Study of some risk factors for developing rheumatoid arthritis

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Objective
The objective of this study was to evaluate some of risk factors for developing rheumatoid arthritis (RA).

Patient and methods
A total of 60 patients with RA who fulfilled the American College of Rheumatology 2010 classification criteria were included, and 20 healthy participants served as a control group. Patients answered questions about age, smoking, full reproductive history, and therapeutic history. Venous blood sampling was taken, and the following investigations were done: erythrocyte sedimentation rate, C-reactive protein, liver enzymes (alanine aminotransferase and aspartate aminotransferase), rheumatoid factor, anticyclic citrullinated peptide, serum calcium and phosphorus, and serum vitamin D level.

Results
The mean age of patients with RA was 52.30 ± 14.71 years. Overall, 5% of patients were current smokers, 61.7% were passive smokers, and 8% were exsmokers. BMI of patients was 30.31 ± 4.73 kg/m^2. Age at menarche was insignificantly earlier in patients than control group (10.10 ± 0.99 vs. 11. 17 ± 1.17 years; P = 0.28). There was severe vitamin D deficiency (<10 ng/ml) in 45% of the patients, insufficient (10–24 ng/ml) in 46.7%, and optimal (25–100 ng/ml) in 8.5%. There was a significant inverse correlation between serum vitamin D levels and RA disease activity score.

Conclusion
RA is more common in women. Obesity, smoking, and reproductive state in women are risk factors for developing RA. Vitamin D deficiency is common in patients with RA, and as the vitamin D level decreases, the disease activity increases.

Keywords:
BMI, rheumatoid arthritis, risk factors, smoking, vitamin D

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Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disease and is evaluated to influence ~1% of the population [1].

Women are affected two to four times more frequently than men. Although RA hazard increases with age, it can show at any stage of life, counting childhood, youth, and adulthood [2].

The current evidence linking parity with RA risk remains inconclusive. Some studies suggest that null parity is either protective against or a risk factor for RA, whereas other studies have failed to identify a significant relationship. Similarly, studies of breastfeeding, oral contraceptive (OC) use, age at menarche, age at first birth, age at menopause, and other reproductive characteristics have yielded inconsistent results. RA signs and symptoms may be improved within the setting of pregnancy and tend to flare-up in postpartum period, implicating excessive or normal levels of female hormones (estrogen and progesterone) as protective factors against RA development [3].

Vitamin D insufficiency is more common in patients with RA and may be one of the causes driving improvement or decline of RA. In RA, as the activity of the disease increase, the serum vitamin D levels tend to diminish. Further research is required so that the antiproliferative, immunomodulatory, and anti-inflammatory properties of vitamin D could be exploited to treat a variety of autoimmune rheumatic diseases [4].

Smoking is thought to be a risk factor for the development of multiple autoimmune diseases, such as systemic lupus erythematosus, primary biliary cirrhosis, Graves' disease, and RA. Smoking modulates the immune system by reducing natural killer cells, depressing hormonal cells and cell-mediated immunity, and leading to dysfunction of T lymphocytes [3].

The exact pathophysiologic effects of smoking on RA are vague. Components of cigarette smoking have been shown to affect synovial inflammation, with reversal of the effect when smoking ceases. In addition, RA remission rates have been reported to be lower in smokers compared with nonsmokers [5].

The part of obesity in RA development and severity is less well set up [6]. Weight in RA has been related with an expanded hazard of mortality and cardiovascular comorbidity and adds up to joint substitution, work incapacity, high therapeutic costs, and impeded quality of life [7]. The long-term function of the joint and activity of disease may be influenced by excess weight [8].

Patients and methods

A prospective study was performed at Rheumatology Unit of Internal Medicine Department and its outpatient clinic. It was performed in the period between May 2017 and May 2018. This study was carried out on 60 patients with RA fulfilling the American College of Rheumatology 2010 criteria in addition to 20 healthy participants as a control group.

