.9792	0.0135	0.9527 to 1.006	<0.0001
RF	µIU/mL	0.7729	0.05148	0.672 to 0.8738	<0.0001
CRP	mg/L	0.8479	0.04527	0.7592 to 0.9366	<0.0001
Creatinine	mg/dL	0.7868	0.04832	0.6921 to 0.8815	<0.0001
U.A	mg/dL	0.6007	0.06368	0.4759 to 0.7255	0.1511
Urea	mg/dL	0.6868	0.05965	0.5699 to 0.8037	0.0077
T.C	mg/dL	0.6250	0.06826	0.4912 to 0.7588	0.0747
TG	mg/dL	0.6747	0.06286	0.5514 to 0.7979	0.0128
HDL	mg/dL	0.7365	0.05316	0.6323 to 0.8406	0.0007
LDL	mg/dL	0.5358	0.06713	0.4042 to 0.6673	0.6101
VLDL	mg/dL	0.5486	0.07209	0.4073 to 0.6899	0.4882
Hb	g/dL	0.7160	0.05821	0.6019 to 0.8301	0.0021
WBCs	(10^3/µL)	0.6208	0.06027	0.5027 to 0.7390	0.0849
Neut.	(10^3/µL)	0.6102	0.06535	0.4821 to 0.7383	0.1278
Lymph.	(10^3/µL)	0.5153	0.06816	0.3817 to 0.6489	0.8276
Mono.	(10^3/µL)	0.6451	0.06711	0.5136 to 0.7767	0.0385
NC	cm	0.7017	0.05848	0.5871 to 0.8164	0.0040
W/H		0.8253	0.04419	0.7387 to 0.9120	<0.0001
W/T		0.8083	0.04644	0.7173 to 0.8994	<0.0001
W/N		0.8024	0.04639	0.7115 to 0.8934	<0.0001
BMI	kg/m^2	0.6764	0.0649	0.5492 to 0.8036	0.0119
IL-37	pg/mL	0.9875	0.008246	0.9713 to 1.004	<0.0001
8-OHDG	ng/mL	0.7451	0.05242	0.6424 to 0.8479	0.0005

