TESTOSTERONE AND ANDROPAUSE IN MALES WITH INFLAMMATORY ARTHRITIDES

Prakashini M V1 https://orcid.org/0000-0002-1278-6042
Sakir Ahmed1 https://orcid.org/0000-0003-4631-311X

1Department of Clinical Immunology and Rheumatology, Kalinga Institute of Medical Sciences, Bhubaneswar, India

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Corresponding author: Sakir Ahmed, E-mail:sakir005@gmail.com

Abstract
Infertility is emerging as one of the leading global health concerns. The spectrum of global diseases has shifted from communicable to non-communicable, with autoimmune diseases being at the crux of it. Infertility among females with autoimmune diseases has been explored. Many inflammatory arthritides affect men in their peak reproductive and functional age. However, data on male infertility in persons having these diseases is scarce.

This topical review explores the multifactorial causation of male infertility in inflammatory arthritis. These individuals tend to have gonadal dysfunction, Sertoli cell dysfunction and hypotestosteronaemia. Individuals with rheumatoid arthritis and spondyloarthritis have also reported a loss of libido owing to poor quality of life, low functional status, and erectile dysfunction. These factors along with social and psychological factors greatly influence the development of persistent sexual ill-health. Another observation is that men who have primary infertility have a higher predisposition to developing autoimmune diseases; particularly in rheumatoid arthritis and spondyloarthritis. The morbidity that comes with pain and deformities resulting from inadequately treated disease or high disease activity, can also result in poor sexual well-being. Many of the males with inflammatory arthritis tend to be voluntarily childless due to the fear of passing the disease on to their off-springs and also a possible flare when the drug therapy is modified to facilitate conception.

Male fertility in autoimmune rheumatic diseases is often a neglected topic in our practice and research. Physicians must be sensitized and receptive to the issues of infertility and sexual well-being in male patients with autoimmune rheumatic diseases.

Keywords: ageing; male infertility; rheumatoid arthritis; spondyloarthritis; inflammatory arthritis.

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Introduction
Rheumatoid arthritis (RA), followed by spondyloarthritis, is the most common cause of chronic inflammatory arthritides, with an estimated prevalence of 0.5 to 1% and 0.2 to 1.6% respectively among the adult population worldwide, with the West reporting more cases than the Asian countries [1–4]. Gender influence on the incidence of inflammatory arthritis such as rheumatoid arthritis (RA) and spondyloarthritis (SpA) is well known. These diseases have a curious relationship with age and sex, with RA being thrice as common in females, in contrast to spondyloarthritides (SpA), which are more prevalent in the male population [5]. Evidence from previous studies has also shown that females with RA tend to have more severe disease, with higher disease activity, faster progression with comparatively lower remission rates [6, 7]. However, most studies have focused on female patients.
There is an unmet need to explore how males have reduced susceptibility to RA and are more inclined to have ankylosing spondylitis (AS). It is not clear if age-related changes such as andropause influence this susceptibility.

AS is predominantly a disease active during the reproductive age group. It is not clearly known why the severity of this disease gradually dies out after the fifth decade of life. There may be ties between the levels of sex hormones and the onset of andropause. It has been long shown that RA and SpA, ankylosing spondylitis (AS) in particular, are associated with lower levels of androgens in both males and females which may translate to more severe disease [8, 9]. Added to this is the observation that in the younger age groups autoimunity is higher in women; but as age advances, the gap narrows [10]. This obvious disparity in the clinical features and their severity among the sexes has prompted research to establish the anti-inflammatory role of testosterone in the disease process.

Another major cause for concern in men with inflammatory arthritis is fertility. Infertility is emerging as one of the pressing health issues affecting millions of people worldwide. According to the available data from WHO, around 48 million couples and 186 million individuals are infertile globally [11]. Studies suggest that there is an increased risk of infertility among people with autoimmune rheumatic diseases (AIRDs) with varying frequency and severity [12]. SpA and RA tend to affect men at their peak reproductive years consequentially resulting in erectile dysfunction, male infertility and hypogonadism [13]. Around 56% of men and 46% of women in RA were reported to have some kind of sexual dysfunction in a cohort of 231 patients studied for fertility disturbances in RA [14]. This decreased fertility is multifactorial, causing a major sociocultural concern for these ailing patients. In addition to infertility, painful mobility or lack thereof owing to arthritis may limit libido and sexual performance in these patients. The perception of difficulty with sexual activity was independently correlated with chronic fatigue, psychological ill-health, functional limitations, and male gender [15]. In an event of acute stress or inflammation, as in inflammatory arthropathies, the hypothalamic-pituitary-adrenal axis is suppressed, with resultant hypotestosteronaemia [16]. This may itself predispose to more severe arthritis in a vicious cycle.

