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IMPACT OF SOCIO-DEMOGRAPHIC CHARACTERISTICS ON THE SEVERITY OF RHEUMATOID ARTHRITIS IN MOROCCO

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ABSTRACT

The etiology of rheumatoid arthritis (RA) remains to date unknown. However, according to the main hypothesis, it has been proposed that several factors are contributing to its development. Among them, we find the socio-demographic factors. The aim of this study is to descript the socio-demographic characteristics and to investigate the association of serological status and disease parameters of rheumatoid arthritis (RA) in Moroccan patients by comparing them with a control group. The study population comprised a cohort of 111 patients with RA recruited from the military hospital in Rabat and 212 individuals of the control group (CG) recruited from the National Blood Transfusion Center of Rabat. All patients were tested for auto-antibodies: cyclic citrullinated peptide (ACPA or anti-CCP2), rheumatoid factor (RF), antinuclear auto-antibodies (ANA), antibodies of antigenic specificity (ENA profile) and anti-DNA. Females showed predominance with 84.68% of RA patients. The descriptive analysis between patients and controls group showed that exists significant differences were found regarding gender, age, BMI, alcohol, inbred marriage and family history. Rheumatoid factor (RF), anti-citrullinated peptide antibody (ACPA or anti-CCP2), antinuclear auto-antibodies (ANA), antibodies of antigenic specificity (ENA profile) and anti DNA were detected in RA patients and it showed a high percentage of 95.5%, 80%, 84.7%, 45% and 5.4%, respectively. Furthermore, both RF and ACPA were presented in 80% of RA patients. We observed that ACPA present a positive correlation for gender. On the other hand, RF presents no significant correlation with socio-demographic characteristics. In this study, we describe disease features that are unique to Moroccan patients and demonstrate that RA has a significant disease burden. Our RA patients with a high prevalence of RF and ACPA appear to

have more active and severe disease and maybe the socio-demographic characteristics increase the probability of having RA disease. Our findings may help provide relevant information on the immunological profile of our RA patients.

Keywords: Rheumatoid arthritis, Socio-demographic characteristics, Rheumatoid factor, anti-cyclic citrullinated peptide, Antinuclear auto-antibodies, Moroccan Patients

1 INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune, multisystem, inflammatory, progressive disease of uncertain etiology characterized by joint pain, swelling, stiffness and destruction of the synovial joint, resulting in severe impairment and premature mortality (Guillemin, 2005). It is estimated to affect between 0.5% and 1.0% of the global adult population and affects women more than men (Sokka *et al.*, 2009). Consequently, they have a major impact on the daily experience, professional activity and family life of the patient. Of many studies have highlighted the deterioration of the quality life time of these patients (Ambriz Murillo *et al.*, 2015) Risk factors for RA include genetic susceptibility factors, gender, age, smoking, infectious agents, hormonal factors and ethnic factors (Othman *et al.*, 2016).

In Morocco, the incidence of RA is not yet clearly established. However, the disease has a significant impact on the socio-professional activity and the economic situation of patients (Kalla *et al.*, 1988). This has an impact on the involvement of patients in paid employment, their performance at work inside and outside the home, and their participation in family, social and leisure activities (Othman *et al.*, 2016), (Abdel-Nasser, Rasker and Vaikenburg, 1997), (Almeida, Almeida and Bertolo, 2014). Previous studies have highlighted a poorer quality of life (especially physical health) in patients with RA compared to the general population (Bullinger and Quitmann, 2014). Factors associated with poorer quality of life in RA are older age, female gender, lower economic status, lower education level and lack of physical activity (Ibn Yacoub *et al.*, 2012b).

The research and management of these socio-demographic characteristics aim to preserve or even improve the patient's quality of life and his or her life expectancy, thus being able to limit the psychosocial consequences. Several antibodies have been described in recent years in patients suffering from PR, but not all have been successfully integrated into routine clinical practice (Mewar and Wilson, 2006). Two important autoantibody systems have been described in RA, of which rheumatoid factors (RF) and autoantibodies against citrullinated peptides / proteins (ACPA) are widely used. This allows the diagnosis and follow-up of the majority of patients with RA (Ibn Yacoub *et al.*, 2012b) (Fang, Ou and Nandakumar, 2019a), (Singwe-Ngandeu *et al.*, 2010). In addition, these markers are very specific in the diagnosis of RA. ACPA tests serve as predictors of disease course and outcome (MIMORI, 2005a). Previous studies have shown that ACPA is present in 60-80% of patients with RA with a high specificity of over 95% (Mewar and Wilson, 2006). The distribution of clinical features is important because new biologic therapies may change the disease burden.

