Chem. Biol. Lett. 2021, 8(4), 238-247 Review Article

Chemical Biology
LETTERS

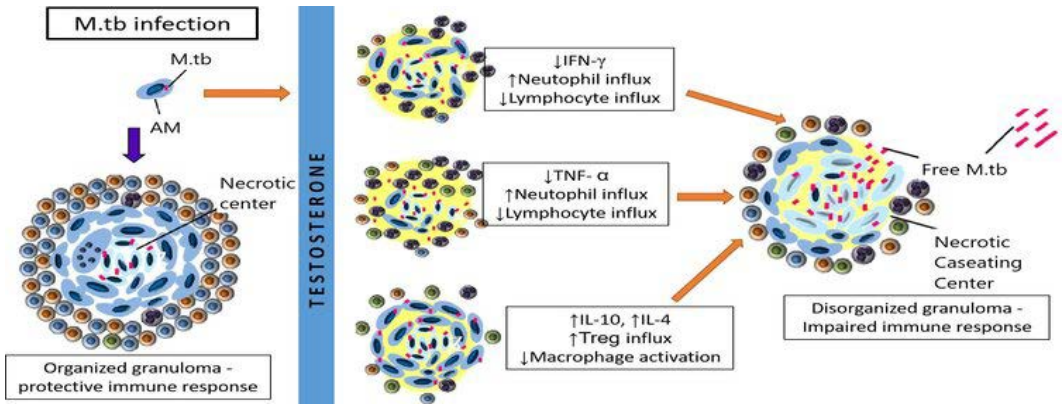
Testosterone in the pathogenesis of tuberculosis

Parul Shrivastava,[1*] Tamishraha Bagchi[2]

[1]*ITM Vadodara University, Plot 6512, Ajwa Nimeta Road, Ravaal, Taluka Waghodia, Vadodara, Gujarat, India. .*
[2]*BioTechniques Laboratory, DBL enterprises, Waghodia, Vadodara, Gujarat, India*

Submitted on: 17-July-2021, Accepted and Published on: 10-Sept-2021

ABSTRACT



Tuberculosis is a leading cause of death from infectious diseases worldwide with more than 1.5 million deaths occurring annually. Males have been known to be more susceptible to tuberculosis than females. Sex hormones could be an important factor governing this gender bias. Here, we discuss the evidence that testosterone may be a crucial factor in male susceptibility to tuberculosis considering that testosterone impairs important factors which have a significant bearing on the outcome of tuberculosis. We also discuss possible underlying mechanisms through which testosterone modulates the immune response that is necessary for host resistance to tuberculosis. We discuss various models that have helped to uncover the role of testosterone in the outcome of infection by *M. tuberculosis*. Studying the role of testosterone on the various components that constitute the immune response to the disease have provided valuable insights into the sexual dichotomy observed in male bias in tuberculosis morbidity.

Keywords: Testosterone, tuberculosis, gender bias, pathogenesis, immune response

INTRODUCTION

Sex steroid hormones namely progesterone, estradiol and testosterone are produced by gonads, the adrenal gland and the placenta. They are released into the blood stream and exert their effect on the peripheral tissues and central nervous system.[1] Several physiological mechanisms in the body including reproduction, cell proliferation and differentiation, development, apoptosis, inflammation, homeostasis, metabolism and brain functions have been known to be governed by steroid sex hormones like progesterone, estradiol and testosterone.[2] These hormones either act as ligand-dependent transcription factors or as membrane receptors that induce various signal transduction pathways.[2]

Interestingly, sex steroid hormones have also been known to modulate immune cell activity including those of lymphocytes, macrophages, granulocytes and mast cells which lead to both physiological and pathological implications.[3] Additionally, sex steroid hormones are also involved in "interkingdom signalling" i.e., the communication between the microorganism and the mammalian host cell thereby effecting the pathogen virulence factor activation as well as control and outcome of infection.[4]

*Corresponding Author: Dr. Parul Shrivastava, ITM Vadodara University, Plot 6512, Ajwa Nimeta Road, Ravaal, Taluka Waghodia, Vadodara, Gujarat, India.
Tel: 7043341951
Email: parul_shrivastav@yahoo.com

Cite as: *Chem. Biol. Lett., 2021, 8(4), 238-247.*
URN:NBN:sciencein.cbl.2021.v8.253

 ISSN: 2347–9825 http://pubs.thesciencein.org/cbl

The gender bias observed in tuberculosis is suggestive of the role of sex hormones in immunoregulation of the disease. While estradiol is known to have pro-inflammatory effect that confers protection against bacterial infections, testosterone on the other hand due to its interaction with specific receptors is associated with immune suppression.[5] In the present review we discuss as to how testosterone modulates the key players involved in pathogenesis and immune response, eventually making males more prone to infection than females.

