

Original Research Article

Don't Judge Disability with its Visibility: Gender Variation in Frequency of Rheumatoid Arthritis with its Clinical Parameters

Dr. Misbah Vaqar Patoli^{3*}, Dr. Fasiha Sohail^{2*}, Dr. Sumera Nawaz, Dr. Muhammad Fahad Zakir^{1*}, Dr. R. Annum Rahim, Dr. Ghania Niazi and Dr. Farzeen Tanwir

Abstract

¹Post Graduate Trainee, Department of Medicine, Ziauddin University and Hospital, Karachi, Pakistan

E-mail:

fahad_bawani@hotmail.com

Tel: +92-333-2324002

²Assistant Professor, Department Of Medicine, Ziauddin University and Hospital, Karachi, Pakistan

E-mail: faseehamazhar@gmail.com

Tel: +92-333-2324002

³Post Graduate Trainee, Department of Medicine, Ziauddin University And Hospital, Karachi, Pakistan

E-mail: dr.misbahirfan@gmail.com

Tel: +92-333-2324002

The Objectives of this study is to determine the frequency of clinical features of rheumatoid arthritis in males and females in local population of Karachi. A descriptive prospective was conducted in tertiary care hospital in Karachi from August 1, 2017 till February 28, 2018. Careful selection of patient based on their clinical presentation and initial laboratory workup for RA factor was done and treated on the line of Rheumatoid arthritis and followed up in OPD for response with treatment. A total of 1600 patients were enrolled for study. Total of 1438 patients participated in the study and 162 patients were lost to follow up after discharge from hospital. Females were found to be predominant as compared to males. Majority of sample size was found in age group 21-40 and 40-61 years of age. RA factor was found negative in most of cases. Rheumatoid arthritis is a heterogeneous disease with gender variability. Sex related factors influence disease activity and severity, it should be considered as treatment responses and side effects may vary in both. In our study predominantly females of reproductive and middle age group reported to have clinical symptoms but found to have negative laboratory results.

Keywords: Disability, Visibility, Gender variation, Rheumatoid Arthritis

INTRODUCTION

Rheumatoid arthritis is systemic autoimmune disorder that primarily affects joint leading to swollen, painful, and stiff joint with reduced functional capacity. RA is the most common form of inflammatory arthritis with prevalence ranging from 0.5 to 1% and annual incidence of 3 per 10,000 adults (Gabriel, 2001). Gender medicine is a phenomenon focused on the difference between males and females in terms of health and disease. Over the past years, gender variation has shown significant variability in clinical presentation, natural history and response to drugs in several rheumatic diseases (Voulgari et al., 2002; Eder et al., 2013; Wolfe et al., 1968). Although the disease occurs in both genders but expressed differently in rheumatoid arthritis where female

to male ratio is 3:1 (Van and McGuire, 1994). Hormonal aspects and genetic factors are likely to be involved in this overpresentation, but the exact mechanism is still unclear (O'Brien et al., 2007; Koepsell et al., 1994). Some hormonal risk factors for women which lead them to earlier exposure include age at menarche, use of oral contraceptives, lactation and short fertile period (Brennan et al., 1997; Carette et al., 2000; Brun et al., 1995; Jawaheer et al., 2006). Among females disease occurrence increases from the age of menarche and peaks around menopause. Although male patients had significantly later onset of RA, rare in patients age less than 45 years (Brennan et al., 1997). Females reported to have more pronounced pain perception and severe

symptoms with limitation in daily physical activity and high work insufficiency rates as compared to males, but it correlates with specific disease activity markers (Unruh, 1996; Barsky et al., 2001; Sherrer et al., 1987; Puolakka et al., 2006; Forslind et al., 2007). Many observational studies have showed significant worse outcomes in females as compared to males (Da Silva and Hall, 1992; Mancarella et al., 2007). Apart from these males with RA have higher death rates when compared. Recent studies showed males have higher response to treatment and major predictor of remission in early RA (Da Silva and Hall, 1992; Burmester et al., 2007). On the other hand male gender is experiencing serious side effects and serious infections throughout life (Takeuchi et al., 2008; Schellekens et al., 2000). Currently in clinical practice RA factor and ACPA are utilized for their diagnostic and prognostic values (Leeb et al., 2007). Disease activity measures show variable gender based difference as females tends to have high ESR than males (Miller et al., 1983; Jawaheer et al., 2006).

