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Case Report

Association between Menopausal Status and Rheumatoid Arthritis Progression: A Case-Control Study

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ABSTRACT

Rheumatoid arthritis, a widespread autoimmune inflammatory joint disorder characterised by the presence of autoantibody elevation in serum, especially Rheumatoid Factor (RF) and Antibodies to Citrullinated Proteins/Peptides (ACPAs). It affects both males and females of all ages. Risk factors includes various genetic and environmental parameters as well as dietary habits. The case-control study comprised 200 participants diagnosed with Rheumatoid Arthritis, residing in Punjab, and aged between 30 to 60 years. Demographic and socioeconomic data were compiled through a self-administered information sheet followed by statistical analysis. The study found that post-menopausal women experienced severe symptoms as compared to pre-menopausal and male counterparts indicating age and hormones as risk factors for developing RA. The present study concluded that hormonal fluctuations following menopause may contribute to increased bone resorption, consequent inflammation and heightening RA symptomology in postmenopausal women.

Keywords: Anthropometric Variables, Case-Control Study, Inflammation, Hormonal Fluctuations, Menopausal Changes, RA Symptomology.

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INTRODUCTION

Rheumatoid arthritis, a widespread autoimmune inflammatory disorder, impacts approximately 0.5-1% of the global population. Notably, rheumatoid arthritis is generally categorised into seropositive and seronegative subtypes, with seropositivity defined by the presence of autoantibody elevation in serum, especially Rheumatoid Factor (RF) and Antibodies to Citrullinated Proteins/Peptides (ACPAs) (Smolen *et al*., 2016). The disease is characterised as Inflammatory Arthritis (IA) that satisfies established classification criteria, encompassing the 1987 criteria formulated by the American College of Rheumatology and the 2010 criteria developed by the American College of Rheumatology/European League Against Rheumatism (Deane *et al*., 2017).

Prevalence

The global prevalence of rheumatoid arthritis is steadily around 1% and shows a consistent pattern of higher rates in women (Smolen *et al*., 2016). The incidence of RA differs by age and population when viewed from an epidemiological perspective. Various research studies have been conducted to study incidence rates in different locations and pinpoint the factors behind these differences (Silman and Pearson, 2002).

Gender and Age

Numerous studies concur that age is independently associated with the severity of disease. RA is a long-standing, inflammatory condition, and more women than men are affected (Englund *et al*., 2010). Research suggests that hormonal influences can impact the likelihood of developing RA (Pikwer *et al*., 2009). It has been observed that fewer women have RA during pregnancy, and those who do become pregnant often experience a decrease in their symptoms - a state known as clinical remission (Hazes *et al*., 2011). Interestingly, people with RA tend to have low levels of testosterone, and the disease is more common in women during the time leading up to and following menopause (Doran *et al*., 2002). Given these findings, it's likely that hormonal fluctuations play a vital role in the development and progression of RA. Hormones may also have various effects on the age at which RA develops, as well as the presence or absence of certain antibodies associated with the disease (Scott *et al*., 2011). Research by Kuiper *et al*. (2001) established a direct correlation between advanced patient age and heightened disease severity among a group of patients, both men and women, over a period of six years, examining factors such as disease activity, joint damage, and mobility issues. The results of this study found that women who get diagnosed with rheumatoid arthritis at an older age tend to experience more severe symptoms, including higher disease

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activity, greater joint damage, and more mobility problems. Older onset cases had higher CRP, ESR, and D28 levels than middle-aged onset cases (Pawlowska *et al.*, 2011).

Hormones and Menopause

The postmenopausal state and age of females independently and collectively contribute significantly to the etiology, intensity, and progression of rheumatoid arthritis. Research has been done to compare the symptoms of rheumatoid arthritis in premenopausal and postmenopausal women. Research conducted by Beydoun *et al.* (2013) revealed that women experiencing menopause at an early age, prior to 40 years, exhibit an elevated propensity to develop rheumatoid arthritis post-menopause. A higher prevalence of seropositivity among women with early rheumatoid arthritis has been linked to an earlier age of menopause onset (Wong *et al.*, 2015). Mollard *et al.* (2018) established an association between decreased hormone levels during menopause and accelerated progression of rheumatoid arthritis. The analysis indicates a correlation between menopausal status and declining functional efficacy in RA patients, specifically women. Moreover, the onset of menopause appears to exacerbate the progression of this decline. Consequently, it is evident that menopause has a substantial effect on the magnitude and velocity of functional deterioration in female RA patients.