A better understanding of the role of testosterone in pathogenesis and outcome of tuberculosis could pave ways to more effective therapy. Marked increase in anti-inflammatory cytokines following testosterone replacement therapy has been observed in hypogonadal men.[6] Baillargeon et al. suggested the potential role of testosterone replacement therapy in decreasing the risk of middle-aged men in respiratory hospitalization and reduced disease progression in patients with COPD.[7] It will therefore be interesting to see the effect of testosterone replacement therapy on different biological pathways such as type of cytokine profile and corresponding T helper cell type and its role in decreasing tuberculosis disease progression.

TUBERCULOSIS

Tuberculosis has been known to plague mankind worldwide. In fact, the mortality rate of *M. tuberculosis* (*M.tb*) is one of the highest among the microbial pathogens.[8] The Global tuberculosis report of 2020 from the World Health Organisation (WHO) reported that approximately 10 million people developed active tuberculosis disease.[9] Many challenges still remain like the limited understanding of the protective immune response, improving sub-optimal treatment, emergence of multi drug resistant tubercle bacilli, development of effective vaccine and designing rapid accurate diagnostic tests.[10] Increased male susceptibility to tuberculosis infection than females and studying the role of testosterone in modulating the immune response will contribute to better understanding of pathogenesis and immune response to tuberculosis.

Pathology of tuberculosis

The infection with *M.tb* may either lead to an asymptomatic early infiltrate that may either resolve spontaneously or progress to a caseous necrosis formation, or alternatively the infection is contained in the post-primary granulomas that are later calcified[11] (Figure 1).

Tuberculosis infection is initiated by inhalation of droplet nuclei formed by coughing. The inhaled mycobacteria upon reaching the pulmonary alveoli are phagocytosed by the alveolar macrophages and generally killed.[12] The macrophages that fail to kill the invading mycobacteria release chemokines which in turn attract inflammatory cells like neutrophils, monocytes derived macrophages NK cells, B and T cells. Chemokines and cytokines play a major role in initiating and coordinating the organised and sequential recruitment and activation of cells at the site of *M.tb* infection.[13] The first cells to arrive at the site of infection are the neutrophils which subsequently activate macrophages and dendritic cells.[14] These activated macrophages and dendritic cells present antigens to T cells using both MHC class I and MHC class II molecules. Subsequently, the T cells facilitate the killing of *M.tb* by secreting interferon-γ (IFN-γ) and TNF and further activating the macrophages.[15] Hertz et al. demonstrated that expression of CCL19 in H37Rv infected C57BL/6 mice was significantly lower in males compared to females. CCL19 is known to recruit CCR7-expressing dendritic cells (DCs) and T cells to (ectopic lymphoid structures) ELS. Additionally, CXCL13 chemokine was also reduced in male which is linked to poor follicle formation and T cell recruitment.[16]

The B cells are known to limit *M.tb* infection possibly by opsonisation, activation of complement, promoting GC (germinal centre) reactions, formation of plasma and memory cells and modulating inflammation.[17] Additionally, the dendritic