METHODOLOGY

Setting: Tertiary care hospital and clinics of Karachi

Target population: All patients meeting the inclusion criteria will be selected for study.

Study design: Descriptive prospective study

Duration of study: One year

Sample size: Total numbers of 1600 patients were enrolled for the study. Total of 1438 participated, while 162 patients were lost to follow up.

Sampling technique: Consecutive sampling

Sample Selection

Inclusion Criteria

- Eligible patients will be between the ages of 15 till 75 years.
- Both males and females.

Exclusion Criteria

- Age less than 15 years or more than 75 years
- Patient with any other autoimmune disease

Data collection procedure

Three researchers were assigned, for the collection and

enrollment of patient's data. Patients meeting the inclusion criteria have been selected from Inpatient and Outpatient Department. All data was gathered on preformed questionnaire after written informed consent.

Data analysis procedure: Data analysis will be carried out by using SPSS version 22.

Statistical analysis: z test applied

DISCUSSION

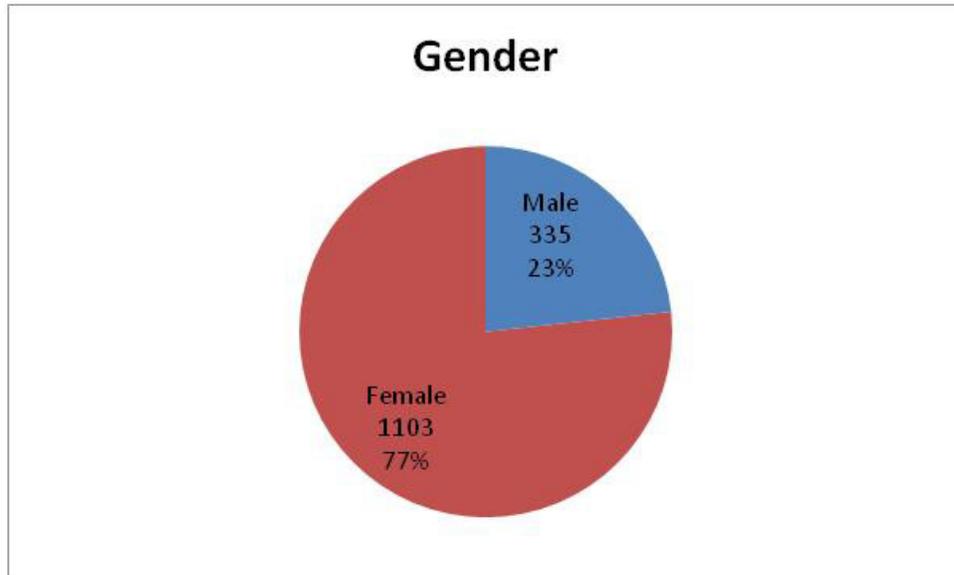
In our study we observed obvious difference in frequency, prevalence, severity of disease, age at onset and autoantibody production of RA in both genders (Jawaheer et al., 2006).

Gender variation has shown significant difference in the past and our study with female predominance. Many factors play a contributing role in causing this variability (Voulgari et al., 2002; Eder et al., 2013; Wolfe et al., 1968). In this study the ratio of male and female was 23% and 77% with total number of 1103 females and 335 males respectively. In previous large cohort study, RA disease activity was found worse in women and originated from measures of disease activity (Sokka et al., 2009). Graph 1

