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Review Article



Risk factors involved in the development of Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammation condition that affects over 17.6 million people. It primarily attacks joints making them stiff, swollen, painful and tender. This condition is usually linked to morbidity and mortality, and hence, knowing its risk factors is quite crucial. These are, but not limited to, diet, smoking, airborne, genetics, periodontitis, being a female, microbiota, and non-communicable diseases that respond to socioeconomic status. The inherent implication of how these factors synergize in enhancing the RA likelihood should not henceforth be overlooked while developing preventive strategies. Thus, this review serves to shed light on the correlation between these predisposing factors and the joint effect on development of this condition.

Keywords: Genetics, rheumatoid arthritis (RA), environmental factors, socioeconomic factors

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1. Introduction

Rheumatoid arthritis or RA is a very common autoimmune disorder that heavily involves chronic inflammatory processes which affects a large population in the world. Accurately determining the precise number of individuals affected by RA poses a significant challenge; nevertheless, global projections for the year 2020 indicate that approximately 17.6 million people worldwide are grappling with the disease. (1) Rheumatoid arthritis primarily targets the joints, manifesting through symptoms such as joint pain, tenderness, swelling, and stiffness. While RA has the potential to impact any synovial joint in the body, it typically initiates in the small joints of the hands and feet. Consequently, RA is characterized by elevated levels of inflammation, which contribute to a heightened sense of fatigue that interferes with various aspects of daily life. (2) The substantial inflammatory response also leads to significant fatigue and impacts multiple facets of daily living. If the disease is not treated or not ended the condition could lead to complete joint destruction and therefore physical deformity.

Rheumatoid arthritis affects both men and women but is more common among women. The probability of the disease occurrence in women is two to three times higher, and most of all elderly women often suffer from it. The most common age of onset of the disease is 60-70 years. (3) The last decade has seen significant progress in the

therapeutic interventions of RA. There has been the advent of novel therapeutics which have been effective in the management of RA. Therapies which started early have also been found to be helpful and particularly, significant improvement has occurred with the significant gaps in how the disease is managed (4,5) But, even though a number of therapies have been shown effective in treating and managing RA, some patients fail to get sustained clinical responses that lead to satisfactory long-term outcomes. Several key factors add to the lack of positive long-term outcomes in the management of RA. Some of these are factors that propel the increased risk of having RA. Research has identified both modifiable and non-modifiable risk factors involved in how RA develops. Understanding the risk factors related to the onset of rheumatoid arthritis is important since almost all of them increase the risk of developing the disease and shift the disease course and its prognosis. For RA researchers, defining risk factors may lead to important discoveries about the underlying pathological mechanisms that lead to the onset or worsening of RA and lay the ground for the planning of efficient prevention measures. Therefore, this review explores the potential risk factors which could lead to the development of rheumatoid arthritis including how they contribute to the etiology and pathogenesis of the disease.

2. Risk Factors of Developing RA

While the precise reasons for developing rheumatoid arthritis are still unclear, many risk factors have been associated with the disease's occurrence. These influences are classified into two types-modifiable traits where the factors are the environmental factors, and non-modifiable traits where the factors are the genetic traits, hormonal, and reproductive traits. Social factors also increase the chances that the disease would manifest, especially those from the low socioeconomic status possessing a greater risk of getting the disease.

3. Environmental Risk Factors

Whilst the very many non-modifiable risk factors are also included in the development of rheumatoid arthritis, environmental factors increase one's likelihood of being infected with the disease. The three main categories in which the environmental factors of RA may be classified include genetic background, lifestyle factors, and occupational factors. They encompass communities, lifestyle factors, individual diet intake, airborne exposures, and socioeconomic factors.