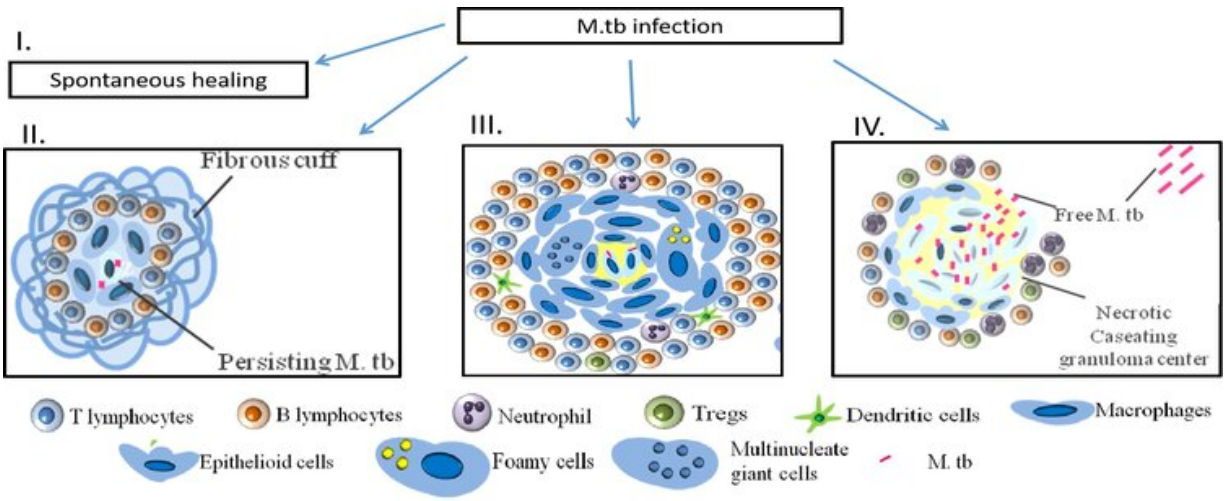


Figure 1. Outcomes of tuberculosis infection: Following infection by *M.tb* I) in an immunocompetent person the infection may resolve spontaneously or II) it may form organized granuloma that III) forms fibrous cuff and calcification at a later stage. In a susceptible person IV) the disease progresses to form caseating necrotic center surrounded by fewer number of lymphocytes resulting in tissue damage and spread of infection.

cells in the airways and parenchyma, phagocytose *M.tb* and migrate to the draining lymph nodes to initiate both CD4 and CD8+ T cell dependant responses.[18,19] The recruitment of inflammatory cells to the site of infected macrophages leads to formation of a granuloma. Granuloma consists of highly differentiated multinucleate giant cells, epithelioid cells and Foamy cells and all these cells are surrounded by a rim of lymphocytes.[20]

Within the granuloma, CD4+ T lymphocytes secrete IFN-γ which in turn activates the infected macrophages. Additionally, CD8+ T lymphocytes can kill the infected cells directly. In some cases, however the bacteria may not be eliminated in granuloma and they continue to remain dormant leading to latent tuberculosis infection which may get reactivated at a later stage.[21] Alternatively, in other cases of the disease, *M.tb* organisms escape the bactericidal effects of alveolar macrophages, continues to multiply in it and eventually cause lung tissue damage. The inflammatory cells including blood monocytes and neutrophils migrate to the site of infection due to chemokines released by these infected macrophages. The monocytes thus recruited, then go on to mature to form antigen presenting alveolar macrophages and dendritic cells. Later, these DCs migrate to the lymph nodes leading to further recruitment and activation of T lymphocytes.[22,23] The T lymphocytes upon arrival at the site of infection proliferate resulting in formation of early stage granuloma in which the macrophages are activated for killing *M.tb*.[23] At this stage 90% of people may have latent infection; yet they may continue to remain asymptomatic although *M.tb* may be surviving within the alveolar macrophages. However latent *M.tb* infection can undergo reactivation at a later stage owing to decline in host immunity or failure to maintain immune signals resulting in disruption of granuloma leading to lung cavitation and pulmonary disease.[23,24]

Immune response to tuberculosis

M. tuberculosis is an intracellular pathogen and has the ability to arrest phagosome maturation at an early stage and eventually inhibits phagolysosomal fusion. The phagolysosomal fusion is an essential step which is required for the killing of any invading pathogen.[25] In contrast, in the event of phagolysosome fusion, the resident *M.tb* in the mildly acidic environment of the infected cell gets exposed to reactive oxygen intermediates that are generated from phagocyte oxidase (NOX2) and are eventually destroyed. This is following immunological activation of macrophages by IFN-γ, when the phagosome matures and fuses with lysosome in the activated macrophages. Additionally, within these activated macrophages nitrite forms nitrous acid, which dismutates to nitric oxide (NO) and another toxic radical, nitrogen dioxide which are detrimental for survival of *M.tb*. However, *M.tb* has devised mechanisms to survive in the acidic, nitro-oxidative phagolysosome of activated macrophages and escape from the various interdependent forms of stress.[26-29]

In the absence of initial domination by *M.tb*, the activated macrophages and dendritic cells at the site of infection present the processed *M.tb* antigens to the T cells. Thus activated, Th1 helper cell population produce IFN-γ and TNF-α that in turn contribute to the recruitment and activation of innate immune cells, like monocytes and granulocytes.[30,31] Interestingly, studies have demonstrated that Th1 cell response has been associated with resistance and Th2 cell response has been associated with susceptibility and pathology in tuberculosis infection.[32-35] IFN-γ, a Th1 cytokine is known to be the principal mediator of protective immune response against *M.tb* infection.[32,34] Additionally Th1 cells are known to secrete the cytokine tumour necrosis factor (TNF)-β (lymphotoxin-alpha) that activates T cells and macrophages leading to local organization of the granulomatous response. Contrastingly, the Th2 responses, that consists of secreted cytokines such as interleukin (IL)-4, IL-5 and IL-10, are associated with tuberculosis pathology.[33,34] In fact, IL-10 is known to play a major role in reduced resistance and development of chronically progressive TB. Additionally, IL-10 not only has the ability to downregulate the Th1 cytokine response but also deactivates macrophages.[35] It has been demonstrated that human subjects expressing higher IL-10 levels correlate with ineffective bacilli Calmette–Guérin (BCG) vaccination.[36] In fact, our study demonstrated the immunosuppressive role of IL-10 in multinucleated giant cell formation, which is formed from the fusion of monocytes and is a characteristic feature of granulomas.[37] CD8+ T cells on the other hand directly kill the *M.tb* infected cells via granule-mediated function (via perforin, granzymes, and granulysin) or Fas-Fas ligand interaction to induce apoptosis.[19] Additionally they are also known to secrete cytokines such as IFN-γ, TNF-α and IL-2 in particular, that further contribute to a protective immune response.[38] Both the CD4+ and CD8+ T cell populations that define a dense cellular boundary around the necrotic center in granuloma play a major role in restricting the spread of *M.tb* infection.[39] It has been observed that in immunocompetent *M.tb* infected people, the granulomas are characteristically small, compact and have presence of large number of IFN-γ producing CD4-T cells. Whereas in immunodeficient people the granulomas are large, rich in activated macrophages and surrounded by very few lymphocytes.[40] Large caseating granuloma and fibrotic scarring are the major causes of tissue injury.[41]

