Original Article

The Influence of Early Menopause in Women with Rheumatoid Arthritis; A Systematic Review

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Abstract

Background: Rheumatoid arthritis is a chronic disease affecting the immune system and it particularly targets synovial joints, bringing about inflammation and causing functional limitations. **Objective:** To explore the evidence showing the influence of early menopause in women with rheumatoid arthritis. **Methods:** In this systematic review, all the literature from 2010 to 2019 was searched with specific keywords "menopause, premature menopause, early menopause, rheumatoid arthritis, rheumatic diseases" with the use of Boolean operators. Databases that were thoroughly searched included Google Scholar, PubMed and HEC digital library. After careful screening, 10 studies that met the inclusion criteria were included in the review. The quality of these articles was assessed using the AXIS tool for those cross-sectional studies. **Results:** These studies indicated that post-menopausal women are at higher risk of developing rheumatoid arthritis and they are more likely to have early or premature menopause (in ≤45 years). At baseline, the post-menopausal women had high health assessment questionnaire scores than pre-menopausal women. **Conclusion:** This review states that menopausal women are highly at risk of developing rheumatoid arthritis, especially those experiencing this at an early age and this condition can also worsen arthritic symptoms. Hormonal changes may influence pathways that are distinct from those leading to severe and progressive rheumatoid arthritis.

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Introduction

Rheumatoid arthritis (RA) is a chronic disease affecting the immune system and it particularly targets synovial joints, bringing about inflammation and causing functional limitations. It is the most widely recognized for chronic joint pain, and an important reason for morbidity and mortality. RA is described as

painful swollen joints that can seriously hinder physical activity and quality of life (QoL).[1] Patient with RA are at risk of developing a respiratory illness, osteoporosis, arthritis, cardiovascular infection, malignancy and mortality.[2] The cause of rheumatoid joint inflammation is idiopathic and its diagnosis is difficult. Early assessment and proper treatment can improve results in rheumatoid joint inflammation. Critical joint damage happens initially in the development of RA. Different attributes of RA involve the acute onset of the disease, proximal joints involvement, higher erythrocyte sedimentation rate (ESR) at the beginning, positive RA factor, and poor physical findings.[3]

RA has an overall prevalence of around five for every 1000 adults. The study of disease transmission of RA has a genetic impact. The incidence of RA is generally steady with a pervasiveness ranging from 0.5-1.0%. The disease influences females, 2 to multiple times more frequently than men and happens at any age. The peak frequency is in the 6th decade.[4] Around the world, the commonness of RA is accepted to go from 0.4%-1.3%. In 2005, an expected 1.5 million, or 0.6% of grown-ups 18 years or more had RA. Although RA can happen in patients at any age, the occurrence was found to ascend with age; among those matured 18 to 34, 8.7 per 100,000 individuals were influenced; in those matured 65 to 74 years, 89 for each 100,000 were influenced and in those 85 years or more, 54 for every 100,000 were influenced. Estimated, the lifetime danger of RA to be 4% among females and 3% among males.[5]

The life expectancy decline is around 3 to 10 years. Though physical impairments in females are common, these restrictions may initially introduce in midlife instead of later life. Indeed, even at midlife, more female patients report a decline in daily life activities.[6] The cause of RA is unknown, however endogenous substances such as connective tissue proteins and modified immunoglobulins can be involved.[7] Early investigation, proper treatment and anti-rheumatic drugs have notably improved the prognosis. The most salient component is the involvement of hands, wrists, feet, and knees (polyarthritis), though different joints can be influenced.[8] Rheumatoid arthritis can be difficult to handle, and many patients require continuous management. The pillar of RA treatment is that the disease-modifying anti-rheumatic drugs (DMARDs), might be successful at first but should be stopped because of issues with the effectiveness. Patients may present with monoarthritis or oligoarthritis.[9]

Menopause is characterized by the last menstrual duration (archived by the absence of menses for a year), yet side effects generally happen prior, to a period named peri-menopause. Menopause shows a period of important clinical and hormonal changes.[10] An individual female lives 33% of her life in the post-menopausal state. Menopause concurs with the presence of a significant number of the basic arthritic conditions.[11] It was assumed that a potential impact of changes in sex hormone levels affects the pathogenesis of RA, particularly the elderly females. Females with RA have a low occurrence of RA during pregnancy, yet a high rate of disease progression and flare during the postpartum period. Females who experience early menopause are vulnerable to having RA compared with females who experience a typical or late menopause.[12] The time of menarche, parity and menopause have no relationship with the onset of this disease. As far as the life stage of more danger, SLE and other rheumatic conditions are destined to happen in females during their reproductive years. It is believed that variations in hormonal levels at the time of menopause may be associated with rheumatoid arthritis pathogenesis.[13]