All the patients and controls in the study were subjected to the following:

(1) History taking, which includes 'age and smoking status' from personal history, 'disease duration' from the history of present illness, a special full reproductive/obstetric history section, as well as therapeutic history.
(2) Detailed clinical examination was done, with special emphasis on joint examination.
(3) Venous blood sampling was taken, and the following investigations were done: Erythrocyte sedimentation rate (ERP), C-reactive protein (CRP), liver enzymes (alanine aminotransferase and aspartate aminotransferase), rheumatoid factor, anticyclic citrullinated peptide (CCP), serum calcium and phosphorus, and serum vitamin D level (total 25-hydroxy vitamin D_2–D_3)].
(4) BMI was measured (kg/m^2).
    (a) Underweight: BMI is less than 18.5.
    (b) Normal weight: BMI is 18.5–24.9.
    (c) Overweight: BMI is 25 to 29.9.
    (d) Obese: BMI is 30 or more.
(5) Disease Activity Score 28 (DAS28) was calculated.

Ethical approval

The study protocol was approved by the Ethics Review Board of Faculty of Medicine, Assiut University, and informed consent was obtained from all participants according to the Declaration of Helsinki.

Statistical analysis

Data were collected and analyzed using statistical package for the social science, version 20 (IBM Corp., Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD or median (range), whereas nominal data were expressed in the form of frequency (%). χ^2-test was used to compare the nominal data of different groups in the study, whereas Student's *t*-test was used to compare the mean of two different groups.

Pearson's correlation was used to determine the correlation between DAS and vitamin D level and other continuous variables (r > 0.2 indicates nil correlation, 0.2: 0.4 indicates mild correlation, 0.4: 0.6 indicates moderate correlation, 0.6: 0.9 indicates strong correlation, and 1 indicates perfect correlation).

P value was significant if less than 0.05.

Results

A total of 60 patients with RA fulfilling the American College of Rheumatology 2010 classification criteria (13 of them were males and 47 females) were included, and 20 healthy participants served as a control group (nine of them were males and 11 females).

The mean age of patients with RA was 52.30 ± 14.71 years. Overall, 5% of the patients were current smokers, 61.7% were passive smokers, and 8% were exsmokers. BMI of patients was 30.31 ± 4.73 kg/m^2 (Table 1).

There was a statistically significant difference among both groups concerning different laboratory tests (Table 2).

It was noticed that there is severe deficiency in vitamin D in 45% of the patients with RA (<10 ng/ml), insufficient (10–24 ng/ml) in 46.7%, and optimal (25–100 ng/ml) in 5%. However, in healthy group, there was insufficiency in 45% and optimal vitamin level in 55% (Table 3). Age at menarche was insignificantly earlier in patients than control group (10.10 ± 0.99 vs. 11.17 ± 1.17 years; P = 0.28) (Table 4). RA improved in four cases during pregnancy and got worse in only one case. Although during puerperium, there was flare-up of the disease in three patients of the five who got pregnant during the course of the disease (Table 4).

It was noticed that disease activity score had significant positive correlation with CRP, ERP, rheumatoid factor, and anti-CCP but it had significant negative weak correlation with vitamin D level (r = –0.32, P = 0.0) (Figs. 1–5).

Discussion

RA is a chronic, autoimmune inflammatory disease with a female predominance and is estimated to affect ~1% of the world's population [1].

Table 1 Demographic data of patients and controls

	Patients (*n*=60)	Control group (*n*=20)	*P* value
Age (years)	52.30±14.71	48.90±12.98	0.11
Sex			
Male	13 (21.7)	9 (45)	0.06*
Female	47 (78.3)	11 (55)	
Smoking status			
Current smoker	3 (5)	2 (10)	0.01*
Passive smoker	37 (61.7)	10 (50)	
Exsmoker	8 (13.3)	7 (35)	
Nonsmoker	12 (20)	1 (5)	
BMI (kg/m^2)	30.31±4.73	27.89±5.39	0.43

Data are represented as mean±SD and frequency (%). *P<0.05, significant.

The etiology of RA is unknown, but genetic factors were associated with the disease condition and its severity. Multiple environmental and lifestyle factors were also associated with its development [3,8].