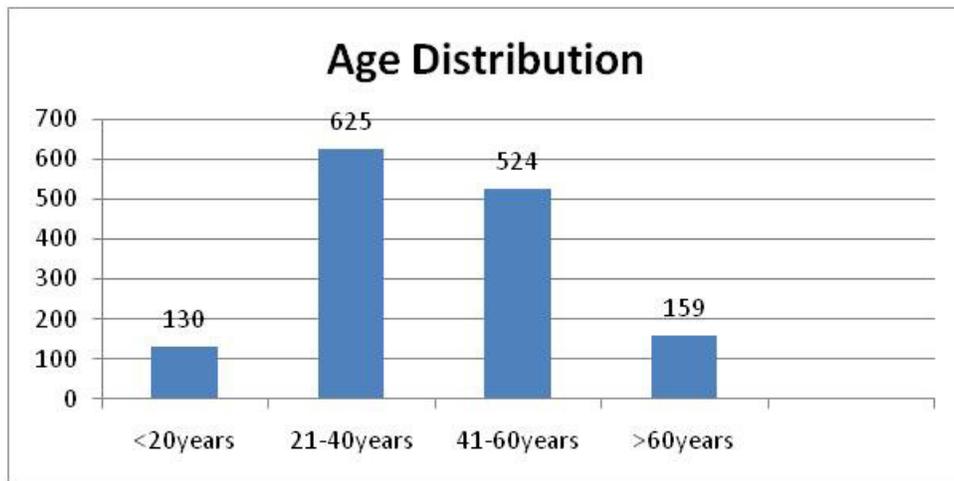
Age groups divided into four categories. Total numbers of 130 patients were less than 20 years, peak age of patients were found in 21 to 40 years (reproductive group) with 625 patients, 524 patients were in age group from 41 to 60 years (middle age), and 159 patients was greater than 60 years old (elderly). Many genetic and hormonal factors contribute predominance of reproductive age group in females including age at menarche, breast feeding, menopause, hormonal disturbance (Carette et al., 2000; Brun et al., 1995). In majority of cohort studies done previously, women of middle age group are affected greater than 70% (Jawaheer et al., 2006). Graph 2

RA factor was found to be positive in 12% (n= 174) of patients, borderline in 4% (n= 51), and in about 84% (n=1213) patient RA factor turned out negative. Graph 3

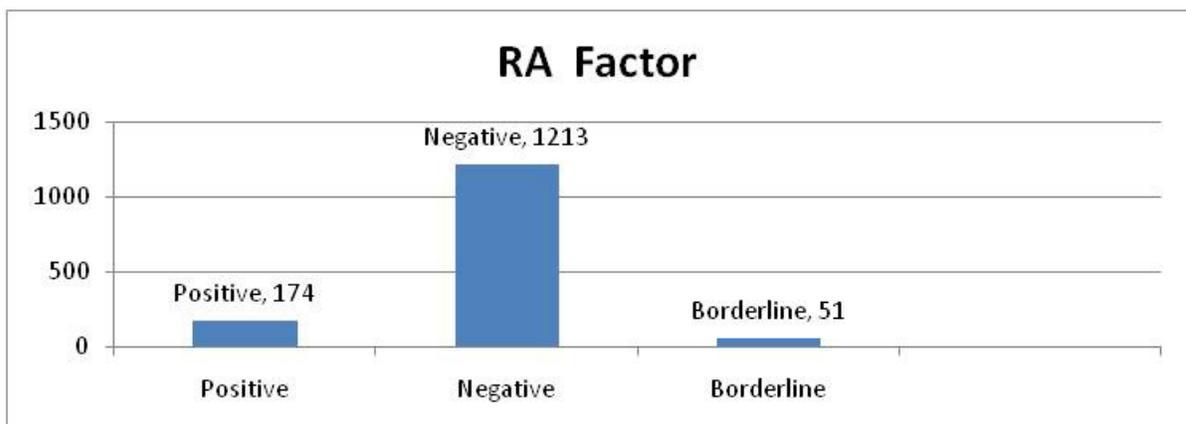
Peak incidence in women was found in age 21 to 40 years with 505 females. In males' peak incidence was found in age 41 to 60 years with almost 136 patients followed by 388 females in age group of 41-60years and 120 males in age group 21-40. Male gender reported to present in later age group with good response to treatment and remission, but this is all dependent on specific disease activity markers (Brennan et al., 1997). With all this outcome male gender found to experience serious infection in their life and early death (Da Silva and Hall, 1992; Burmester et al., 2007). Hormonal and behavioral changes are contributing factor toward the