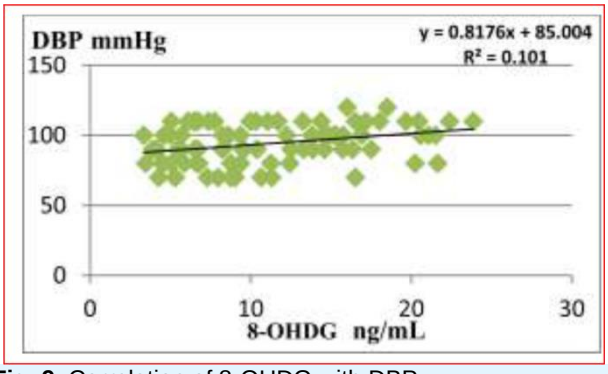

Fig. 9. Correlation of 8-OHDG with DBP

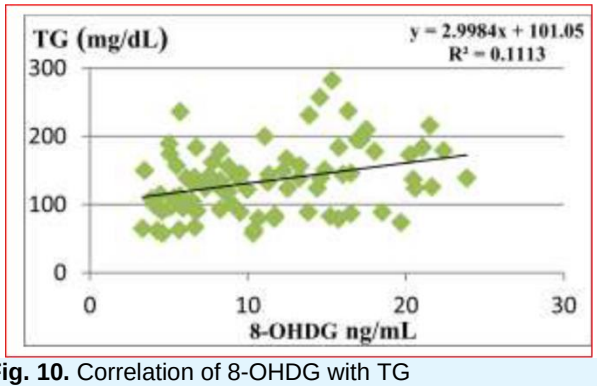

Fig. 10. Correlation of 8-OHDG with TG

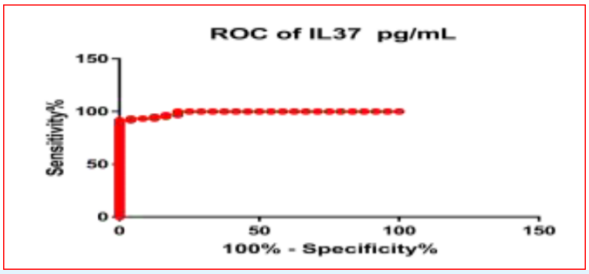

Fig. 11. ROC curve displaying AUC of IL-37 in RA patients

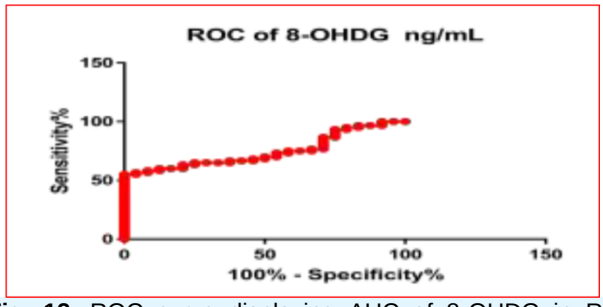

Fig. 12. ROC curve displaying AUC of 8-OHDG in RA patients

0.8479 and SE: 0.0524] (**Fig. 12**). Moreover, ESR provided an excellent discriminatory efficacy between healthy individuals and patients with RA [AUC = 0.9792; P < 0.0001; 95% CI: 0.9527 to 1.006 and SE: 0.0135] (**Fig. 13**), while anthropometric measurements (W/H, W/T and W/N) showed a very good discriminatory efficacy between healthy individuals and patients with RA [AUC = 0.8253; P < 0.0001; 95% CI0.7387 to 0.9120 and SE: 0.0442] (**Fig. 14**), [AUC = 0.8083; P < 0.0001; 95% CI: 0.7173 to 0.8994 and SE: 0.0464] (**Fig. 15**) and [AUC = 0.8024; P < 0.0001; 95% CI: 0.7115 to 0.8934 and SE: 0.0464] (**Fig. 16**), respectively.

Other parameters, with the exception of CRP, did not demonstrate good means for discriminating between healthy individuals and patients with RA, as can be seen in **Table 3**.