In this study, we describe and compare Socio-demographic Characteristics in RA patients with control groups and research if it is a significant correlation of these characteristics with positive RF and positive ACPA. Our findings may help to enrich the Moroccan database concerning the profile of our RA patients.

2 MATERIAL AND METHODS

2.1. Study population

This study involved 111 RA severe patients hospitalized and 212 control group (CS). RA patients were recruited from the Rheumatology in the rheumatology department of the Military Hospital (Rabat, Morocco). Exclusion criteria for RA patients: other types of inflammatory arthritis, including psoriatic arthritis, reactive arthritis, spondylarthropathies and inflammatory arthritis related to bowel disease.

The group control (GC) eligible blood donors recruited at the National Blood Transfusion Center (Rabat, Morocco). Exclusion criteria for GC must not have autoimmune and/or inflammatory disease.

Socio-demographic characters were collected using a pre-established operating sheet which included the following parameters: Socio-demographic data including: gender, age, body mass index (BMI), Menopause, Marriage status, Inbred marriage, smoking, alcohol, history family, depression, professional status and Father's/Mother's origin.

All involved patients signed a written informed consent. This study was approved by Ethics Committee for Biomedical Research in the Faculty of Medicine and Pharmacy of Rabat (CERB), (IORG Number: IORG0006594) Morocco. The committee's reference number: 70/17.

2.2. Immunological tests

All sera (patients and GC) were tested by IIF for antinuclear auto-antibodies detection (ANA), anti DNAdb and also tested by ELISA for the identification of the search for soluble anti-antigen antibodies ENA Profile (SS-A, SS-B, Sm, Sm / RNP, jo1 and Scl70), for anti ccp2 and for RF.

All tests were performed at the autoimmunity laboratory of the National Institute of Hygiene (Rabat, Morocco) using an automated system (Biorad system PhD™) and immunodot.

2.2.1. Indirect immunofluorescence (IIF)

Antinuclear auto-antibodies was detected by IIF using Hep-2 cells (Bio-Rad Laboratories, CA) who is as highly sensitive substrates .The clinically significant titer was 1:160. Test for anti-DNA antibodies was performed by IIF using Crithidia luciliae (Bio-Rad Laboratories, CA) as substrate and the clinically significant titer was 1:5.

2.2.2. Enzyme – linked immunosorbet assay (ELISA)

The detection the antibodies of specific Nuclear Antigen (ENA profile) was performed by ELISA (Bio-Rad Laboratories, CA) tested six antigens such as anti-smith antibody (Sm), anti-ribo-nucleoprotein antibodies (RNP), anti-Ro antibody (anti SSA), anti-la antibody (anti-SSB), anti histidyl-tRNA synthetase antibodies (jo1) and anti-topoisomerase I antibody (Scl-70) and also tests for anti-CCP2 (ACPA) was performed by ELISA (Bio-Rad Laboratories, CA cutoff value 5 U/mL for positivity) and rheumatoid factor (RF) IgM by Elisa (Euro immune cutoff value 20 U/mL for positivity).
Serum samples were processed in initial dilution of 1:101, 1:101and 1:201 for the detection of anti-anti-ANA6 profile, anti CCP2 and RF respectively.

2.3. Statistic analyses

Socio-demographic characters were described as mean and standard deviation (SD) and number and percentage for categorical data.
Statistical analyses were performed using STATISTICA StatSoft 12.0 Software (Tulsa, Oklahoma, USA). The relationship between the socio-demographic characters of patients with RA and control groups was determined using Chi-square $\chi 2$. Prevalence ratio (PR) was used for the assessment of risk factors. Statistical significance for all tests was set at the level of $p \leq 0.05$ using descriptive statistics.
All patients were stratified based on RF and ACPA status into four groups: RF+/ACPA+, RF+/ACPA−, RF−/ACPA+, and RF−/ACPA−. Comparisons of demographic and treatment characteristics between different RF and ACPA status were performed using the Chi-square test $\chi 2$, Prevalence ratio (PR) as appropriate for categorical data. A p-value of <0.05 was considered statistically significant.

