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REVIEW

Environmental factors and hormones in the development of rheumatoid arthritis

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Abstract The etiopathogenesis of rheumatoid arthritis (RA) is partially understood. Genetic, environmental, and hormonal factors and their interactions are considered to play an important role on disease development. The relative contribution of environmental factors to RA development is probably larger than previously thought. The aim of this review is to appraise robust evidence about the role of environmental and hormonal risk factors for RA. We will discuss inhaled pollutants, nutritional habits, infectious, hormonal, and reproductive factors. As some of these factors are potentially modifiable, understanding their impact on RA development opens new opportunities for potential interventions and disease prevention.

Keywords Rheumatoid arthritis · Risk factors · Environmental factors · Hormonal factors · Reproductive factors

Introduction

Rheumatoid arthritis (RA) has become a model for autoimmune diseases, both to understand the development of autoimmunity and to study novel therapeutic interventions [1]. RA is the most prevalent systemic autoimmune inflammatory disease affecting between 0.5 and 1% of the adult population worldwide. The etiopathogenesis of RA is only partially understood but is believed to result from a multi-step process, whereby environmental factors induce specific post-translational modifications of proteins, which in turn trigger a pathologic activation of the immune system in genetically susceptible individuals, ultimately leading to the clinical onset of the disease. Specific pre-clinical phases of RA development have been proposed (Fig. 1) [2, 3].

A genetic contribution to the development of RA has long been suspected because of the increased risk in first-degree relatives of patients with RA [4, 5]. A variety of susceptibility genes have been identified, notably different alleles of the HLA-DRB1 gene that share a common sequence in the third hypervariable region, referred to as the "shared epitope." However, the overall risk associated with established genetic markers remains modest and the relatively low penetrance of the disease suggests that environmental factors play an important role in the etiology of RA [6]. Nevertheless, individual environmental factors, such as smoking, have generally demonstrated only weak associations with RA. Over the last years, striking gene-environment interactions have been discovered, which have changed our concepts of RA etiopathogenesis. The importance of gene-environment interactions [7, 8] is growing, because it opens opportunities for potential interventions and disease prevention.

In the following pages, we will review specific environmental risk factors for RA, without attempting to be comprehensive. Many studies regarding environmental and hormonal factors show controversial results. Some of these conflicting outcomes may be related to heterogeneity in the definition of the exposure, in the study designs and in the study populations. We will consider environmental factors broadly, as potentially modifiable exposures, in contrast to genetic factors. We will discuss inhaled pollutants, nutritional habits, chronic infections, hormonal and reproductive factors, focusing on the most robust findings or on results that have been replicated.

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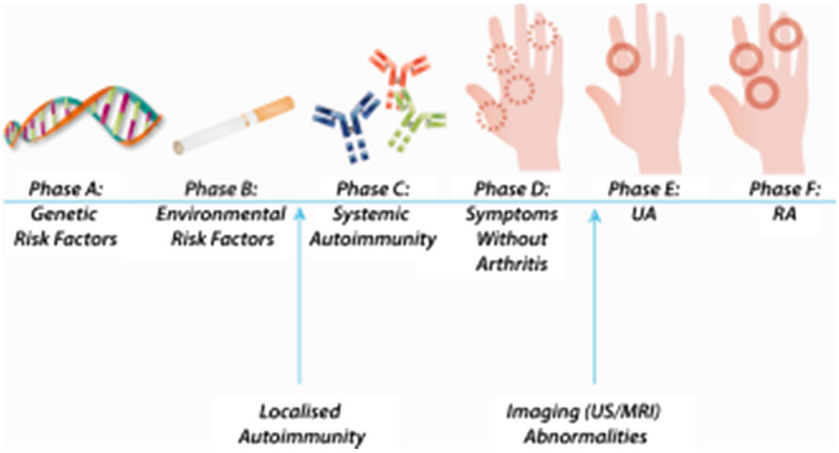

Fig. 1 Phases of RA development. *UA* undifferentiated arthritis, *RA* rheumatoid arthritis. Reproduction with authorisation from [3]

We will underscore gene-environment interactions or environment-environment interactions, when these have been established. Other environmental factors, such as acute infections, geographic or ethnic differences, socio-economic status, stress or specific industrial pollutants have also been associated with the development of the disease [9–13]; however, these findings still need confirmation.