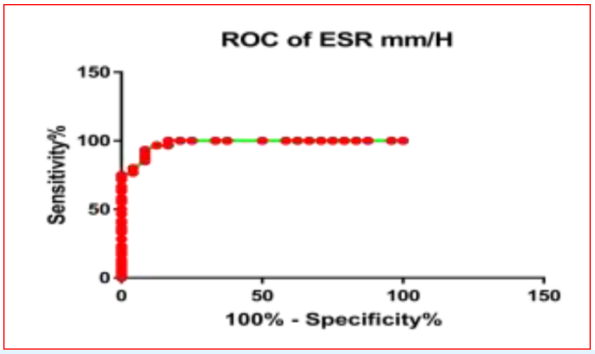

Fig. 13. ROC curve displaying AUC of ESR in RA patients

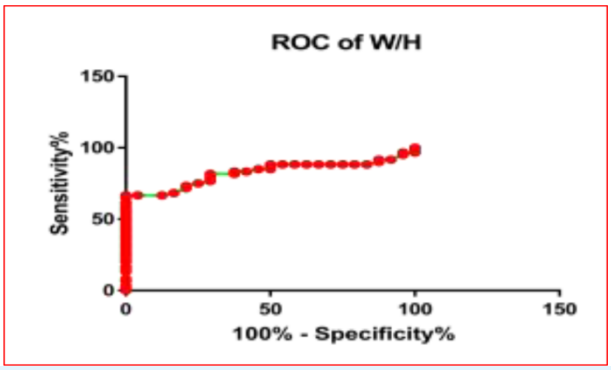

Fig. 14. ROC curve displaying AUC of W/H in RA patients

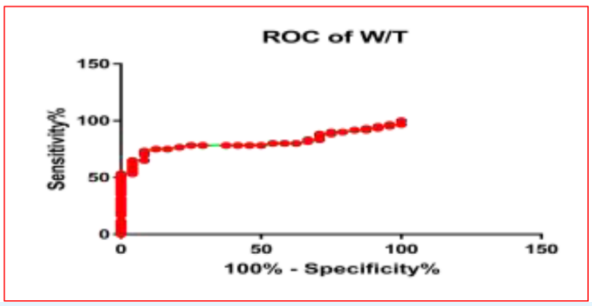

Fig. 15. ROC curve displaying AUC of W/T in RA patients

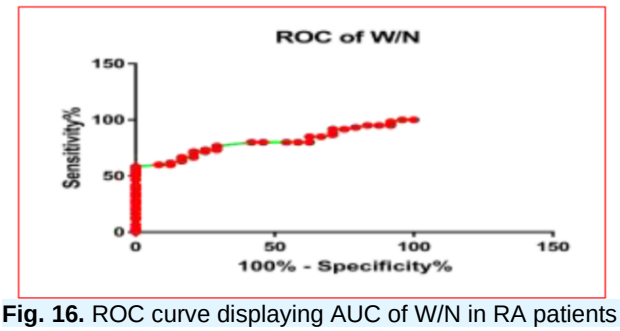

Fig. 16. ROC curve displaying AUC of W/N in RA patients

DISCUSSION

RA is an autoimmune inflammatory infection involving articular synovial propagation or lacking a general inflammatory response (Biswas et al. 2013). The imbalance among pro- and anti-inflammatory interleukin actions (McInnes and Schett 2007) is complicated in the pathogenesis of RA. Thus, encouraging the expression of anti-inflammatory interleukins and/or preventing the expression of pro-inflammatory interleukins (Huang et al. 2017) provides a possibly approach for RA treatment. A recently recognized anti-inflammatory interleukin, IL-37, can prevent the expression, manufacture, and role of pro-inflammatory interleukins (World Health Organisation 2000), and plays a complicated role in the development of autoimmune illnesses (Liu et al. 2010, Song et al. 2013). A study has demonstrated, IL-37 levels were found to be significantly higher in RA patients than in HCs, and we hypothesize that amplified IL-37 levels may be encouraged via oxidative stress indicators like 8-OHDG. IL-37 prevents unnecessary inflammatory responses by facilitating a negative feedback state in RA patients. However, augmented IL-37 could not absolutely deactivate the worsening properties of 8-OHDG in RA infection (Song et al. 2018).

To increase our knowledge concerning the function of irritation and oxidative stress in persons who are at a high risk for developing RA, we tested IL-37 as an irritation indicator and 8-OHDG as oxidative stress indicator, we established that many high-risk indicators for RA were related to increased concentrations of IL-37, including, obesity-linked factors, HDL, ESR, RF, creatinine, CRP and TG. As hypothesized, we detected that WBCs counts and hypertension were greater in patients with RA than in HCs.

Nevertheless, IL-37 concentrations were also clearly related with the AMs like W/H, W/T and W/N, as well as with ESR and mono. cells, while serum 8-OHDG concentrations presented a positive relationship with the AMs such as W/H and W/T, and as well as with SBP, DBP and TG.

The results of the present study give support to the notion that there may be local associations between irritation and oxidative stress in certain AMs for patients with RA.

Recently, cumulative signs have revealed that IL-37 is involved in rheumatic autoimmune illnesses. As an immunosuppressive interleukin, IL-37 can prevent inborn and adaptive immune reactions through downstream signaling trails. Once IL-37 is reduced in the peripheral mononuclear blood cells of RA patients, the production of IL-1, IL-6, IL-12, TNF-α, granulocyte-macrophage colony- stimulating factor (GM-CSF), and granulocyte colony- stimulating factor (G-CSF) were up-regulated after LPS activation (Tetè et al. 2012), suggesting that IL-37 may interact with Toll-like receptor 4 (TLR-4) and prevent inborn immune replies via greatly decreasing the generation of proinflammatory mediators (Tetè et al. 2012, Nold et al. 2013). IL-37 expressively repressed the stimulation of Th2/Th17 cells in mice with sensitive bronchopulmonary aspergillosis, demonstrating that IL-37 may stimulate an adaptive immune reply (Moretti et al. 2014).

RA is an inflammatory infection in which the creation of superoxide anion radicals (O^{2-}) is elevated in inflammatory cells such as polymorphonuclear leucocytes. An augmented occurrence of chromosome abnormalities and parallel chromatid connections has been found in mitogen- activated lymphocytes in patients with RA (Emerit and Michelson 1980, Weitberg et al. 1983), which is perhaps the result of prompted DNA injury. The augmented levels of oxidative cellular DNA injury, which are shown via elevated concentrations of 8-OHDG in lymphocyte DNA, probably come from the connected irritation in the illness. Such dynamic irritation could lead to augmented free radical creation in inflammatory locations. There is, nevertheless, no clear evidence that chronic irritation can encourage elevated concentrations of 8-OHDG in target tissues, although non-specific DNA injuries, like strand disruptions, are pronounced in RA patients (Chong et al. 1989).

Previous studies on the blood of RA patients shows clear evidence of the presence of increased of oxidative stress indicators involving DNA injury. In RA patients, ROS formed via neutrophils penetrates into the synovial liquid, which is believed to be involved in the pathogenesis of the illness. ROS attacks fats and proteins and produced causes impairments to tissues and DNA. The DNA injury resulting from fat peroxidation has been associated with the pathogenesis of inflammatory illnesses (Seven et al. 2008). Native and systemic growth in inflammatory interleukins has effects on the augmented manufacture of ROS and the raised concentration of fats, proteins and DNA compounds involving MDA, isoprostane and 8-OHDG (Frijhoff et al. 2015). Amplified concentrations of inflammatory interleukins, neutrophils, macrophages and lymphocytes existing in synovial liquid leads to rises in ROS outputs, which are connected to an increased incidence of RA (Kennedy et al. 2011).