Search strategy
PubMed/MEDLINE, Scopus and Web Of Science were queried using relevant search strings incorporating “testosterone”, “andropause, and “ageing” in various combinations with “rheumatoid arthritis” and “spondyloarthritis”. The authors selected articles as per their experience and opinions to transcribe this review [17].

**Androgens in inflammatory arthritis**

It has been postulated that oestrogens contribute to the increased risk of RA in females [7]; while androgens have been hypothesized to have a protective effect on inflammation [18]. Additionally, studies have demonstrated that testosterone tends to be low in male patients with RA and those with hypotestosteronaemia have a more aggressive disease course [8, 9, 19].

Many theories have been suggested over the years to explain the relationship between testosterone and disease activity in RA. The heightened inflammatory response in active disease is associated with increased levels of interleukin-6 (IL-6), which has been shown to suppress the secretion of adrenal androgens [20]. If the low androgen levels are a consequence of disease activity or vice versa is a pressing question that many studies have tried to account for. Low levels of androgens have been demonstrated to correlate inversely with disease activity and markers of inflammation, with the levels of testosterone increasing once RA was optimally treated [19, 21]. To conclude, androgens may affect the disease in two ways – they can have a direct role in preventing the disease in males (more often in younger males) and can affect the severity and course of the disease in male RA (Figure 1).

Since the correlation between low free testosterone in the serum and disease activity in RA was established, a few researchers attempted intervention with testosterone for the treatment of active disease, with a resultant positive outcome in both sexes. However, this was demonstrated in a few case series and studies with small sample sizes, and hence a definite benefit of supplementing the hormone could not be validated [22–24].

SpA is the other group of inflammatory arthritis where a disbalance between “osteohormones” has been shown to contribute to the pathogenesis of inflammation and joint erosions. The DKK-Wnt pathway has been identified as the main culprit for disease initiation and propagation in patients with SpA, including axial SpA (or ankylosing spondylitis) and psoriatic arthritis (PsA). There is an evident disparity in the sex distribution in SpA, with axial SpA being more common in males, who also tend to develop more
severe radiographic damage [25]. However, an entity defined as non-radiographic axial SpA occurs more frequently in females [26, 27]. Akin to RA, patients with SpA have a reduced testosterone reserve, and slightly increased estradiol with reversal of oestradiol testosterone ratio. Th17 cells producing IL-17 are one of the major drivers of inflammation and bone loss in SpA. In murine models, it has been demonstrated that estrogen suppresses IL-17 mediated osteoclast differentiation; and mice that have undergone oophorectomy demonstrated an increased number of Th17 cells and circulating IL-17 [28].

In conclusion, testosterone has been shown to have anti-inflammatory properties. However, patients with inflammatory arthritis tend to have a reduced testosterone reserve, which correlated with disease activity and the extent of joint damage.

Age and male fertility in inflammatory arthritis

Inflammation per se has been associated with dysregulation of the hypothalamic-pituitary-adrenal axis with a resultant hypotestosteronaemia. Low serum testosterone levels have been consistently demonstrated in inflammatory arthritis, with a stronger association with RA, where it predisposes to infertility in diseased males.

In addition to hypogonadism and erectile dysfunction, age also has a role in the causation of infertility in men with AIRDs. Childbearing decisions and potential are associated not only with one’s health, but also influenced by many social and economic factors. RA and SpA usually affect men in their peak reproductive age groups. This is also the age at which men are in their most productive years in terms of human resource development and financial gain. These diseases can be highly disabling when not treated optimally, which results in a reduction of performance years with added costs of treatment and childbirth. The disease along with these social and economic factors affects male fertility a great deal.

A large iFAME (Inflammation and Fertility in Men) cohort from the Netherlands studied the impact of inflammatory arthritis on markers of male fertility. In men with inflammatory arthritis, the fertility rate significantly reduced with longer disease duration and also as compared to the general population. It was interesting to note that, along with reduced fertility rates, childlessness, both voluntary and involuntary, was also higher in these men, with the ones with an earlier disease onset having a higher probability of childlessness [29].

Recently, a novel concept of inflamm-aging is gaining traction, where individuals with chronic inflammation, vis-à-vis autoimmune diseases, appear to have accelerated ageing as compared to the healthy population[30]. This was especially demonstrated in RA, where patients appeared to be two years older at the onset of the disease and this ageing only accelerated with time, with frailty, nutritional deficiencies and cachexia being some of
being some of the most important contributing factor. CXCL9 is another important chemokine, that has been associated with accelerated ageing and worsening CV mortality. Higher levels of CXCL9 in the blood correlated with an increased risk of falls, which can be attributed to frailty, which is commonplace in inflammatory arthritis [31]. The main cause of CXCL9 overproduction is hypothesized to be cellular ageing per se. This process increases the production of DAMPs, leading to accelerated inflammation and arthritis. These DAMPs mostly act through the inflammasome pathway and regulate signals like IL-1β, CXCL9, etc. [32]. IL-1 is one of the key cytokines in the mediation of inflammation in RA, responsible for bone resorption and cartilage destruction [33]. In addition, there is a close association between IL-1 family cytokines and inflammatory bowel disease (IBD), multiple sclerosis, RA, and ankylosing spondylitis. A strong association between AS and IL-1RN*2 gene polymorphisms was demonstrated in a study including 106 AS patients and healthy controls [34]. In conclusion, inflammatory arthritis like RA and AS have accelerated ageing by virtue of many cellular and molecular events, with polymorphisms of IL-1 family and frailty and nutritional deficiencies adding on to the burden of inflamm-aging.