3 RESULTS

3.1. Demographic features

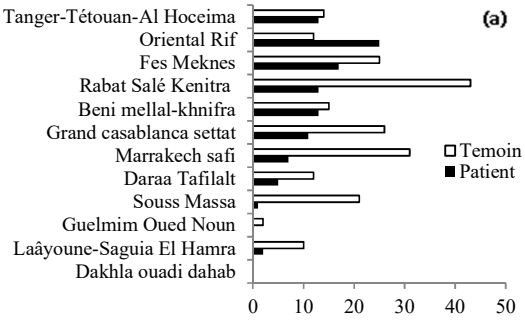
The socio-demographic data of RA patients and GC are presented in Table 1. We found that the average age of RA patients was 57.09 ± 12.21 years (ranging from 18 to 83 years) and 37.18 ± 12.21 (19-59 years) for CG. A female preponderance of 84.68% (94 women / 17 men) was observed in RA patients, while in the GC, men were more concerned by 51.89% vs 48.11% in women), since, they were no matched by age and sex. The married in RA was 99 %, while in GC was70.7%. The menopause in RA 30%, while in GC was 10.3% (Table 1).

Table 1: Baseline Socio-demographic characteristics of RA patients and control groups

	RA Patients	**Control groups**
Total	111	212
Women	94 (84.7 %)	102 (48.1 %)
Men	17 (15.3 %)	110 (51.9 %)
Age	57.09 ± 12.21	37.18 ± 12.21
BMI	27.47 ± 5.04	26.10 ± 4.19
Menopause	33(30%)	22(10.3%)
Marriage status	110 (99 %)	150(70.7%)
Inbred marriage	23 (20.7 %)	29 (13.7 %)
Smoking	14 (12.6 %)	28 (13.2 %)
Alcohol	13 (11.7 %)	5 (2.4 %)
History family	39(35.1%)	42(19.8%)
Depression	7 (6.3 %)	8 (3.8 %)
Professional Status		
Housekeepers	13 (12 %)	27 (12.7 %)
Civil servants	7 (6 %)	91 (42.9 %)
Retirees	15 (13 %)	1 (0.5 %)
Trader	0	2 (0.9 %)
Housewives	73 (69 %)	91 (42.9 %)

BMI: *Body Mass Index*

We also found that the location of origin of the parents of our RA patients was very high in the north of the country compared to the south (Fig. 1a and Fig. 1b).



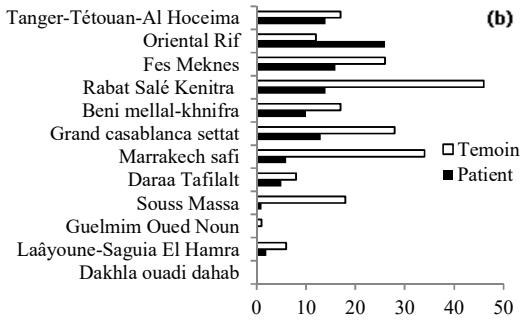


Fig. 1: Father's origin (a) and Mother's origin (b) of RA patients.

35% had a family history of RA disease in our patient compared to the control group. Also, we observed 12.6% smoking and 11.7% alcohol in RA patients, but in CG in 13.21% smoking and 2.34% alcohol. The depression was observed in 7 patients with RA (6.31%) but 3.77% in 8 cases for CG. Regarding professional status, we observed that housewives was higher (69%) followed by 13% are retired, 12% are housekeepers and 6% are civil servants in the RA group. While in the GC, civil servants and housewives were the highest 42.9% followed by housekeepers 12.7% (Table 1).

3.2. Correlations analyses between socio-demographic characters and patients with RA and control groups

The correlations analysis socio demographic and patients with RA and GC (Table 2) showed a significant correlation between the two groups for the following factors: gender, age, Inbred marriage, alcohol, and family history with higher and positive Pearson index X^2 ($P < 0.01$). Also, we found a negative correlation for smoking character, but no significance was observed with BMI and depression characters. But present a negative correlation pour gender and age.

Table 2: Correlations analyses socio-demographic and patients with RA and control groups.