Smoking

Data from extensive studies have revealed that smoking was among the most common risk factors that heightened the risk of presenting RA. (6-10) There are several clinical studies and meta-analysis papers that showed a relationship between smokers and RA development with stronger risk prioritization observed among persons who had been smokers for a long time.10 Smoking leads to getting RA both in men and women. Some of the findings reflect the fact that the percentage of men increases the risk of the disease and women are the opposite while other studies show that men probably suffer more than women. (11) A meta-analysis conducted by Sugiyama et al. led to the conclusion that the risk of acquiring RA increases approximately two times more in not heavy smokers compared to those who never smoked and the risk is 1.3 times for women; Smoking constituted a heavier lifetime load, in RA real risk to smoking heaviest than was that who smoked or having had a heavier lifetime burden of smoking but who had already stopped smoking or those without a heavier lifetime burden of smoking. (12,13) The higher predisposition of rheumatoid arthritis in active smokers can be explained by more than one hypothesis. The most widely held today is nitrosation of protein peptides in the lungs which is caused by smoking. We understand that this process induces the creation of antibodies to ACPAs, with this being ultimately the development of RA. (14,15) This mechanism is particularly observed in individuals having a copy of a (SE) allele. The role of SE genetics is largely acknowledged as carrying about 40% of the genetic load in the development of RA. (14) Smoking is not only associated with RA but points to the potential synergy of these two factors in the increased risk. (16) The presence of rheumatoid factor, even without actual RA, may suggest biological interaction of these two factors leading to a higher likelihood of development of the In addition, the risk factor of RA known among smokers may be imputed to the fact that smoking only heightens the inflammation, angiogenesis and immunity at the joints.

Researchers have found that smokers' tissues have been exposed to tobacco in the smoker's blood and that this has been associated with joint pain and swelling. These findings supported the claim that the higher risk of the development of RA is directly linked to smoking. (17)

Periodontitis

Smoking has long been identified to produce periodontal disease in many individuals, and this disease has been associated with the risk of RA development in them. According to research, there is a positive correlation between periodontitis and the risk of developing RA. (18-20) Bacteria that have an altered composition develop a chronic inflammatory state of the gingiva in periodontal disease, which is further characterized by the breakdown of the periodontal ligament, cementum and alveolar bone. (19) Actual periodontitis biofilm, which is composed of bacteria such as *Porphyromonas gingivalis*(Pg) and *Aggregatibacter actinomycetemcomitans*(Aa) that have also been isolated from the joints of patients that have RA, could be the reason behind the association between periodontitis and RA. Furthermore, the pathophysiologic mechanism of bone-destroying disease in RA and periodontal disease shares some similarities. (21) Periodontal disease destroys the alveolar bone and periodontal soft tissue which leads to the deepening of the reflex of the tooth and eventual tooth loss. (19) Similarly, RA causes synovial inflammation destroying cartilage and affecting bone joints hence resulting in loss of function. (19) The similarities and inflammatory nature of the disease could explain why there exists a correlation between periodontal disease and RA.

Airborne Exposures

In cigarette smoke, the amount of oxidative molecules implicated in swollen joints and inflammation rises as well. Workplace silica is a noxious silica seen in construction, mining, and ceramics industries and it is the risk factor for declining silica to RA. Numerous investigations resulted in data on the elevated risk of developing RA, especially ACPA-positive RA. Moreover, the presence of traffic-related air pollutants and other airborne exposures to dust of textile fibers and inorganic dust increases the risk for autoimmune rheumatic disease. (22)

Dietary Risk Factors

Along with genetic factors, the dietary aspects have also been identified as a possible cause of acquiring RA. Health experts have now found out that some foods lower the likelihood of one developing RA while others increase the risk. These foods include low levels of vitamin D, antioxidants, and high levels of sugar and salt, iron, and excess red meat. Hu et al. found that a healthy diet was really good for females as it decreased their chances of contracting RA especially those who were aged below the age of 55. (23-25) People who were more likely to include highly sweetened sodas in their diet opened up to a high risk of testing seropositive RA with up to 63% rise in probability. (25) Also, when it comes to rheumatoid arthritis, a diet that had a high proportion of red meat was also proven to be a contributing factor. Pattison et al.

followed a group of patients with RA for a decade and found out that they had an increased risk of developing arthritis if their red meat intake was higher. (26) This finding is further supported by Hu et al. who stated a very close connection between the prevalence of rheumatoid arthritis in a population and the level of red meat that their people consumed. As explored in Deane et al. studies, patients who did not have definite signs of RA but received supplements that had omega-3 fatty acids had lower odds of developing RF and ACPA-positivity positivity.