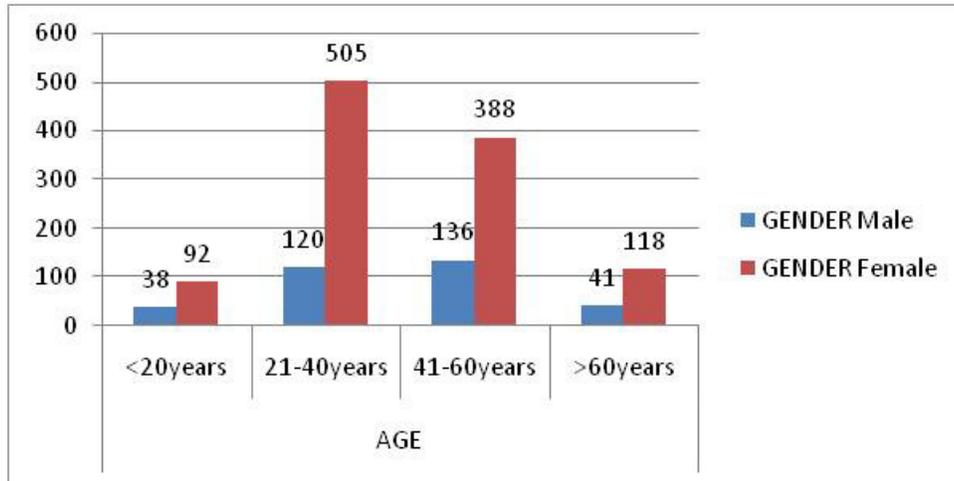
GRAPH 1.



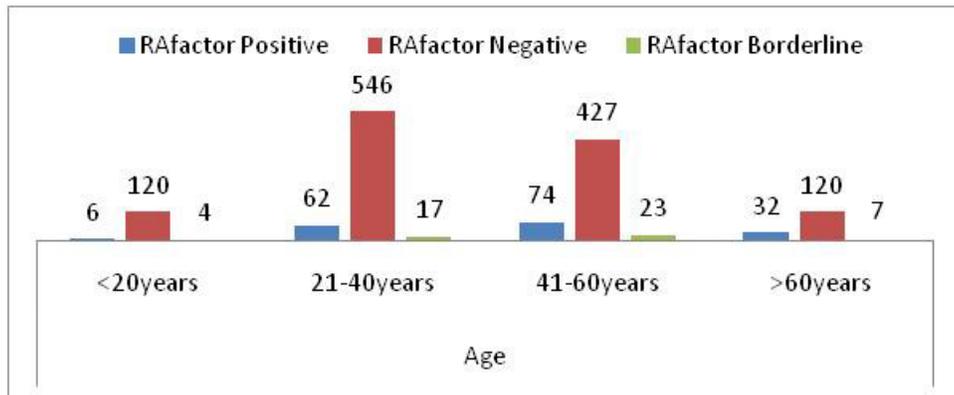
Graph 2.



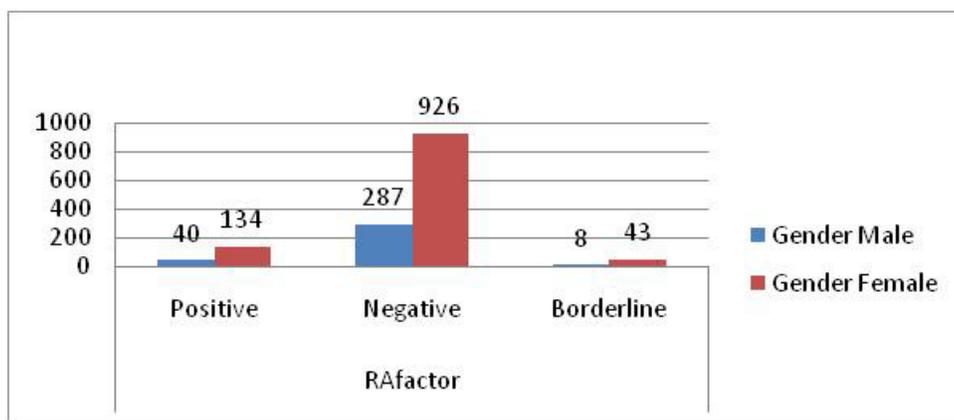
Graph 3.



Graph 4.



Graph 5.