Variables	X^2	P_{value}	Prevalence Ratio	CI
Gender	33.68	< 0.01*	0,31	0.44-0.52
Age	98.54	< 0.01*	0,14	0.44-0.52
BMI	1.24	0.27	0,84	0.44-0.52
Inbred marriage	176.41	< 0.01*	1,36	0.44-0.52
Smoking	0.15	0.70	0,91	0.44-0.52
Alcohol	12.11	< 0.01*	2,25	0.44-0.52
Depression	1.06	0.30	1,38	0.44-0.52
History family	9.11	< 0.01*	1,62	0.44-0.52

BMI: *Body Mass Index* ***CI:*** *Confident Index*
****Significant correlation (Pvalue<0.01)***

3.3. Immunological manifestations

The prevalence of auto-antibodies detected in all sera of our study was presented in table 3. In 111 patients with RA, we found that RF were detected in 80% of patient RA (89/111), while the GC, RF were present in 24.5%. For anti ccp2 or ACPA were detected 95.5% in patients with RA while the GC, ACPA were present 2.4%.

Table 3: Profile of auto-antibodies of the patients with RA and control groups.

	Patient	Control groups
Rheumatoid factor (RF)	106 (95.5 %)	52 (24.5 %)
ACPA (anti CCP2)	89 (80 %)	5 (2.4 %)
Serologic status ACPA/RF		
• ACPA (+) & RF (+)	89 (80 %)	0
• ACPA (+) & RF (-)	0	5 (2.4 %)
• ACPA (-) & RF (+)	16 (14.4 %)	52 (24.5 %)
• ACPA (-) & RF (-)	5 (4.5 %)	155 (73.1 %)
ANA	94 (84.7 %)	14 (6.6 %)
Anti dsDNA	6 (5.4 %)	0
ENA profile	50 (45 %)	7 (3.3 %)

ACPA: *Anti-Citrullinated Peptie Antibodies,* ***dsDNA:*** *anti-deoxyribonucleic acid antibodies,* ***ANA:*** *Antinuclear antibodies,* ***ENA:*** *anti extractable nuclear antigens antibodies.*

Furthermore, status serologic the RF and ACPA in patient RA, we found 80% with RF + / ACPA +, 14.4% with RF + / ACPA−, 0% with RF− / ACPA + and 4.5% with RF− / ACPA -. While, in the GC, status serologic RF and ACPA no frequency was found in RF+/ ACPA+.

In our study, patients with RA with RF + / ACPA + constituted a strong element in favor of a positive diagnosis of RA and also prognosis and have the highest proportion of correct EULAR responses than those with RF− / ACPA−. For patients with RF + / ACPA− and RF− / ACPA + considered sero-positive patients with at least one of the two tests. The prolonged presence of FR at high concentrations is considered a chronic inflammatory process without specifying the etiology; and also considered less aggressive RA with less joint damage and a more favorable course than patients with high serum concentrations of FR and APCA.

In CG with RF + / ACPA − and RF− / ACPA + considered that these antibodies appear very early in the serum sometimes up to 15 years before the onset of symptoms in a healthy individual.
Concerning ANA were detected in 84.7%, while in GC, ANA was detected in 6.6%.
For anti dsDNA were detected (5.4%) in RA and no cases have been detected in the GC. The frequency of the ENA profile detected in (45%) in RA, while in GC ENA profile detected in 3.3%.
We conclude that IgM-RF and anti-CCP2 tests with sufficiently high specificity can assist in the early detection of RA in high-risk populations.

3.4. Socio-demographic factors outcomes stratified by RF and ACPA status

The Table 4 shows an association of demographic characteristics with positive RF and ACPA in patients with RA. We found that prevalence ratio, and Pearson X^2 for APCA higher and present a positive correlation for gender, BMI, smoking, depression, infection, menopause. As well as, APCA were present a correlation negative for age, history familial, diabetes, fracture. As well, we detected a significant correlation in gender ($p<0.01$).

Table 4: Association of Socio-demographic characteristics of RA patients with positive RF and ACPA.