Studies explored how a decrease in estrogen levels, especially during menopause, may affect the development of autoimmune disease in people with Rheumatoid Arthritis (RA). As women enter menopause, their estrogen levels drop, potentially disrupting the delicate balance between genetic predisposition and immune regulation. The primary genetic factor for RA is a particular variation on the HLA-DRB1 gene, often referred to as the 'shared epitope'. Other genes involved in immune function, such as those encoding PADI4, an enzyme that alters proteins, and PTPN22, a gene that helps regulate immune cell signaling, also play a crucial role in RA. Under normal circumstances, estrogen acts as an immunomodulator, helping to regulate immune cell activity (Sapir-koren *et al.*, 2016). However, in postmenopausal women, the loss of estrogen may upset this balance, allowing these genes to have a greater impact. Specifically, susceptible women who experience estrogen deficiency may develop certain immune cells that are prone to attack healthy tissues, leading to the release of inflammatory chemicals and the production of antibodies that contribute to RA and perpetuate the cycle of inflammation (Motta *et al.*, 2025).

METHODOLOGY

Subjects

The study comprised 200 participants, comprising 119 females and 81 males, from Rajindra Hospital, Patiala. This included patients diagnosed with Rheumatoid Arthritis, residing in Punjab, and aged between 30 to 60 years. Conversely, individuals harboring concurrent joint diseases or comorbid medical conditions were excluded from the study.

Data collection

Demographic and socioeconomic data, in conjunction with clinical parameters, were compiled through a self-administered information sheet, encompassing variables such as joint pain, morning stiffness, knee pain, and the presence of swollen joints.

Statistical analysis

A chi-square test was utilized to investigate disparities in clinical attributes between RA-positive female and male populations.

RESULTS

The Table 1 represents the clinical characteristics among a group of 20 younger men and a group of 61 older men. Notably, the older men exhibited considerably more severe joint-related symptoms, including knee pain, which achieved statistically significant differences in comparison to their younger counterparts. Conversely, no statistically significant differences were found in regards to morning stiffness and swollen joints among the two age groups.

A comparative analysis of clinical characteristics between pre-menopausal women (n=54) and post-menopausal women (n=65) found statistically significant distinctions in knee pain and joint swelling (Table 2). Post-menopausal women exhibited heightened knee pain and joint inflammation in comparison to pre-menopausal women, indicating a potential exacerbation of joint-related symptoms with menopause. Conversely, the prevalence and severity of joint pains and morning stiffness were found to be comparably consistent across both groups, with non-significant statistical values.

The data presented in the Table 3 elucidate distinct clinical characteristics between postmenopausal women and older men, encompassing 65 and 61 participants respectively. Notably, postmenopausal women exhibited more severe joint pain, morning stiffness, knee pain and swollen joints in comparison to their older male counterparts, attaining statistically significant values in all instances.

DISCUSSION

The onset of menopause may exert a profound influence on the trajectory of rheumatic disease, with empirical evidence suggesting that joint pain and stiffness prevail at a greater frequency in post-menopausal women relative to their pre-menopausal counterparts (Szoeke *et al.*, 2008). Research has provided substantial evidence that fluctuations in sex hormones are directly implicated in the manifestation of musculoskeletal pain (Gulati *et al.*, 2023). Furthermore, the literature indicates that changes in sex hormone levels during menopause also have a considerable impact on the development and functionality of the