Graph 6

determination of phenotype (Straub et al., 2006; Heliövaara et al., 1993; Krishnan et al., 2003). Studies conducted at Mayo clinic compared genders found erosive disease were earlier in men (Weyand et al., 1998). Graph 4

Most sample population was in reproductive and middle age group with total number of 546 and 427 patients were RA factor negative respectively. Total number of 74 patients were found RA factor positive in middle age group while 62 patients in reproductive age

group. There was a delay in referral of females to early arthritis clinic as compared to males in a report from Netherland (Lard et al., 2001). Graph 5

Total numbers of 926 females were found RA factor negative, 134 positive and 43 borderline positive. While in males 287 males were found to have negative RA factor, 40 were positive and 8 male patients were borderline positive. Graph 6

RESULT

Frequency and severity of clinical symptoms in both sexes were variable and age dependent. Total of 1600 patients were enrolled for study, 1438 patients actively participated in study and 162 patients were lost to follow up in clinics. On the basis of age variability majority of patients were found in reproductive age groups (21-40) and middle age (41-60) of about 625 and 524 patients respectively. Among them females were found to be predominant in reproductive age with 505 patients and males were predominant in the middle age group with almost 136 patients. In our study, on the basis of sex differentiation majority of patients were females with a ratio of 77% and 23% of males. RA factor was found negative in majority of cases in both sexes with total of n=926 females and n=287 males. RA factor was found positive in about 12% of total sample population. Most sample population was found in reproductive and middle age group with total number of 546 and 427 patients. Only 74 patients in reproductive age and 62 patients in middle age group were positive for RA factor.

CONCLUSION

Females were found predominant in reproductive age group with clinical symptoms. RA factor was found negative and most cases were also seen in reproductive age group.