In this study, 60 patients with RA were included, where 47 of them were females and 13 were males (3: 1 ratio), with a female predominance, which agrees with Silman and Hochberg [3].

Among the patient group, 5% were current smokers, 61.7% passive smokers, and 8% exsmokers. However, in the control group, only 2% were current smokers, 10% passive smokers, and 7% exsmokers. The significant difference between both groups may assume that smoking is a risk factor for RA.

These results are consistent with a case–control study about smoking and susceptibility to RA in a Swedish population

Table 2 Laboratory data in both groups

	Study group (*n*=60)	Control group (*n*=20)	*P* value
ESR (ml/h) (N=0 : 22)	88.87±22.98	8.70±2.98	0.00*
CRP (mg/dl) (N=0.8 : 3)	38.33±12.12	12.48±3.81	0.00*
RF (IU/ml) (N=<15)	114.23±23.91	0	0.01*
Calcium (mg/dl) (N=8.5 : 10.2)	7.73±0.97	8.94±1.18	0.03*
Phosphorus (mg/dl) (N=2.5 : 4.5)	4.71±0.81	5.66±1.17	0.04*
Anti-CCP (U/ml) (N=<20)	109.56±32.45	0	0.01*

Data are represented as mean±SD. CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor. *P<0.05, significant.

Table 3 Level of vitamin D in patients and controls

Level of vitamin D	Study group (*n*=60)	Control group (*n*=20)	*P* value
Mean (SD) (ng/ml)	14.33±3.23	25.22±4.67	0.03*
Severely deficient (<10 ng/ml)	27 (45)	0	
Insufficient (10–24 ng/ml)	28 (46.7)	9 (45)	
Optimal (25–100 ng/ml)	5 (8.5)	11 (55)	

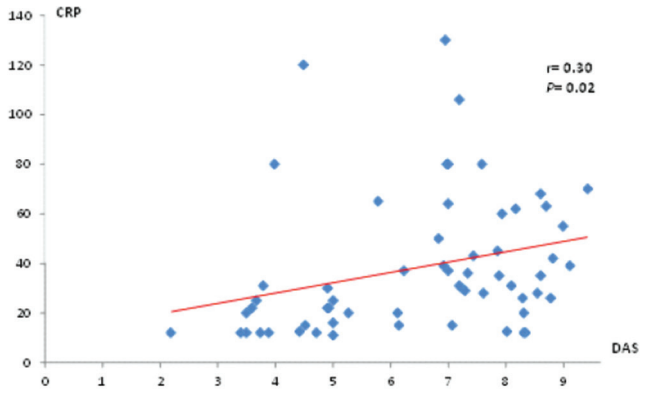
Data are represented as mean±SD and frequency (%). *P<0.05, significant.

Table 4 Possible risk factors for rheumatoid arthritis in this study female participants

	Study group (*n*=60)	Control group (*n*=20)	*P* value
Age at menarche (years)	11.17±1.17	10.10±0.99	0.28
Age at menopause (years)	48.5±3.29	46.06±2.99	0.42
Got pregnant	18 (38.2)	8 (72)	**0.03***
Age at the first pregnancy (years)	18.88±2.02	21.01±1.34	0.52
Number of pregnancies	4 (2–8)	4 (0–7)	0.32
Number of abortions	2 (1–4)	1 (0–3)	**0.01***
Breastfeeding	14 (30)	5 (45.5)	**0.028**
Disease during pregnancy			
Improved	15 (32)		
Get worse	3 (6.2)		
Disease during puerperium			
Improved	13 (27.6)		
Get worse	5 (10.6)		
Use of contraception	10 (21.3)	5 (45.5)	**0.01***