	ACPA			RF		
	X^2	P_{value}	P. R.	X^2	P_{value}	P. R.
Gender	4.68	0.03*	1.29	0.95	0.33	1.06
Age	0.22	0.64	1.07	0.75	0.38	1.05
BMI	1.25	0.26	1.11	0.47	0.49	1.03
Inbred marriage	0.97	0.32	0.89	1.37	0.24	1.06
Menopause	2.14	0.14	0.86	0.26	0.61	0.98
Smoking	1.45	0.23	1.17	0.26	0.61	0.97
Alcohol	1.21	0.27	1.16	0.35	0.56	0.96
Depression	1.74	0.19	1.25	0.35	0.55	1.05
History family	0.04	0.85	1.02	0.53	0.47	1.03

ACPA: *Anti-Citrullinated Peptie Antibodies,* ***RF:*** *Rheumatoid factor,* ***BMI:*** *Body Mass Index,* ***P. R.:*** *Prevalence Ratio.*
****Significant correlation (Pvalue<0.01).***

Regarding RF, we observed prevalence ratio, and Pearson X^2 were higher and present a positive correlation for BMI, history familial. As well as, RF were present a correlation negative for menopause, smoking, alcohol, depression. RF has no significant correlation.

4 DISCUSSION

Rheumatoid arthritis is a heterogeneous disease, with variable clinical presentation and characteristics and whose risk factors are still poorly identified.
In our study, the descriptive analysis between patients and controls group showed that exists significant differences were found regarding gender, age, alcohol, inbreed marriage and family history. Also ,showed that alcohol consumption and smoking status are low compared to what is reported in the literature (El-Zorkany *et al*., 2016). These results are linked to the cultural and religious context (Intriago *et al*., 2019) . We found in RA patients 11% were smokers, this result is similar to what has been reported in the literature (9.2%,10.6%) (Namas *et al*., 2019) . Smoking is well recognized as an important factor in the etiology and severity of RA (Naranjo *et al*., 2010) . This low frequency was due to the high number of women in our series. Regarding consanguineous marriage, we found a high prevalence, which raises the question of genetic predisposition as a potential explanatory factor. We have found that depression has a low prevalence in our population, which explains a considerable reduction in the quality of life, religions and ethnic groups (Katchamart *et al*., 2020b). For RA patients, depression was due to the effect on RA management. Consequently, incapacity for work is more strongly associated with depression. This similar to what was reported in literature (Katchamart *et al*., 2020a) . Also, the professional housewives status was observed to be the highest in our patients with RA, followed by retirees and housekeeper. This result was already observed in a previous Moroccan study (Rkain *et al*., 2006). In RA patients, the age of onset in our study was similar to that of studies in western countries, which describe an age of onset ranging from 40 to 60 years (Sokka *et al*., 2009) . Female sex was also predominant in our series which was similar to results from other parts of the world (Jawaheer *et al*., 2010). It has been reported that female gender is a predictor of disability and that disability progression is three times faster in women (Oliver and Silman, 2006; Sokka *et al*., 2009).
RA is a chronic inflammatory disease, and autoantibody mediated pathology contributes to joint inflammation and destruction (Fang, Ou and Nandakumar, 2019b). Detection of both RF and anti CCP2 or ACPA can predict the extent of joint damage, and RF is also associated with extra articular lesions. Moreover, differential alterations in the levels of these two auto antibodies during treatment reflect different underlying mechanisms operating during RA (Fang, Ou and Nandakumar,

2019b) . In this study, RF and anti CCP2 or ACPAs were present in CG with RF + / ACPA− and RF− / ACPA +, these antibodies are considered to appear very early in the serum, sometimes up to 15 years before the onset of symptoms in a healthy individual (Tron, 2014). While ,RF and anti CCP2 or ACPAs were present respectively 80% and 95% of our RA patients which concords with literature data (Abdel-Nasser *et al*., 2008; Fang, Ou and Nandakumar, 2019b; Trier *et al*., 2019). However, previous studies have shown that Moroccan RA seems most likely severe with less seropositive RF (60%) (Benbouazza *et al*., 2011). In fact, differences in laboratory tests and techniques that have been used to measure RF could explain the differences in the rate of seropositive RF patients. In recent data the positivity of anti CCP2 or ACPA among RA Patients was lower than our data (estimated 60 to 80% with ACPA) (Kurowska *et al*., 2017). In fact, in this study, the authors demonstrated that the second generation ACPA test had a higher sensitivity than the first generation test and a similar specificity that has made it possible to identify different phenotypes of patients with RA (Kurowska *et al*., 2017). We found that patients with the presence of both auto-antibodies had the most severe and aggressive clinical courses, while those with RF or anti-ccp2 or ACPA positivity had intermediate courses and those without these antibodies had modest disease. The number of patients positive for RF (95.5%), ACPA (80%) and ANA 84.7% was consistent with the expected rates in a severe RA population (MIMORI, 2005b; Kim *et al*., 2010; Ibn Yacoub *et al*., 2012c) .The presence of ANA was e due to the presence of the manifestation of extra-articular diseases or were a hallmark of systemic autoimmune rheumatic diseases (SARD) (Sebbag *et al*., 2004; Pérez *et al*., 2017). These results are comparable to those in the literature (Katchamart *et al*., 2015; Kurowska *et al*., 2017).