Inhaled pollutants

Tobacco smoke has long been known to moderately increase the risk of developing RA. A meta-analysis of 16 studies estimated that ever smoking increases the risk of developing RA by 40% (odds ratio (OR), 1.40; 95% confidence interval (CI), 1.25–1.58) [14]. Smoking primarily increases the risk of rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA)-positive (seropositive) RA and only in the presence of specific genetic risk factors (the "shared epitope" or some PTPN22 alleles) [8]. For instance, the combination of a smoking history and two copies of the shared epitope increased the risk of seropositive RA by 21-fold (95% CI, 11–40) [2]. The precise etiopathogenic mechanism by which tobacco induces the development of RA is only partially understood. Tobacco increases the risk of RA only when inhaled but not when chewed (OR, 1.0; 95% CI, 0.8–1.2), suggesting that nicotine is not involved in the etiopathogenesis [15]. Klareskog et al.'s seminal work first demonstrated that smoking induces protein citrullination in the lungs [2]. In the SERA cohort, investigators were able to demonstrate inflammatory airway abnormalities in healthy ACPA-positive subjects, before the development of clinically apparent RA, even in nonsmokers, suggesting that the initial inflammation and immune onset of the disease begins in the lungs [16]. The major histocompatibility complex carrying the shared epitope allele has an increased affinity for citrullinated proteins [17], which provides a rationale of how citrullinated proteins could lead to a loss of tolerance and a pathologic activation of the immune system. Other genetic interactions may modify the association of smoking with RA, in particular enzymes involved in tobacco smoke detoxification. For instance, some studies have suggested an increased risk of RA with smoking in individuals with lower copy numbers of the *GSTM1* gene [18, 19] or NAT2 polymorphisms [20].

Likewise, other inhaled pollutants have shown associations with RA development, particularly in nonsmokers. In the Nurses' Health Study, women living within 50 m from the highway, a proxy for exposure to traffic pollution, had a moderately increased risk of RA (hazard ratio (HR), 1.31; 95% CI, 0.98–1.74), particularly in nonsmokers (HR = 1.62; 95% CI, 1.04–2.52) [10]. These results were replicated in British Columbia, Canada with very similar results [21]. A longitudinal, population-based study in Taiwan found an increasing risk of RA with higher nitrogen dioxide (NO_2) levels, as well as a clear dose response [22]. While there are still inconsistencies in epidemiological studies on air pollution and RA development [23], the overall pattern suggests that air pollution is an environmental risk factor for RA [24].

Several occupational exposures to inhaled pollutants have also been suggested as risk factors for RA development. Over half a century ago, physicians first noticed a striking association between silicosis and RA in miners, entitled Caplan's syndrome [25, 26]. Since then, the association between silica dust and RA has been confirmed in the mining industry [27], and also in occupations outside of mining, such as construction workers or the pottery industry [28, 29]. Interestingly, several studies have found an interaction between silica dust and smoking [30, 31], with a modest elevation of the risk of ACPA-positive RA in nonsmokers (OR, 1.15; 95% CI, 0.42–3.15) and a strong elevation of the risk in current smokers (OR, 7.36; 95% CI, 3.31–16.38) [30]. How inhaled silica dust induces autoimmunity is poorly understood; however, it has been shown that silica particles can activate the innate immune system, promote pro-inflammatory cytokine production and function as an adjuvant for antibody production [32]. Other professional inhaled exposures have been found to increase

the risk of RA. In a Malaysian case-control study, occupational exposure to textile dusts was associated with an increased risk of developing RA in women (OR, 2.8; 95% CI, 1.6–5.2), and a strong gene-environment interaction with the shared epitope in ACPA-positive RA patients (OR, 39.1; 95% CI, 5.1–297.5) [33]. Recent studies have also suggested that certain agricultural pesticides could increase the risk of RA in farmers and their families [34, 35].

Nutritional habits

Patients often attribute the occurrence of an autoimmune disease such as RA to nutritional habits. We will focus on a few nutritional factors that have been convincingly associated with the disease, whether protective or hazardous.

In animal models, it has been known for over 10 years that adding small doses of ethanol to mice's drinking water defers the onset of collagen-induced arthritis and prevents the development of erosions, suggesting preventive properties of low-dose and persistent alcohol consumption [36]. In humans, a meta-analysis of nine observational studies found a significant protective effect of alcohol on the development of RA with an OR of 0.78 (95% CI, 0.63–0.96), which was more pronounced in ACPA-positive RA (OR, 0.52; 95% CI, 0.36–0.76)) [37]. Consistent with these findings, cohort studies in established RA have confirmed that moderate consumption of alcohol decreases the rate of erosive joint damage progression [38].