REFERENCES

- Barsky AJ, Peekna HM, Borus JF (2001). Somatic symptom reporting in women and men. *Journal of general internal medicine*, 16(4), 266-275.
- Brennan P, Bankhead C, Silman A, Symmons D (1997, June). Oral contraceptives and rheumatoid arthritis: results from a primary care-based incident case-control study. In *Seminars in arthritis and rheumatism* (Vol. 26, No. 6, pp. 817-823). Elsevier.
- Brennan P, Bankhead C, Silman A, Symmons D (1997, June). Oral contraceptives and rheumatoid arthritis: results from a primary care-based incident case-control study. In *Seminars in arthritis and rheumatism* (Vol. 26, No. 6, pp. 817-823). Elsevier.
- Brun JG, Nilssen S, Kvåle G (1995). Breast feeding, other reproductive factors and rheumatoid arthritis. A prospective study. *Rheumatology*, 34(6), 542-546.
- Burmester GR, Mariette X, Montecucco C, Monteagudo-Sáez I, Malaise M, Tzioufas AG, Kupper H (2007). Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. *Annals of the rheumatic diseases*, 66(6), 732-739.
- Carette S. I. M. O. N, Surtees PG, Wainwright NW, Khaw KT, Symmons DP, Silman AJ (2000). The role of life events and childhood experiences in the development of rheumatoid arthritis. *The Journal of rheumatology*, 27(9), 2123-2130.
- Da Silva JAP, Hall GM (1992). The effects of gender and sex hormones on outcome in rheumatoid arthritis. *Baillière's clinical rheumatology*, 6(1), 193-219.
- Eder L, Thavaneswaran A, Chandran V, Gladman DD (2013). Gender difference in disease expression, radiographic damage and disability among patients with psoriatic arthritis. *Annals of the rheumatic diseases*, 72(4), 578-582.
- Ende, C. V. D., HAZES, J. W., Cessie, S. L., Breedveld, F. C., & DIJIKMANS, B. C. (1995). Discordance between objective and subjective assessment of functional ability of patients with rheumatoid arthritis. *Rheumatology*, 34(10), 951-955.
- Forslind K, Hafström I, Ahlmén M, Svensson B (2007). Sex: a major predictor of remission in early rheumatoid arthritis?. *Annals of the rheumatic diseases*, 66(1), 46-52.
- Gabriel SE (2001). The epidemiology of rheumatoid arthritis. *Rheumatic Disease Clinics*, 27(2), 269-281.
- Heliövaara M, Aho K, Aromaa A, Knekt P, Reunanen A (1993). Smoking and risk of rheumatoid arthritis. *The Journal of rheumatology*, 20(11), 1830-1835.
- Jawaheer D, Lum RF, Gregersen PK, Criswell LA (2006). Influence of male sex on disease phenotype in familial rheumatoid arthritis. *Arthritis & Rheumatology*, 54(10), 3087-3094.
- Jawaheer D, Lum RF, Gregersen PK, Criswell LA (2006). Influence of male sex on disease phenotype in familial rheumatoid arthritis. *Arthritis & Rheumatology*, 54(10), 3087-3094.
- Koepsell TD, Dugowson CE, Nelson JL, Voigt LF, Daling JR (1994). Non-contraceptive hormones and the risk of rheumatoid arthritis in menopausal women. *International journal of epidemiology*, 23(6), 1248-1255.
- Krishnan E, Sokka T, Hannonen P (2003). Smoking-gender interaction and risk for rheumatoid arthritis. *Arthritis Res Ther*, 5(3), R158.
- Lard LR, Visser H, Speyer I, van der Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JM (2001). Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Ame. J. Med.* 111(6), 446-451
- Leeb BF, Haindl PM, Maktari A, Nothnagl T, Rintelen B (2007). Disease activity score-28 values differ considerably depending on patient's pain perception and sex. *The Journal of Rheumatology*, 34(12), 2382-2387.
- Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, Salaffi F (2007). Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. *The Journal of Rheumatology*, 34(8), 1670-1673.
- Miller A, Green M, Robinson D (1983). Simple rule for calculating normal erythrocyte sedimentation rate. *British medical journal (Clinical research ed.)*, 286(6361), 266.
- O'Brien SM, Fitzgerald P, Scully P, Landers A, Scott LV, Dinan TG (2007). Impact of gender and menstrual cycle phase on plasma cytokine concentrations. *Neuroimmunomodulation*, 14(2), 84-90.
- Puolakka K, Kautiainen H, Pekurinen M, Möttönen T, Hannonen P, Korpela M, Leirisalo-Repo M (2006). Monetary value of lost productivity over a five year follow up in early rheumatoid arthritis estimated on the basis of official register data on patients' sickness absence and gross income: experience from the FIN-RACo trial. *Annals of the rheumatic diseases*, 65(7), 899-904.
- Schellekens GA, Visser H, De Jong BA, Van Den Hoogen FH, Hazes JM, Breedveld FC, Van Venrooij WJ (2000). The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis & Rheumatology*, 43(1), 155-163.
- Sherrer YS, Bloch DA, Mitchell DM, Roth SH, Wolfe F, Fries, JF (1987). Disability in rheumatoid arthritis: comparison of prognostic factors across three populations. *J. Rheumatol.* 14(4), 705-709.

- Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, Géher P (2009). Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis research & therapy*, 11(1), R7.
- Straub RH, Härle P, Sarzi-Puttini P, Cutolo M (2006). Tumor necrosis factor-neutralizing therapies improve altered hormone axes: an alternative mode of antiinflammatory action. *Arthritis & Rheumatology*, 54(7), 2039-2046.
- Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, Kondo H (2008). Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. *Annals of the rheumatic diseases*, 67(2), 189-194.
- Unruh AM (1996). Gender variations in clinical pain experience. *Pain*, 65(2-3), 123-167.
- Van RV, McGuire JL (1994). Estrogen, progesterone, and testosterone: can they be used to treat autoimmune diseases?. *Cleveland Clinic journal of medicine*, 61(4), 276-284.
- Voulgari PV, Katsimbri P, Alamanos Y, Drosos AA (2002). Gender and age differences in systemic lupus erythematosus. A study of 489 Greek patients with a review of the literature. *Lupus*, 11(11), 722-729.
- Weyand CM, Schmidt D, Wagner U, Goronzy JJ (1998). The influence of sex on the phenotype of rheumatoid arthritis. *Arthritis & Rheumatology*, 41(5), 817-822.
- Wolfe AM, Kellgren JH, Masi AT (1968). The epidemiology of rheumatoid arthritis: a review. II. Incidence and diagnostic criteria. *Bulletin on the rheumatic diseases*, 19(3), 524.