Several recent publications have established a strong association between rheumatoid arthritis (RA) and positivity to anti-CCP and RF (Turesson *et al*., 2007; Katchamart *et al*., 2020a). In our study, we found that gender was significantly higher in anti-CCP positive than in RF positive in RA patients. This study suggests a strong association between the severity of RA and the presence of anti CCP2 or ACPA in patients with RA. Specifically, a correlation with four known predictors of the severity of RA: age and familial ATCD revealed a significant association in RA patients with anti CCP2 or ACPA. Our results are consistent with those of other authors recommending that anti-CCP be included in the diagnostic criteria for RA and be used as a marker of disease severity (Alawneh *et al*., 2014; Nehmar, 2020).

In the Moroccan data previously, the main factors associated with ACPA and RF levels were functional disability, structural damage and impaired quality of life (Ibn Yacoub *et al*., 2012a) (Syngle, Singh and Verma, 2019). Our results provide practical suggestions in daily practice. They suggest that the determination of RF and ACPA is useful, not only in the diagnostic and prognostic implication of "early" RA, but it is also useful in the prediction of clinical progress in the setting of a disease. For a long time, people who have RF and ACPA positivity should be treated quickly and aggressively to improve results.

5 CONCLUSION

Our RA patients with a high prevalence of RF and ACPA appear to have more active and severe disease and maybe the socio-demographic characteristics increase the probability of having RA disease. Our findings may help provide relevant information on the immunological profile of our RA patients.

They suggest that the determination of RF and ACPA is useful, not only in the diagnostic and prognostic implication of "early" RA, but it is also useful in the prediction in family history and inbreed consanguin in the setting of this disease.

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REFERENCE

Abdel-Nasser, A. M., Rasker, J. J. and Vaikenburg, H. A. (1997) 'Epidemiological and clinical aspects relating to the variability of rheumatoid arthritis', *Seminars in Arthritis and Rheumatism*, 27(2), pp. 123–140. doi: 10.1016/S0049-0172(97)80012-1.

Abdel-Nasser, A. M. *et al.* (2008) 'Anti-CCP2 is an adjunct to, not a surrogate for, rheumatoid factor in the diagnosis of rheumatoid arthritis: diagnostic utility of anti-CCP2 antibodies in Egyptian patients with rheumatoid arthritis', *Scandinavian Journal of Rheumatology*, 37(5), pp. 329–336. doi: 10.1080/03009740802116208.

Alawneh, K. M. *et al.* (2014) 'Rheumatoid arthritis in Jordan: A cross sectional study of disease severity and

associated comorbidities', *Therapeutics and Clinical Risk Management*, 10(1), pp. 363–366. doi: 10.2147/TCRM.S62954.

Almeida, M. do S. T. M., Almeida, J. V. M. and Bertolo, M. B. (2014) 'Demographic and clinical features of patients with rheumatoid arthritis in Piauí, Brazil – evaluation of 98 patients', *Revista Brasileira de Reumatologia (English Edition)*, 54(5), pp. 360–365. doi: 10.1016/j.rbre.2014.02.018.

Ambriz Murillo, Y. *et al.* (2015) 'Health related quality of life in rheumatoid arthritis, osteoarthritis, diabetes mellitus, end stage renal disease and geriatric subjects. experience from a general hospital in Mexico', *Reumatologia Clinica*, 11(2), pp. 68–72. doi: 10.1016/j.reuma.2014.03.006.

Benbouazza, K. *et al.* (2011) 'Profile and course of early rheumatoid arthritis in Morocco: A two-year follow-up study', *BMC Musculoskeletal Disorders*, 12. doi: 10.1186/1471-2474-12-266.

Bullinger, M. and Quitmann, J. (2014) 'Quality of life as patient-reported outcomes: principles of assessment', *Dialogues in Clinical Neuroscience*, 16(2), pp. 137–145. doi: 10.31887/DCNS.2014.16.2/mbullinger.