Besides eating foods possessing omega-3 fatty acids, fish, diets rich in fruits and vegetables are known to lower RA risk. Because fruits and vegetables are rich in fibre and antioxidants, they are instrumental in lowering the risks of developing RA. The RA risk is found to be lower in people eating too much fruits and vegetables. Taking antioxidants to prevent inflammation is likely the reason why that kind of diet is protective. (27-30)

Alcohol Consumption

Unlike smoking which is linked with an increased risk of RA development, alcohol intake, particularly low to moderate alcohol drinking is a shielding factor against RA. Research has shown that modest consumption of alcohol between 1 to 2 drinks protects against RA. (30,31) One of the rational explanations why alcohol consumption lowers the risk of RA is because it induces downregulation of the immune responses and reduces the making of proinflammatory cytokines. (32)

Leading a Healthy Lifestyle

Another protective factor against developing RA is leading a healthy lifestyle. Obesity and having a high body mass index (BMI) have been linked with a higher risk of RA even though findings are conflicting. Lu et al. institute that being overweight and obese amplifies the risk of having RA among women. (33) Similarly, Crowson et al. found moderate obesity to contribute to the increasing incidence of RA. (34) On the contrary, Tureson et al. found the risk of RA to be lower in men who had a high body mass index. (35) However, although high BMI was protective against RA in men, the same could not be said about women. The study failed to find any association between increased BMI and a lower risk of developing RA in women. Although the findings on the contribution of obesity and higher BMI towards developing RA are mixed, it is a central risk factor that should not be ignored. Generally, leading a healthy lifestyle and eating a quality diet can lower the risk of RA development.

Microbiota and Infectious Agents

Although there is no single infectious agent that is known to cause rheumatoid arthritis, different microbes have been linked with more chances of developing the condition. Microbes, mucosal inflammation, oral and intestinal dysbiosis, and chronic infections are some of the infectious agents that have been attributed to RA. (36) The relationship between mucosal microbes and the role they play in the pathogenesis of RA can be explained by the interaction between microbes and environmental factors. (14) For instance, environmental factors that

include smoking and gut microbiomes interacting may lead to mucosal inflammation which leads to autoimmunity and subsequent development of RA. (14) The oral and gut microbiomes for instance have been linked to the development of RA. (36) Research has shown that intestinal dysbiosis increases the risk of inflammatory rheumatic diseases RA included. (37) The evidence of this association has been seen in animal studies where microbial flora has been shown to be instrumental in the development of arthritis. (37) The involvement of gut microbiota in the progression of RA is reasonable considering the outcomes of human studies that demonstrated the alteration of microbiota in the case of patients with RA. A diminished variety of microflora including a decrease in *Bacteroides* spp. are associated with patients with RA. (36,37)

In addition to microbes, there are external infectious agents that increase the risk of RA. According to Li et al., microbial infections play a significant role in the initiation of RA. (38) Examples of microbes that have been associated with RA are *Porphyromonas gingivalis*, *Proteus mirabilis*, Epstein-Barr virus (EBV), and mycoplasma. Rubella virus, Lyme's disease, hepatitis B/C, and Chikungunya virus have also been associated with increased risk of RA although findings are mixed. (21)

4. Non-Modifiable Risk Factors

Female and Hormonal Factors

RA is a complicated autoimmune illness in which both genetic as well as non-modifiable risk components like age, hormones, and genes may account for the disease presentation. There is an increasing body of evidence by epidemiological studies that show the female gender has a higher prevalence of RA and hormonal pathways are one of the key factors for this gender disparity. Estrogen, a pro-inflammatory hormone, is considered to be the cause of higher RA frequency in women and conversely, progesterone and androgens, being anti-inflammatory, are hypothesized to help protect from the disease to some extent. (39)

A number of sexual frame aspects have been linked with women transitioning into RA. Some of them are: early menopause, miscarriages, breastfeeding, parity (the number of babies a woman has), the age when a woman first gets pregnant, oral contraceptives, and hormone replacement therapy. (14,21,40,41) Some factors (for instance, lactation, oral contraceptives, and parity, alongside hormone therapy) were found to have positive outcomes in particular situations; however, these observations completely spectrum from each other. As an illustration, some research has shown that taking birth control pills prevents women from getting RA but in others, this association has been not observed. (42) On the same note, parity is generally associated with less risk of developing RA, with the protective effect being observed more clearly at two to three or more pregnancies. Firstly, although a few researchers have found a link between reproduction factors like early menopause, birth loss, post-partum, menopause, and anti-estrogen use, and the risk of RA, such a link has not been proven consistently. (43) This indicates a strong interaction of these factors

inside the immune system in the origin of this condition. (21,30)