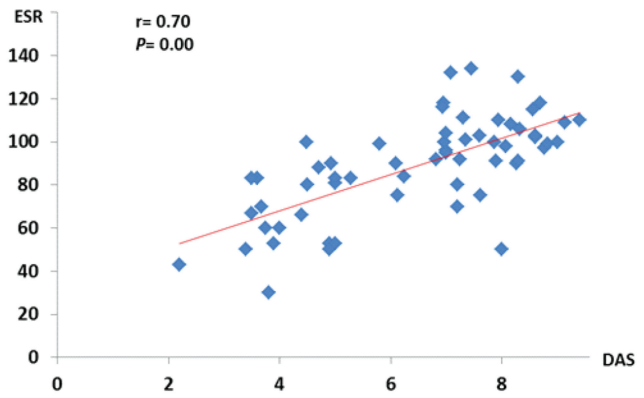
0.03*: Increase incidence of pregnancy reduce the risk factor for developing RA, as in control 72% got pregnant, while in patients 38.2 % only got pregnant (In agreement with our study, Guthrie *et al.* [14] and Reckner *et al.* [15] found that parous women had a lower risk of RA than women without children), **0.01***: The relation between RA and increase risk of abortion, **0.028**: Few researches tell that breastfeeding as well as pregnancy improve the severity and the risk for developing RA (Hughes GC, Choubey D, (2014): Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. Nature Reviews: Rheumatology. Advance online publication 26 August. Data are represented as mean±SD, median (range), and frequency (%). *P<0.05, significant.

Figure 1



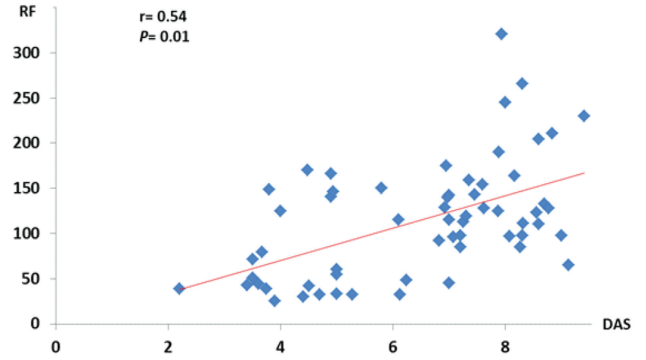
Correlation between Disease Activity Score (DAS) and C-reactive protein (CRP).

Figure 2



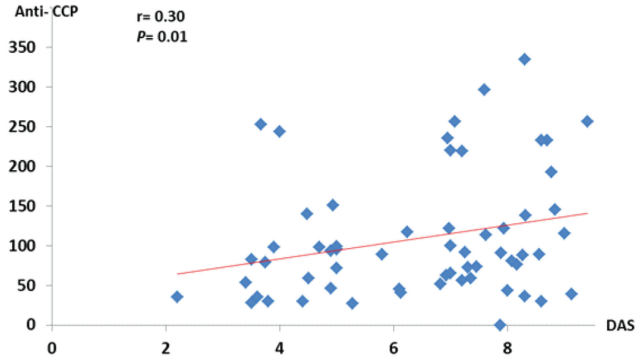
Correlation between Disease Activity Score (DAS) and erythrocyte sedimentation rate (ESR).

Figure 3



Correlation between Disease Activity Score (DAS) and rheumatoid factor (RF).

Figure 4



Correlation between Disease Activity Score (DAS) and anti-cyclic citrullinated peptide (CCP).

by Hedström *et al.* [9], which found that smoking is a risk factor for developing RA, and also smoking duration and index has a positive effect on RA development.

In this study, the mean BMI of patients was 30.31 ± 4.73 kg/m^2. This is consistent with Dar *et al.* [10] who published that obesity increases the risk of RA.

Schulman *et al.* [11] suggested that obesity reduces the likelihood of achieving sustained remission in early RA by nearly half, and being overweight reduces it by a quarter.

Sex hormones may play a role in RA, as evidenced by the disproportionate number of females with this disease, its amelioration during pregnancy, and its recurrence in the early postpartum period [12].

In this study, 18 (36.7%) patients got pregnant, and only five of them happened during the course of the disease. The number of abortion was significantly higher in patients (P = 0.01).

In this study, RA improved in four cases during pregnancy and got worse in only one case. However, during puerperium, there was disease flare-up in three patients of the five who got pregnant during the disease, which was similar to the results found by de Man *et al.* [13].