Is subfertility in men a harbinger of autoimmune diseases?

The fact that inflammation and inflammatory arthritis are associated with male infertility due to hormonal aberrancies has been explored. However, the understanding of the later risk of developing autoimmune diseases in infertile men is limited. A large US claims database analysis revealed that the incidence of certain autoimmune diseases is higher in infertile men, especially in the years following infertility diagnosis or evaluation. The highest risk was for RA, SpA and other connective tissue disorders, even though the risk for other autoimmune diseases like inflammatory bowel disease, Grave’s disease, and multiple sclerosis was also higher than the general population [35]. Akin to the increased prevalence of infertility in men with autoimmune disorders, the reverse is also true, owing to similar mechanisms of hypogonadism in autoimmunity. Men with infertility are known to have lower levels of testosterone as compared to fertile men, which can also be a predisposing factor for the development of autoimmunity by virtue of reduced anti-inflammatory benefits owing to hypotestosteronemia [36].

Beyond hypogonadism: semen quality in inflammatory arthritis

Patients with SpA, AS in particular, have reduced sperm motility, a higher incidence of aneuploidies in the sperm, in addition to hormonal aberrations like higher plasma levels of the follicular stimulating hormone (FSH) and luteinizing hormone (LH) and lower levels of testosterone. Poorer sperm quality is also associated with high disease activity and this mostly improves with optimal treatment of the disease on achieving remission [37]. The most accepted explanation for this is the effect of inflammation of AS having a suppressive effect on the testicular function and the anti-tumour necrosis factor drugs have a positive effect in the restoration of fertility of Sertoli cell function [38]. Drugs like sulfasalazine, and sometimes celecoxib, have also been implicated in literature to alter sperm function. However, this has not been established in prospective studies [39–42]. Similarly, the proposed theory that poor semen quality with aneuploidies affecting male fertility also does not have high-quality supporting data and needs further validation.

Unmet needs

It is not uncommon for people living with AIRDs to consider being voluntarily childless due to fear of flares on altering therapy for conception or transmitting the disease to their offspring [43]. Male infertility in AIRDs is multifactorial and has been a neglected area of research. Inflammatory arthritis is associated with depressed gonadal function, resulting in low serum testosterone and poor sperm quality. However, there have been no population-based studies to date that have researched if men with autoimmune diseases father fewer children. Drugs may be another cause of impaired fertility in men, however, only cyclophosphamide and sulfasalazine have been listed by the US FDA to cause infertility [44]. The use of cyclophosphamide in inflammatory arthritis is negligible and sulfasalazine has not been shown to be associated with a significant reduction in fertility or sperm quality as per the data available. Hence the role of drug-induced infertility in inflammatory arthritis is not paramount and the role of cyclophosphamide in inducing male infertility is out of the scope of this review. Physicians must be sensitized to dealing with problems of sexual health associated with inflammatory arthritis, which includes but is not limited to only infertility. This is a prospective avenue of research as there is a lacuna in good quality population-based studies with healthy controls exploring male infertility associated with autoimmune diseases. With the increasing
incidence of infertility across the world and with growing emphasis on sexual health, sensitization of the treating physicians to these issues and the willingness to address them can be the stepping stone to a healthier society.

**Conclusion**

As the world population ages, fertility issues will form a major burden of global health problems. Male fertility can no longer be ignored. We have explored these concepts in the context of people living with AIRDs. This vulnerable group has problems due to the various mechanisms, including high inflammatory disease activity, and other social and psychological issues that come with coping with all chronic diseases. Sexual problems tend to have a significant negative impact on an individual and also on their quality of life. However, in the process of treating the disease, the clinician often tends to ignore or avoid these sexual and psychological issues of the patient, which may often hamper the quality of life of the ailing individual.

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It is evident in the data described till now that the levels of infertility are higher in males living with autoimmune diseases, as compared to the healthy population. It is not clear whether it is purely an effect or also contributes to the causation of autoimmune disease. There is a big lacuna of research in this area.

**DISCLOSURES**

The authors have no potential conflicts of interest to disclose.

**AUTHOR CONTRIBUTIONS**

Both authors substantially contributed to the drafting and revision of the manuscript. They take full responsibility for the integrity of all aspects of work.