During the postpartum period, with quick falls in endogenous estrogen levels, the risk of RA is higher. The progress to the menopausal state exhibits follicle improvement and ovulation, alongside disturbed feminine bleeding patterns. The normal age at menopause is around 51 years with a later time of menopause corresponding with life span.[14] Patients with RA regularly exhibit articular and periarticular irritation and changes, functional disability, extra-articular signs of RA and drug reactions. Menopausal and related factors might be related to the increased incidence of physical activity limitations among females compared with males.[15] RA patients can be treated with pharmacologic treatment as well as from measures such as exercise regimens and a suitable balance between exercise and rest. The goals of the exercise program are to maintain mobility and to prevent joint damage.[16]

Since most patients with RA experience fatigue and lethargy, sufficient nighttime rest and 30-minute daytime rest periods (or resting of individual joints) are suggested. Physiologically, menopause results in a decrease in estrogen levels and happen between ages 50 and 52 years in industrialized nations with the peri-menopausal around 47.5 years.[17] The World Health Organization characterizes menopause as beginning following 1 year of amenorrhea. RA and postmenopausal females had more radiographic joint damage and higher Disease Activity Score in 28 joints (DAS28) and Health Assessment Questionnaire (HAQ) scores as compared with premenopausal females and males. Explicit assessments of unpredictable feminine cycles, null parity, oral prophylactic use, breastfeeding and hormone substitution treatment (HRT) have revealed some further insight into the job that hormones play in ladies with RA.[18] It has been settled that due to estrogen insufficiency, postmenopausal females have a higher occurrence of osteoporosis, RA and fractures than males. In postmenopausal females, the hip, spine and wrist are the zones generally vulnerable to fracture. Among these osteoporotic fractures, the hip is of more noteworthy concern, since it may cause disability and mortality in this way.[19] Sleep disturbance in RA patients has uncovered that 54 to 70% of RA patients report issues identified with their rest, including trouble nodding off, poor rest quality, inattentiveness, waking during the night and unnecessary daytime tiredness. Alternately, rest disruption may add to the pain, malaise, fatigue and mood swings in affected patients. Sleep quality is a significant segment of QoL, and rest disruption influences personal satisfaction in patients with RA. It has been shown that the higher depression, weakness and pain scores in patients with RA are identified with physical inactivity.[20]

Menopause has been proposed as the initial step of a causal pathway that, in light of hormonal changes, in the end, brings about organ dysfunction and many disorders. Moreover, loss of ovarian function through menopause is related to the action of the renin angiotensin-aldosterone framework, endothelial impairment, immune dysfunction and inflammation. These cycles are related to diabetes, hypertension and obesity. Thus, early-onset and premature menopause, which happens in females younger than 40 years and mature at 40 to 44 years, has an increased rate of mortality and morbidity as a result of the early suspension of the defensive impact of endogenous estrogen. Accordingly, the beginning of menopause would bring about a more serious and higher risk of RA.[21] Premature menopause is attributed to menopause that happens before age 40 and early menopause that happens at or before age 45. Early menopause can be induced or spontaneous; whenever induced, it tends to be because of medications such as chemotherapy or surgery such as oophorectomy. In any case,

females who experience estrogen insufficiency at an age well before regular menopause are presently perceived to be at increased risk of mortality. Females with spontaneous premature menopause are at increased chance for osteoporosis, earlier onset RA, low bone density, fractures, endothelial dysfunction, and coronary artery disease.[22] Induced menopause may result from cancer treatments including chemotherapy and radiation or premenopausal bilateral oophorectomy. Menopause from these causes has been very common because of the improved achievement in the treatment of disease in youngsters, teenagers, and regenerative age females. The process of prophylactic reciprocal oophorectomy at the time of hysterectomy has been done.[23] Bone degeneration takes place following menopause. Early menopause happens in life, the lower the bone thickness will be in later life. Accordingly, oophorectomy before age 45 is a major risk factor for osteoporosis and arthritis. Indeed, even in females who go through reciprocal oophorectomy after regular menopause, the danger of osteoporotic fracture might be increased as compared with females having healthy ovaries.[24] Estrogen treatment lessens the risk of fracture and prevents bone loss following oophorectomy. All through the regenerative years, the frequency of RA in females is more than twice the rate in males. Based on this and also on perceptions of improvement of RA during pregnancy, a significant function of regenerative hormones has been involved in the pathophysiology.[25]