Another well-known "cardio-protective food," omega-3 fatty acids, have been suggested to be protective against the development of autoimmunity associated with RA. In a first-degree cohort of RA relatives, healthy individuals who developed ACPAs were less likely to use omega-3 supplements (OR, 0.14; 95% CI, 0.03–0.68) and had significantly lower concentrations of omega-3 fatty acids in red blood cell membranes [39]. In a large, longitudinal cohort from Sweden, long-lasting intake of omega-3 fatty acids higher than 0.21 g/day decreased the development of subsequent RA by 52% (95% CI: 29% - 67%) [40], as well as a regular consumption of fish at least once per week (risk ratio (RR), 0.71; 95% CI, 0.48–1.04). A meta-analysis examining the association between fish consumption and subsequent development of RA suggested a trend towards a protective effect with one to three portions of fish per week (RR, 0.76; 95% CI, 0.57–1.02) [41]. A randomized controlled trial in early RA, demonstrated that adding fish oil supplements to a standard therapy with conventional anti-rheumatic drugs increased significantly the chance of clinical remission (HR, 2.09; 95% CI, 1.02–4.30), supporting the hypothesis of anti-inflammatory properties of omega-3 fatty acids [42].

High salt consumption has also been suggested as a risk factor for the development of RA, in particular in smokers [43]. In a prospective cohort from northern Sweden, high sodium intake more than doubled the risk of RA among smokers (OR, 2.26; 95% CI, 1.06–4.81) but not in nonsmokers. Furthermore, this interaction between smoking and high sodium intake was stronger for ACPA-positive RA. In the Nurses' Health Study, regular consumption of sugar-sweetened sodas significantly increased the risk of developing RA. The association was independent of obesity and other socio-economic factors and tended to be stronger for late-onset RA (HR, 2.64; 95% CI, 1.56–4.46). Interestingly, no causal relation was found with diet soda or between sugar-sweetened soda and seronegative RA [44]. Furthermore, akin to high sodium intake, the authors describe an interaction between sugar-sweetened soda consumption and smoking, with a higher risk of developing RA in women who regularly drank sugar-sweetened sodas and had smoked more than 10 pack-years.

Obesity is increasing all over the world, with well-established consequences on a number of chronic diseases. The role of obesity as a risk factor for RA is still debated, but a majority of studies suggest it is a risk factor for RA in women [45]. Obese women (BMI ≥30.0 kg/m^2) in the Nurses' Health Study tended to have an increased risk of RA, in particular in those diagnosed at earlier ages (HR, 1.65; 95% CI, 1.34–2.05) and with adolescent obesity (HR, 1.35; 95% CI, 1.10–1.66) [46]. Similar results were found also in Europe, with obesity increasing the risk for seronegative RA in Swedish women (HR, 1.6; 95% CI, 1.2–2.2) [47]. In men, the effect of obesity is less obvious and some studies have even described a reduced risk of RA in men [48].

Chronic infections

Several infectious agents have been proposed as risk factors for RA; however, findings have not been conclusive. Some viral infections, such as parvovirus B19, chikungunya, and hepatitis C, are known to cause acute and chronic arthralgias and persistent arthritis; however, the association with the development of classifiable rheumatoid arthritis is not solid [49–51]. In a large population-based cohort, chronic hepatitis C was associated with an increased risk of RA, hazard ratio (HR, 2.03; 95% CI, 1.27–3.22) [52]. However, the diagnosis of RA in chronic hepatitis C is difficult to establish because of false-positive auto-antibodies, such as rheumatoid factor and ACPA [53].

Lyme disease caused by the bacterium *Borrelia burgdorferi* is associated as well with chronic arthritis. RA cases diagnosed after Lyme disease have been reported [54, 55]. However, the distinction between active Lyme infection in joints, post-infectious Lyme arthritis, and another form of inflammatory arthritis, such a RA can be challenging [55].

A population-based case-control study (N = 6401) examined the association of recent infections with the risk of RA and found that gastrointestinal and urogenital infections were associated with a lowered risk of RA, OR of 0.7 (95% CI, 0.6–0.8) and OR of 0.8 (95% CI, 0.7–0.9), respectively. This finding

was hypothesized to be related to antibiotic treatment; however, no information about antibiotic use was specified [56].