Genetics

Aside from the hormonal changes, genes have a big role to play in how RA develops. Familial and twin studies report a higher likelihood of RA among first relatives contributing up to 40-50% of seropositive RA cases. (14) The probability of being affected by RA is critically higher in the monozygotic twins (twins born out of a single egg via fertilization of sperms) of the patients with RA in comparison with the dizygotic twins or general population, reflecting the prominence of the genetic component in RA etiology. (44) A number of genetic loci including the MHC have been implicated in the raised risk of RA. Furthermore, the MHC is the most prominent one. Certain alleles have been identified within the MHC genome for example HLA-DRBI, and have appeared to be correlated with a high risk of developing RA in many populations. (45) Studies substantiate the shared epitope (SE) hypothesis based on the amino acid positions, 70 and 71 of the susceptibility genes, and they have been associated with higher risks in RA development among affected individuals. (140) According to the SE alleles classification, there are five groups (SI, S2, S3P, S3D and X); however, S2 and S3P are closely linked with APCA positive RA, while the rest of the groups are linked to a lower risk. However, S3P, S2 and X groups are considered to be at risk for such antibodies. (46,47) This way, RA is a complicated rheumatic disease, where a combination of non-obviable risk factors contributes to it, including gender, hormones, and genetics. There is a cultural apprehension about homosexuality as a whole, which leads further to the prevention of access for homosexuals to space programs. In fact, the knowledge of these risk factors is of tremendous importance in the context of individuals who are more likely to develop RA and the development of focused prevention and overall treatment approaches.

5. Socioeconomic Factors

Socioeconomic status has been shown among many researchers as one of the key factors of the cause and progression of RA. Multiple researches proved that low socioeconomic status is associated with a heightened likelihood of developing RA. (48,49) Moreover, this group faces worse health outcomes in comparison with higher-income individuals. (48) According to the research carried out by Yang et al. the RA risk is higher among people having poor incomes than those residing in urban areas. Thus, the situation was that people of the low economic class were more likely to suffer from reduced quality of life and limited functional ability because of this medical condition.

The educational level is the other sociocultural factor which is tied up with rheumatoid arthritis, especially seropositive RA. (50-53) People who have a lower-level education were discovered to be more vulnerable to the condition. With occupation or rather job creation a study shows that it could lead to RA in individuals who are handling their work manually or white-collar work. (21,54) This elevated risk is more likely the product of exposure to dust and silica among the occupations due to

the association of these substances with the higher occurrence of RA in these jobs. (55)

The occurrence of joint consequences such as inflammation and rheumatoid arthritis in blue-collar and manual jobs can also be attributed to physical workload. (56,57) The connection between socioeconomic status and the increased likelihood of disease occurrence is known.

6. Conclusion

The reviewed studies serve to underscore the multi-dimensional nature of the variables that are involved in RA, including genetic, environmental and social determinants. Genetic factors, including family links, implement their most prominent influence on RA and importantly, the first-degree relatives' incidence of the disease is estimated to be on the rise. Other SE alleles besides those mentioned have been proven to contribute to high risks for RA. Environmental factors consisting of smoking, inhaling different substances, irritants including silica and organic dust, diet, infections and periodontitis all contribute to RA development. Individuals who have much red meat in their diet, sodium and sugar have a high risk of RA while those who eat omega-3 fatty acids, olive oil, fish, fruits, and vegetables diet are likely to experience a protective effect. The studies have also confirmed that people who consume low to moderate alcohol could prevent several types of diseases. Generally, leading a healthy lifestyle lowers RA risk. Another factor concerns gender with females tending to be 3 times more likely to be affected by the disease. Lower estrogen levels could be attributed to higher rheumatoid arthritis in women. Socioeconomic factors, for example, low income, low level of education, and jobs in blue and white-collar industries also have an association with increased risk of RA. Understanding the risk factors that are involved in the development of rheumatoid arthritis is vital in understanding the pathophysiology of the disease and how different factors interact to contribute to a higher risk of getting the disease. Understanding how these factors interact can lead to the development of accurate prediction models that help to identify individuals at risk of developing the disease and put prevention measures in place to lower this risk.

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Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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