Females going through early or premature menopause, encounter the early loss of other ovarian hormones and estrogen. It has an impact on cardiovascular, musculoskeletal and psychosocial factors as an enhanced risk of early mortality. The utilization of hormonal treatment has appeared to decrease a few of these risks, despite not all of these.[26] So, different clinicians suggest giving hormonal treatment until the regular period of menopause. It is critical to individualize hormonal treatment for females with early estrogen inadequacy, and higher measurements might be expected to estimate physiological focuses found in premenopausal females.[27] Premature ovarian insufficiency (POI) or early menopause is a typical reason for infertility in females and influences around one percent of young females. The primary factors are amenorrhea, elevated levels of serum gonadotropins and absence of ovulation.[28]

In women, RA, multiple sclerosis (MS) and Systemic lupus erythematosus (SLE) are related to lower estrogen levels. Early age at menopause is related to increased risk of disease, and after menopause, illness course changes in SLE and RA. This joint pain more often influences females, along with estrogen decline in menopause. Estrogen (E2) may have an innate immunity response that disappears with menopause. During pregnancy, when females are shielded from RA, galactosylation rises and afterward turns back three months after delivery, when the chance of having RA is increased. E2 has been appeared to diminish galactosylation of human IgG in healthy people, which may clarify the expanded danger of rheumatoid arthritis in menopausal females.[29] Elderly onset rheumatoid arthritis (EORA), beginning at age of 60 years or more, is different from the presentation of YORA (younger-onset rheumatoid arthritis). Longitudinal investigations have indicated a more functional decline in patients, radiographic damage and disease activity. These distinctions were found in seropositive patients. Seropositive EORA was found to be related to HLA-DR4. Heterogeneity in the pathogenesis of seronegative EORA is upheld by the acknowledgment of subsets that cover the clinical indications of different disorders. Therefore, inflammatory osteoarthritis and crystal-induced arthritis might be hard to differentiate from EORA.[30] The purpose of this study was to systematically review the

evidence showing the influence of early menopause in women with rheumatoid arthritis. This review had gathered studies from the last decade using the same diagnostic criteria.

Methods

This systematic review was completed in five months from July 2019 to November 2019. All the literature from 2010 to 2019 was searched with specific keywords "menopause, premature menopause, early menopause, rheumatoid arthritis, rheumatic diseases" with the use of Boolean operators "OR" and "AND". Databases thoroughly searched were Google Scholar, PubMed and HEC digital library. Only cross-sectional studies that involved menopausal women with RA, available in full-length text and published in the English language were included in the review. Only abstracts, irrelevant, unclear studies, interventional studies and studies with copyright or permission issues were excluded. A total of 320 studies were found initially that were related to the topic and after careful screening, only 10 were found meeting the inclusion criteria. (Figure-I)

Quality assessment

AXIS tool (range 1-20) was used for cross-sectional studies and includes items relevant to this design only, it does not include a numerical scale that can be used to produce a quality assessment score; instead, the tool aims to assess the individual characteristics of a study cumulatively. Two assessors independently rated each study for eligibility and methodological quality and extracted data. Disagreements were solved after consensus and a third reviewer arbitrated if consensus could not be reached. (Table-I)

Risk assessment

Four studies yielded results with non-response biases which directly meant that there would be an increased risk in the power of detecting the risk of developing RA among women with menopause.