The incidence of RA was found to have a link to higher values of Wt., W/H, W/T, W/N, SBP, DBP, ESR, RF, creatinine, urea, UA, TC, TG, WBCs, BMI and, lower HDL, and Hb content are, all related to worsening and prolonged irritation in ongoing RA illnesses (Pasceri 1999).

The outcomes of this study reveal clear differences in the circulation of abdominal fat between RA patients and HCs, with; significant variations in BMI. Greater quantities of visceral fat were closely linked to an increase in a number of cardiometabolic risk factors in RA patients in comparison to HCs. In RA patients a number of inflammatory and noninflammatory mediators may lead to these detected changes, involving certain elements that are adaptable for controlling RA (e.g., regulating accumulative contact to glucocorticoids). Our findings, which show a link between RA and higher W/H, W/T, W/N and BMI, also show that both subcutaneous fatty acids (SFA) and visceral fatty acids (VFA) were related with CV risk factors (SBP, DBP, TC, HDL and TG).; Nevertheless, only visceral fat stayed closely related with risk factors for developing RA, later accounting for further AMs. Therefore, augmented visceral fat may explain the higher risk of CVD detected in RA patients (Avina-Zubieta et al. 2008). The initial causes of elevated VFA and SFA in RA patients may be multifactorial. In the current study, we recognized three RA disease reasons relationships associated with augmented VFA in both men and women: W/H, W/T and W/N. The reason for the relationship between these AMs and VFA is not clear. Since there is no identified biological relation among RA and adipose increase, the link may be associated with RF, as a disease severity indicator. Nevertheless, other indicators for the severity of RA that were evaluated in our study (e.g., ESR, CRP) showed no relation to VFA.

The outcome of this study presented W/H, W/T, W/N and obesity as risk factors for developing RA., Similarly, these AMs are linearly related with IL-37 and 8-OHDG. A reasonable hypothesis to explain the increased risk of developing RA in overweight persons is that obesity may stimulate autoimmunity via a range of mechanisms involving the excretion of adipokines (Versini et al. 2014). Although, no specific biological mechanism has been identified to account for this positive relationship, the present study supports Lu et al.'s findings that indicated a positive relationship between increasing BMIs and the development of RA (Lu et al. 2014).

Area under the curve (AUC) was used as a means of testing of the diagnostic power of the AMs made in this study. The larger the AUC, the larger the discriminatory power of the AMs. IL-37 was the best predictors of RA, with W/H, W/T and W/N also being reliable predictors of it. The current study observed that BMI, W/H, W/T and W/N were also linked with RA. Though W/H was the best predictor of RA, all other AMs exhibited good or high sensitivities and specificities for the diagnosis of RA. Notably, W/H, W/T and W/N were simple, easy to determine, and dependable predictors for RA. Our study demonstrated that patients with higher NC values presented as higher risks for developing RA. Thus, it seems to be clinically appropriate to use NC as a scale of extreme fat in the upper area of the body, as a result of its ease of use, slight contact of the singular evaluated, and as risk factor for the development of RA. This scale is provides a potential low-cost way for measuring the probability of developing RA and the loss of biological roles in large groups. Previous studies have demonstrated that the upper part of the body (neck) is largely responsible the of systemic free fatty acids from the visceral region, in obese individuals (Nielsen et al. 2004, Korbag et al. 2019, Zamani Meymian 2020).

The limitations of our study were as follows. Firstly, the sample size was not large enough. Thus, a larger sample size should be used for further research in this area. Moreover, a number of other significant variables,

such as GSHPx, CAT, SOD, 4-hydroxynonenal and MDA, should be investigated to estimate the oxidative injury and antioxidant roles in the body.

Oxidative stress is a dynamic and complicated condition, and it needs more exploration in this context, including in relation to the tools used for its calculation and identification, and its role in the diagnosis of illnesses involving RA.

Our data showed that IL-37 and 8-OHDG concentrations are related with W/H, W/T and W/N as indicators of RA. This study has thus shed new light on the complex interplay between inflammation and oxidative stress in RA.

This research supports the use of W/H, W/T and W/N preoperatively to identify the likelihood of developing RA, as they provide an easy and reliable assessment method. However, in cases in which the measurement of both height and weight is not possible, NC may provide a useful surrogate measurement, because it can be obtained only with a tape measure at no cost.

Finally, we have shown that higher concentrations of 8-OHDG are associated with the development of RA, and those findings explain the significance of fat peroxidation and its implications for the pathophysiology of RA. The measurement of fat peroxidation biomarkers in the blood could thus be beneficial for checking RA. Therefore, it can be concluded that oxidative damage plays a central function in the development of RA.

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