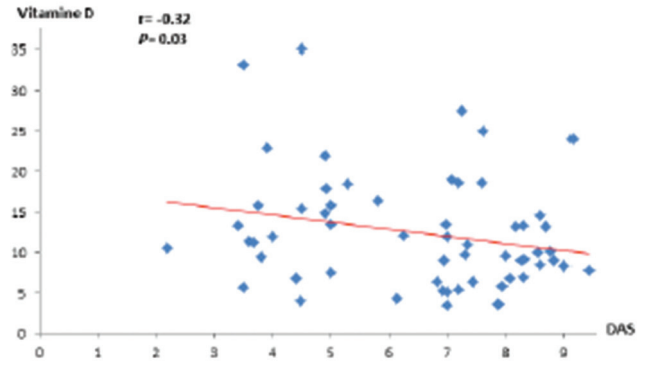
In agreement with our study, Guthrie *et al.* [14] and Reckner *et al.* [15] found that parous women had a lower risk of RA than women without children. Although Jørgensen *et al.* [16] reported an increased risk of onset in the postpartum period, other studies show no relation between parity and RA.

Moreover, Krause *et al.* [17] published that ~50% of pregnant women with RA have low disease activity, and 20–40% achieve remission by the third trimester; however, nearly 20% will have worse or moderate-to-high disease activity during pregnancy.

Moreover, Silman *et al.* [18] stated that ~90% of women with RA experienced flare-ups during the postpartum period.

In our study, the frequency of abortion was significantly higher in the study group (P = 0.01), with two women

Figure 5



Correlation between Disease Activity Score (DAS) and vitamin D.

who had abortion during the course of the disease versus 1 in the female controls. These women did not stop taking drugs during pregnancy nor had a medical consultation before pregnancy. These results raise concerns on the rate of unplanned pregnancies in women with RA and should prompt future research on counseling, contraception use, and unplanned pregnancies [19].

In this study, only 10 female patients were using contraceptive methods. This agrees with a Swedish case–control study in 2017, which reported that OC use appears to reduce the risk of developing RA by 13% [20].

Regarding vitamin D level, it was noticed that there was severe deficiency in 45% of the patients, insufficient in 46.7%, and optimal in 5%, whereas in the healthy group, there were 45% insufficient and 55% optimal.

In agreement with our study, the studies conducted by Ibrahim *et al.* [21]. Yagiz *et al.* [22] found significantly lower vitamin D levels in patients with RA, as compared with control population, thus supporting the possible role of vitamin D in the pathogenesis, activity, and treatment of RA.

We noticed that 45% of the healthy control group had vitamin D insufficiency, which might be related to decreased sun exposure, for variable religious (Muslims hijab) or cultural reasons that can carry considerable risk factors among healthy and diseased population [23].

Moreover, in our study, there was a significant inverse correlation between serum vitamin D levels and RA disease activity score, which is supported by the research of Bragazzi *et al.* [24].

Furthermore, there was a positive significant correlation between ERP and CRP, rheumatoid factor, and anti-CCP on one hand and DAS on the other hand. This was in agreement with Ghozlani *et al.* [25], who noticed that disease activity score had significant positive correlation with the same aforementioned laboratory investigations.

Conclusion

RA is more common in females. Obesity, smoking, and reproductive state in women were risk factors for developing RA. Vitamin D deficiency is common in patients with RA. There is a significant inverse correlation between serum vitamin D levels and RA disease activity score.

Recommendations

Women with RA should be counseled before getting pregnant, and their treatment must be re-evaluated.

Concerning contraception in the women with risk of developing RA, and female patients with RA, combined OCs are preferable.

Smoking is a very common risk factor for developing RA, even after 10 years of cessation or more.

Obesity is also considered a major risk factor for developing RA and even is a cause of early complications and death.

Vitamin D supplement is important for patients with RA to decrease activity of the disease. Moreover, normal people in Egypt should be screened for vitamin D level; however, because of the high cost of the test, prophylactic dose could be given to high-risk individuals for RA.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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