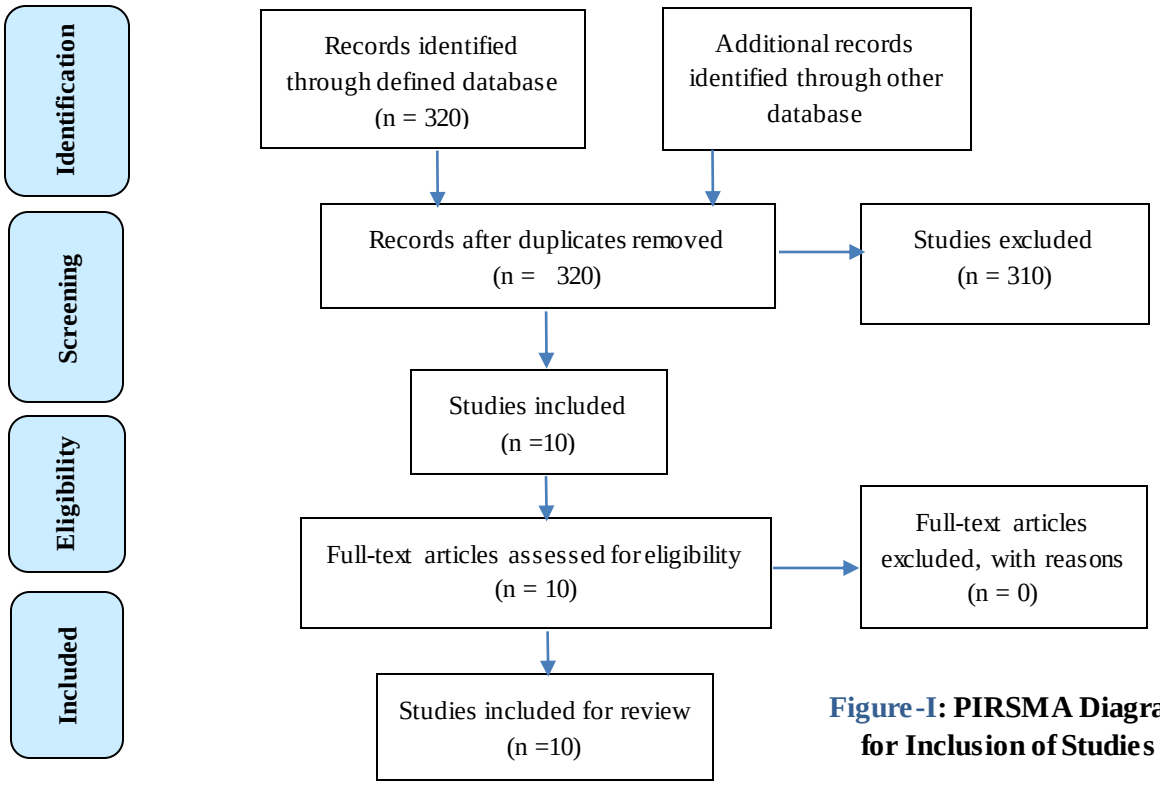

Figure-I: PIRSMA Diagram for Inclusion of Studies

Data extraction

For each study, the following characteristics were collected: name of the first author, year of publication, sample size, and the risk of RA among menopausal women. When definitive and non-definitive RA was diagnosed, only definitive RA was extracted. The clinical characteristics associated with rheumatoid arthritis such as age, gender, comorbidities and physical function were identified and in different studies and discussed, compared with previous studies.

Discussion

This review showed that menopausal women are at a higher risk of developing RA. Women who reported rheumatoid arthritis were more likely to have early or premature menopause (≤45 years) and menopause have also been shown to worse RA symptoms. This may propose a connection between chronic inflammation or factors and hormonal changes identified with RA..[4] The females who arrived at menopause after 51 years of age had a minimal risk of having RA and the females whose menopause happened before the age of 45 were at risk of developing RA.

Hormonal components may affect infection introducing in elderly people contrasted with a more young population, just as between RF-positive and RF-negative RA.[10] Menopausal females with early menopause were mostly seropositive and have more pain reported by the patients. Of the postmenopausal females with early RA remembered for our investigation, 17% of the menopausal females with early menopause were mostly seropositive and have more pain reported by the patients. Of the postmenopausal females with early RA remembered for our investigation, 17% of the patients revealed early menopause. Different examinations have demonstrated that a more prominent level of ladies with RA had early menopause than postmenopausal ladies without RA. A study found that 20% of ladies with RA had early menopause contrasted with 12% of controls 14 and the recurrence is like our investigation.[9] Another examination found that 25% of patients with RA revealed age at menopause as <45 years. Different examinations have discovered that early menopause is related to increased risk for RA. It concluded that a higher level of postmenopausal patients with RA have had early menopause.[3] Females experience three phases of hormonal changes throughout their life; menopause, pregnancy, and postpartum. It has been seen that the rate of rheumatoid arthritis is decreased during pregnancy, which may be decreased during pregnancy, which may be described by the increased accumulation of various circling hormones.[6]