immune system, thereby contributing to sex differences in disease susceptibility (Ngo *et al*., 2014). Recent studies suggest that the menopause represents a critical juncture in the interaction between aging and immune function, which may have profound implications for the onset and progression of rheumatic diseases (Han *et al*., 2021). A recent study investigated the influence of gender on immune function thereby indicating that oestrogens play a pivotal role in the development of autoimmunity. It has been observed that women with premature ovarian insufficiency and those experiencing late-onset menopause provide a unique framework for investigating immune alterations associated with oestrogen deficiency (Moulton, 2018). Another study suggested that menopause may contribute to the onset of autoimmune responses and modify the progression of immune-mediated rheumatic conditions, highlighting the significant role of hormonal fluctuations in immune regulation (Motta *et al*., 2023). Mollard *et al*. (2018) demonstrated the functional status of premenopausal and postmenopausal women. It was observed that postmenopausal women with rheumatoid arthritis exhibit greater functional disability as compared to their premenopausal counterparts. According to this study, results may be influenced by factors such as prolonged disease duration and the progressive degenerative changes inherent to rheumatoid arthritis. However, the potential contribution of estrogen deficiency associated with menopause should not be overlooked (Shah *et al*., 2020).

CONCLUSION

This study investigated the relationship between age and symptoms in patients afflicted with Rheumatoid Arthritis (RA). The comparative analysis of younger and older male cohorts revealed a positive correlation between advancing age and heightened joint pain severity, affirming age as a pivotal factor influencing RA symptom severity.

Conversely, postmenopausal females exhibited statistically significant elevations in knee pain and joint swelling in comparison to premenopausal counterparts, indicating that RA symptoms tend to peak around the menopausal transition and persist into postmenopausal stages.

Table 1: Differences regarding clinical characteristics among younger men and older men.

Clinical characteristics	Younger men (*n*=20)		Older men (*n*=61)		Chi-square value	*p*-value
	Yes	No	Yes	No		
Joint pains	16	4	60	1	8.7667	0.003068*
Morning stiffness	12	8	27	34	1.4942	0.221563
Knee pain	2	18	25	36	6.5066	0.010748*
Swollen joint	11	9	24	37	1.5044	0.219994

*Statistically significant=$p<0.05$.

Table 2: Differences regarding clinical characteristics among Premenopausal women and Postmenopausal women.

Clinical characteristics	Premenopausal women (*n*=54)		Postmenopausal women (*n*=65)		Chi-square value	*p*-value
	Yes	No	Yes	No		
Joint pains	52	2	64	1	0.5627	0.453169
Morning stiffness	34	20	42	23	0.0349	0.851807
Knee pain	5	49	45	20	43.5437	<0.00001*
Swollen joint	16	38	49	16	24.9129	<0.00001*

*Statistically significant=$p<0.05$.

Table 3: Differences regarding clinical characteristics among Postmenopausal women and older men.

Clinical characteristics	Postmenopausal women (*n*=65)		Older men (*n*=61)		Chi-square value	*p*-value
	Yes	No	Yes	No		
Joint pains	64	1	37	24	28.2793	<0.00001*
Morning stiffness	42	23	27	34	5.262	0.021796*
Knee pain	45	20	25	36	10.169	0.001428*
Swollen joint	49	16	24	37	16.7723	0.000042*

*Statistically significant=$p<0.05$.

Statistical analysis revealed pronounced differences in symptoms among postmenopausal females and older males, suggesting that gender may contribute to RA symptom severity.

The distinctions between female and male patients, as well as postmenopausal and premenopausal females, appear to be primarily driven by the hormonal modifications attending menopause.

Notably, the present study concluded that hormonal fluctuations following menopause may contribute to increased bone resorption, consequent inflammation and heightening RA symptomology in postmenopausal women.

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ABBREVIATIONS

RA: Rheumatoid Arthritis; **RF:** Rheumatoid Factor; **ACPAs:** Antibodies to Citrullinated Proteins/Peptides; **IA:** Inflammatory Arthritis; **ACR:** American College of Rheumatology; **EULAR:** European League Against Rheumatism; **CRP:** C-Reactive Protein; **ESR:** Erythrocyte Sedimentation Rate; **D28:** Disease Activity Score 28; **HLA-DRB1:** Human Leukocyte Antigen-DR isotype Beta 1; **PADI4:** Peptidyl Arginine Deiminase 4; **PTPN22:** Protein Tyrosine Phosphatase Non-Receptor Type 22; **UGC-CSIR:** University Grants Commission-Council of Scientific and Industrial Research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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