El-Zorkany, B. *et al.* (2016) 'Comparison of comorbidities of the Egyptian rheumatoid arthritis patients to the global cohort of the COMORA study: a post-hoc analysis', *Clinical Rheumatology*, 35(5), pp. 1153–1159. doi: 10.1007/s10067-015-3142-4.

Fang, Q., Ou, J. and Nandakumar, K. S. (2019a) 'Autoantibodies as Diagnostic Markers and Mediator of Joint Inflammation in Arthritis', *Mediators of Inflammation*, 2019, pp. 1–22. doi: 10.1155/2019/6363086.

Fang, Q., Ou, J. and Nandakumar, K. S. (2019b) 'Autoantibodies as Diagnostic Markers and Mediator of Joint Inflammation in Arthritis', *Mediators of Inflammation*, 2019, pp. 1–22. doi: 10.1155/2019/6363086.

Guillemin, F. (2005) 'Prevalence of rheumatoid arthritis in France: 2001', *Annals of the Rheumatic Diseases*, 64(10), pp. 1427–1430. doi: 10.1136/ard.2004.029199.

Ibn Yacoub, Y. *et al.* (2012a) 'Health-related quality of life in Moroccan patients with rheumatoid arthritis', *Clinical Rheumatology*, 31(10), pp. 1471–1477. doi: 10.1007/s10067-012-2037-x.

Ibn Yacoub, Y. *et al.* (2012b) 'Rheumatoid factor and antibodies against citrullinated peptides in Moroccan patients with rheumatoid arthritis: association with disease parameters and quality of life', *Clinical Rheumatology*, 31(2), pp. 329–334. doi: 10.1007/s10067-011-1820-4.

Ibn Yacoub, Y. *et al.* (2012c) 'Rheumatoid factor and antibodies against citrullinated peptides in Moroccan patients with rheumatoid arthritis: Association with disease parameters and quality of life', *Clinical Rheumatology*, 31(2), pp. 329–334. doi: 10.1007/s10067-011-1820-4.

Intriago, M. *et al.* (2019) 'Clinical Characteristics in Patients with Rheumatoid Arthritis: Differences between Genders', *Scientific World Journal*, 2019. doi: 10.1155/2019/8103812.

Jawaheer, D. *et al.* (2010) *Gender, body mass index and rheumatoid arthritis disease activity: results from the QUEST-RA study NIH Public Access Author Manuscript*, *Clin Exp Rheumatol*.

Kalla, A. A. *et al.* (1988) 'Clinical assessment of disease activity in rheumatoid arthritis: evaluation of a functional test.', *Annals of the Rheumatic Diseases*, 47(9), pp. 773–779. doi: 10.1136/ard.47.9.773.

Katchamart, W. *et al.* (2015) 'Associations of rheumatoid factor and anti-citrullinated peptide antibody with disease progression and treatment outcomes in patients with rheumatoid arthritis', *Rheumatology International*, 35(10), pp. 1693–1699. doi: 10.1007/s00296-015-3271-8.

Katchamart, W. *et al.* (2020a) 'Prevalence of and factors associated with depression and anxiety in patients with rheumatoid arthritis: A multicenter prospective cross-sectional study', *International Journal of Rheumatic Diseases*, 23(3), pp. 302–308. doi: 10.1111/1756-185X.13781.

Katchamart, W. *et al.* (2020b) 'Prevalence of and factors associated with depression and anxiety in patients with rheumatoid arthritis: A multicenter prospective cross-sectional study', *International Journal of Rheumatic Diseases*, 23(3), pp. 302–308. doi: 10.1111/1756-185X.13781.

Kim, H. H. *et al.* (2010) 'Correlation of Anti-Cyclic Citrullinated Antibody with Hand Joint Erosion Score in Rheumatoid Arthritis Patients', *The Korean Journal of Internal Medicine*, 25(2), p. 201. doi: 10.3904/kjim.2010.25.2.201.

Kurowska, W. *et al.* (2017) 'The role of anti-citrullinated protein antibodies (ACPA) in the pathogenesis of rheumatoid arthritis', *Central European Journal of Immunology*, 42(4), pp. 390–398. doi: 10.5114/ceji.2017.72807.