The most prevalent chronic infection consistently associated with RA is periodontitis. RA patients have a higher prevalence of chronic periodontitis and tooth loss compared with patients without RA [57, 58]. A longitudinal population study based on the First National Health and Examination Survey (NHANES I) suggested that subjects with periodontal disease and missing teeth (p for interaction = 0.05) had an increased risk of developing RA. In severe periodontal disease associated with an edentulous state, the risk of incident RA was almost doubled (OR, 1.92; 95% CI, 1.0–3.7) [59]. *Porphyromonas gingivalis*, a common periodontal pathogen associated with chronic periodontitis, is known to express an endogenous peptidylarginine deiminase (PAD) that is able to citrullinate different human proteins [60]. Citrullinated proteins are present in serum, synovial, and periodontal tissues of RA patients. DNA of *P. gingivalis* has been found in the synovial tissue [61, 62]. Factors that contribute to the loss of tolerance to the citrullinated proteins are still unclear. Studies have not found an association between the presence of antibodies to periodontal bacteria and RF seropositivity [63]. An additive interaction between ACPA positivity, the shared epitope and antibodies against the *P. gingivalis* virulence factor, arginine gingipain-type B (RgpB) has been reported (OR, 5.7; 95% CI, 4.2–7.6) [64]; however, other studies have not found an association between anti-RgpB and later development of RA [65]. A recent study reported an association with another periodontitis related bacteria, *Agregatibacter actinomycetemcomitans*, which induces citrullination and dysregulates activation of citrullinating enzymes in neutrophils. In addition, *A. actinomycetemcomitans* was associated with ACPA positivity (p = 0.01) in a sample of 196 patients with RA [66]. Nevertheless, in spite of the biological arguments for the role of periodontitis in RA development, the causal relationship is still not clearly established. The association between periodontitis and RA could be confounded by behavioral and environmental exposures common to both conditions [67]. Furthermore, the entity of periodontitis has often been poorly defined in scientific investigations [57, 59].

Microbiota comprises the diverse population of bacteria that live in the human body. Changes in nutrition, immune competence, incidence of disease, and use of medications, such as antibiotics, could alter the composition of the microbiota, generating an imbalance between beneficial and harmful species. A dysbiotic microbiota has been observed in many conditions, including obesity, diabetes, and inflammatory bowel diseases [68, 69]. In RA patients, oral and gut dysbiotic microbiota has been reported as well [70, 71]. Particularly, increased occurrence of *Prevotella* species have been identified in patients newly diagnosed with RA [72, 73]. Dysbiotic microbiota in RA patients is partially resolved after disease-modifying anti-rrheumatic drug (DMARD) treatment. In addition, fecal, dental, and salivary samples from RA patients who show improvement with treatment contain a greater number of virulence factors than those without improvement [71]. As the reports of dysbiotic microbiota are based on association studies, causality is difficult to establish with the information available so far. Interestingly, in DR4-transgenic mice, a sex-biased mouse model of collagen-induced arthritis, the fecal microbiota differed in males and females. In females, the microbiota was dysbiotic and less dynamic, and males showed significantly higher abundance of Bacteroides [74]. These findings suggest that gut microbiota could contribute to the sexual dimorphism of RA.

Hormonal and reproductive factors

RA is more prevalent in women. The female-to-male sex ratio of the disease varies between 4:1 in patients younger than 50 years to less than 2:1 in the older population [75, 76]. The reason for the increased prevalence in females is still unclear. An increased risk of developing RA has not been reported in X-chromosome dosage disorders, such as Klinefelter syndrome, characterized by an extra chromosome [77, 78]. In addition, the familial aggregation of RA is not preponderant in women, suggesting that the familial risk is not related to chromosome X [79].

There are many controversies regarding the role of hormonal factors in the development of RA. For example, both factors related to high and to low estrogen exposure have been associated with increased risk of RA. In a simplistic manner, it has been proposed that estrogens have a pro-inflammatory and androgens an anti-inflammatory effect. However, estrogens can have both stimulatory and inhibitory effects on the immune system [80]. Overall, a host of studies suggest that factors related with the decline of estrogens are risk factors and those related with high exposure to estrogens are rather protective factors.

Two examples of factors characterized by a decline of estrogens are menopause and the use of anti-estrogen agents. Post-menopause has been associated with an increased risk of developing seronegative RA in a large cohort study (HR, 2.1; 95% CI, 1.5–3.1), and particularly early age at menopause defined as <44 years old (HR, 2.4; 95% CI, 1.6–3.5) [81]. Other studies have confirmed this finding with even earlier ages at menopause [82, 83].