Therefore, in postpartum the chance of RA is by all accounts is higher, potentially because of extraordinary fall in hormonal levels. The 3rd hormonal change is during menopause when E2 declines. Among pre-menopausal patients, parous females, in general, have less primary joint damage over time as compared to nulliparous females.[11] Specifically, early menopause is considered to be the major risk factor for RA. A reduction in estrogen levels may in this manner add perfectly cell separation slanted towards the Th1 (T-helper 1).[12] A steady decrease in the function of the hypothalamic-pituitary-gonadal axis is viewed as a critical component in the advancement of menopause. It is suggested that ladies with a less-responsive HPG axis, prompting an increased risk of menopause, women with a background marked by early menopause in whom RA created were bound to have a gentle sickness course, and more averse to advance to serious RA.[13]

Table-I: AXIS tool for quality assessment of included studies

Items	Wendy Marder et al	Mitra Pikwer et al	Camilla Bengtsson et al	C.E.I Szoeke et al (14)	Lauren E. Wong et al	Pikwer M et al	Riley Bove et al	Sapir Koren Rony et al	Deshire Alpizar et al	Alpizar-Rodriguez et al
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7	none	N	N	N	none	none	none	N	none	N
8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
11	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
13	N	Y	Y	N	N	N	N	Y	N	Y
14	none	N	N	N	none	none	none	N	none	N
15	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
16	Y	Y	Y	Y	Y	Y	N	Y	Y	N
17	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
18	Y	Y	N	N	Y	Y	N	Y	Y	Y
19	N	N	N	N	N	N	Y	N	N	N
20	Y	Y	Y	Y	Y	Y	N	Y	Y	N

**Y: yes*
**N: no*
**None: non-response*

Table-II: Characteristics of studies included

Author	Sample	Age	Gender	Duration	Source	Outcome measures
Mitra Pikwer (2014)	906	45 to 60 years	Females	4 to 16 weeks	Google Scholar	RA was highly anticipated by an early menopause
C. E. I. Szoeke (2011)	981	45 to 65 years	Females	12 weeks	PubMed	Females who reported RA were more likely to be early or premature menopausal
Deshire Alpizar-Rodriguez (2018)	1667	45 to 55 years	Females	23 weeks	Google Scholar	RA women having early menopause have a worse presentation of functional incapacity
Lauren E. Wong (2015)	534	Below 65 years	Females	1 month	PubMed	Early menopause, is related to seropositivity in females with early RA
Riley Bove (2013)	430	40 to 66 years	Females	3 months	PubMed	Increased risk of RA with early menopause and milder disease course
Camilla Bengtsson (2017)	1096	30 to 55 years	Females	15 weeks	Google scholar	Menopause at an early age was related to an expanded danger of RA
Pikwer M (2012)	134	35 to 60 years	Females	12 weeks	Google Scholar	Females with a background of early menopause had a high risk of developing RA
Alpizar-Rodriguez (2020)	320	45 to 55 years	Females	18 weeks	PubMed	Early menopause, most firmly connected with ACPA positivity
Sapir Koren Rony (2016)	876	Not mentioned	Females	2 months	Google Scholar	Menopause at an early age had a higher risk of RA
Wendy Marder (2015)	534	40 to 65 years	Females	20 weeks	Google Scholar	The patients with early menopause were more likely to be RF positive

Rheumatoid arthritis occurrence among females has recently been found to happen at age 45-64 years. The danger of both serologic RA aggregates is raised (predominantly seronegative RA) during the early menopausal age years, and occurring at age of 55-59 years, later than the mean period of menopause in these groups (age 51-52). RA hazard was weakened after age 60, yet just for seropositive RA.[15] It was proposed that menopausal factors are associated with the resulting improvement of RA, especially seronegative RA, yet those different elements may add to the pinnacle frequency after menopause. Strangely, in the age group 45-49, the danger was higher for seronegative RA (HR 2.1) and just non-fundamentally connected with seropositive RA (HR 1.2) which mirrors the outcomes that characteristic menopause at an early age is primarily connected with seronegative.[16] One of the main limitations of the present study was that it included only full-text articles from a defined time frame so many restricted-access articles could not be included. Further reviews including more studies may contribute to further evidence which can further aid in early diagnosis, treatment and better quality of life.

Conclusion

This systematic review concludes that early menopause is one of the main hormonal factors that were associated with an increased risk of developing RA. For the prevention and treatment of this disease, further research is required involving a larger sample size. Hormonal changes may influence pathways that are distinct from those leading to severe and progressive RA.

Declarations

Consent to participate Written consent had been taken from patients. All methods were performed following the relevant guidelines and regulations.

Availability of data and materials: Data will be available on request. The corresponding author will submit all dataset files.

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