Gender bias

Infection by *M.tb* is one of the most studied models with respect to sexual bias in respiratory tract infections. According to Global Tuberculosis Report 2020, tuberculosis continues to remain one of the top ten causes of death worldwide.[10] In fact, India alone accounts for 26% of the global TB burden. The major risk factors of tuberculosis include malnutrition, smoking, diabetes, poverty, overcrowding and poor housing (socio-economic factors) besides gender.[42] In the Global tuberculosis report 2020 by WHO, it was reported that male:female (M:F) ratio of TB incidence in 2019 varied from 1.3 to 2.1 worldwide. Interestingly however, the M:F ratio in children remained close to 1, further emphasizing on the role of sex hormones in increased male susceptibility to tuberculosis.[10] Several studies have demonstrated strong association between male gender and tuberculosis.[42-48] Additionally, compared to females, males have a higher rate of mortality and poor outcome of tuberculosis infection.[49,50]

In trying to understand the male-female dichotomy, Rhodes et. al. demonstrated significantly increased IFN-γ response against tuberculin purified protein derivatives in BCG unvaccinated males than females. Hence, it appears that the uncontrolled inflammatory response and poor prognosis during *M.tb* can therefore be attributed to stronger immune response displayed by males.[51] Additionally, males also exhibit higher levels of Platelet derived Growth factor Subunit B (PDGFB), serum C-reactive protein, and specific antibodies against *M. tb* infection displaying a much stronger innate and humoral immune response than females. The females on the other hand show higher levels of C-X-C motif chemokine ligand 9 (CXCL9).[52,53] CXCL9 is known to stimulate T lymphocyte and is known to be a biomarker for antigen specific IFN-γ production and IFN-γ secreting cells.[54,55] The fact that this gender bias is not observed in children or young adolescents, underlines the crucial role sex hormone plays in pathogenesis of tuberculosis.[56]

Studies have also been conducted to know if co-infection affects the susceptibility to tuberculosis infection and its gender bias factor. HIV co-infection has been known to be one of the major predisposing risk factors for *M.tb* infection.[57] HIV however disproportionately affects women more than men.[58] It was reported that in 2017, South Africa had 12.6% HIV positive population with a M:F ratio of 1:3.4. However, despite higher prevalence of HIV among females, tuberculosis prevalence and mortality in men remained higher suggesting that even coinfection with HIV doesn't alter higher male tuberculosis susceptibility compared to that of females.[18]

Role of testosterone in bacterial infections

Testosterone has been known to exert its effects largely through androgen receptor (AR) signalling. AR gene on X chromosome codes for AR. Unbound AR is located in the cytoplasm bound to heat shock proteins (HSPs) and chaperone proteins. However, when an androgen ligand like testosterone or dihydroxy testosterone (DHT) binds to AR, the AR, dissociates from HSPs and chaperone proteins, and translocates to the nucleus. In the nucleus, the ligand bound AR binds to androgen response elements (AREs) at specific sites on the chromosome, leading to regulation of specific genes. It is thereby facilitated with coactivators and corepressors to regulate the target gene expression.[59,60] In both human and murine models, several immune cells including that of innate immune system are known to express AR thereby playing a major role in hormonal modulation of several pathological conditions[61] (Figure 2).

Testosterone is known to be immunosuppressive by increasing IL-10 expression in neutrophils,[62] decreasing TLR4 expression in macrophages thereby elevating pro-inflammatory responses[63], decrease antibody responses[64] as well as T cell proliferation.[65]

In fact, sexual dichotomy can be observed in both innate and adaptive arms of immune response owing to the immunosuppressive effect of testosterone and immunoenhancing effect of estrogen.[66] Th1:