Mewar, D. and Wilson, A. G. (2006) 'Autoantibodies in rheumatoid arthritis: a review', *Biomedicine & Pharmacotherapy*, 60(10), pp. 648–655. doi: 10.1016/j.biopha.2006.09.002.

MIMORI, T. (2005a) 'Clinical Significance of Anti-CCP Antibodies in Rheumatoid Arthritis', *Internal Medicine*, 44(11), pp. 1122–1126. doi: 10.2169/internalmedicine.44.1122.

MIMORI, T. (2005b) 'Clinical Significance of Anti-CCP Antibodies in Rheumatoid Arthritis', *Internal Medicine*, 44(11), pp. 1122–1126. doi: 10.2169/internalmedicine.44.1122.

Namas, R. *et al.* (2019) 'Demographic and Clinical Patterns of Rheumatoid Arthritis in an Emirati Cohort from United Arab Emirates', *International Journal of Rheumatology*, 2019, pp. 1–10. doi: 10.1155/2019/3057578.

Naranjo, A. *et al.* (2010) 'Smokers and non-smokers with rheumatoid arthritis have similar clinical status: Data from the multinational QUEST-RA database', *Clinical and Experimental Rheumatology*, 28(6), pp. 820–827.

Nehmar, R. (2020) 'Contribution à l ' étude de la pathogénèse de la polyarthrite rhumatoïde : analyse des mécanismes régulateurs de la réponse inflammatoire To cite this version : Contribution à l ' étude de la pathogénèse de la Polyarthrite Rhumatoïde Analyse des mécanisme'.

Oliver, J. E. and Silman, A. J. (2006) 'Risk factors for the development of rheumatoid arthritis.', *Scandinavian journal of rheumatology*, 35(3), pp. 169–74. doi: 10.1080/03009740600718080.

Othman, M. A. *et al.* (2016) 'Correlation of Demographic and Clinical Characteristics with Rheumatoid Factor Seropositivity in Rheumatoid Arthritis Patients', *Malaysian Journal of Medical Sciences*, 23(6), pp. 52–59. doi: 10.21315/mjms2016.23.6.6.

Pérez, D. *et al.* (2017) 'Predictive autoimmunity using autoantibodies: screening for anti-nuclear antibodies', *Clinical Chemistry and Laboratory Medicine*. doi: 10.1515/cclm-2017-0241.

Rkain, H. *et al.* (2006) 'Socioeconomic impact of rheumatoid arthritis in Morocco', *Joint Bone Spine*, 73(3), pp. 278–283. doi: 10.1016/j.jbspin.2005.03.021.

Sebbag, M. *et al.* (2004) *Intérêt clinique et rôle physiopathologique ... ... de la réponse auto-immune contre les protéines citrullinées dans la polyarthrite rhumatoïde 1 Clinical and pathophysiological significance of the autoimmune response to citrullinated proteins in rheumatoid arthritis*, *Revue du Rhumatisme*.

Singwe-Ngandeu, M. *et al.* (2010) 'Diagnostic value of anti-cyclic citrullinated peptides and association with HLA-DRB1 shared epitope alleles in African rheumatoid arthritis patients', *Arthritis Research & Therapy*, 12(2), p. R36. doi: 10.1186/ar2945.

Sokka, T. *et al.* (2009) 'Women, men, and rheumatoid arthritis: Analyses of disease activity, disease characteristics, and treatments in the QUEST-RA Study', *Arthritis Research and Therapy*, 11(1). doi: 10.1186/ar2591.

Syngle, D., Singh, A. and Verma, A. (2019) 'Impact of rheumatoid arthritis on work capacity impairment and its predictors', *Clinical Rheumatology*. doi: 10.1007/s10067-019-04838-1.

Trier, N. H. *et al.* (2019) 'Specificity of Anti-Citrullinated Protein Antibodies in Rheumatoid Arthritis', *Antibodies*, 8(2), p. 37. doi: 10.3390/antib8020037.

Tron, F. (2014) 'Les auto-anticorps comme biomarqueurs', *Presse Medicale*, 43(1), pp. 57–65. doi: 10.1016/j.lpm.2012.11.025.

Turesson, C. *et al.* (2007) 'Rheumatoid factor and antibodies to cyclic citrullinated peptides are associated with severe extra-articular manifestations in rheumatoid arthritis', *Annals of the Rheumatic Diseases*, 66(1), pp. 59–64. doi: 10.1136/ard.2006.054445.