An interesting study analyzed the incidence of RA in users of anti-estrogen agents in a large US national database for breast cancer. The use of anti-estrogen agents, both selective estrogen receptors modulators and aromatase inhibitors, was associated with RA, with a dose- and duration-dependent effect (for >12 months, OR, 2.4 (95% CI, 1.9–3.0) and OR, 1.9 (95% CI, 1.6–2.1), respectively) [84].

Examples of high estrogen exposure are the use of hormonal treatment, such as oral contraceptives (OCs) and hormonal

replacement therapy (HRT). The effect of OCs use on RA is controversial [85, 86]. Meta-analyses investigating the association between OCs and development of RA concluded a non-significant association. However, the studies were heterogeneous, in particular the dose and the duration of OC exposure varied between studies [87–89]. In several analyses of the duration of treatment, longer use of OCs was protective [90]. OC use for ≥8 years was associated with a decreased risk of ACPA-positive RA (OR, 0.8; 95% CI, 0.7–0.9) and ACPA-negative RA (OR, 0.9; 95% CI, 0.7–1.0) [91]. The fact that older studies tended to show a stronger protective effect for RA suggests a potential dose effect, due to increased estrogen dose in OCs in the past [88]. Overall, the available evidence supports a protective effect of OCs against RA, in particular when used for long periods or at high dose. Regarding hormonal replacement therapy (HRT) a protective association of combined HRT use on ACPA-positive RA has been described in a population-based case-control study (OR, 0.3; 95% CI, 0.1–0.7) but not for estrogen-only HRT (OR, 0.8; 95% CI, 0.5–1.6) [92].

Multiple hormonal changes

Some conditions are characterized by multiple hormonal changes, such as pregnancy and breastfeeding. Pregnancy is associated with high levels of estrogens, but their effect is modified by other hormonal changes, such as high progesterone [80]. In prospective cohorts, pregnancy has been described as protective against developing RA [93, 94]. In a prospective case-control study in women with recently diagnosed RA, parity was significantly associated with a lower risk of RA (RR, 0.6; 95% CI, 0.4–0.8) [95]. Breastfeeding has been consistently associated with decreased risk of RA [13, 96]. In a systematic review, breastfeeding for less than 12 months was protective against RA (OR, 0.8; 95% CI, 0.6–0.9) and a longer breastfeeding period had a stronger protective association (OR, 0.6; 95% CI, 0.4–0.7) [97]. On the contrary, the post-partum period, characterized by a decline of estrogens and other hormonal changes, has been consistently associated with an increased risk of RA [94, 98], particularly during the first year post-partum (OR, 3.4; 95% CI,1.5–9.9) [93].

Androgens

Men with RA have decreased androgen levels, while the androgen levels in women are not different compared to controls [99–101]. Lower androgen to estrogen ratios have been detected in both female and male RA patients [102]. In addition, increased estrogen formation has been described in the synovial tissue of patients with RA [103–105]. In a retrospective cohort study using US administrative health data, 123,460 males aged >19 years with untreated hypogonadism had an increased risk of developing RA (HR = 1.31; 95% CI, 1.3–1.5) compared with men without hypogonadism [106]. In contrast, in women from the Nurses' Health Study, no significant association was found between total or free testosterone (measured at a single time point prior to RA onset) and risk of RA development [107]. Androgens have been less studied in pre-clinical phases of RA. In a small case-control study, serum androstenedione levels were significantly lower in women before RA diagnosis compared with controls [108].

Nonhormonal reproductive factors

Pregnancies complicated by pre-eclampsia have been associated with an increased risk of RA (RR, 1.4; 95% CI, 1.1–1.8) [109]. The same research group confirmed pre-eclampsia as a risk factor for RA in a larger group of women (HR, 1.9; 95% CI, 1.1–3.6) [110]. One hypothesis for the increased risk of RA during pre-eclampsia as well as during the post-partum period is fetal microchimerism, which is the acquisition of fetal cells and/or DNA persisting in the maternal circulation. It is believed that persisting microchimeric cells carrying one of the SE alleles could confer to the mother additional susceptibility to RA [111]. The rationale is supported by a higher frequency SE microchimerism in RA cases (DRB1*01 microchimerism, 30 vs. 4% ($p = 0.001$) and DRB1*04 microchimerism, 42 vs. 8% ($p < 0.001$)) [112, 113].

Conclusions

The understanding of environmental factors and their interactions with other patient-related factors on the development of RA has increased with larger observational studies. The relative contribution of environmental factors to RA development is probably larger the previously thought [6, 114]. As some of the environmental and hormonal factors are potentially modifiable, understanding their impact on RA development opens new opportunities for potential interventions and disease prevention.

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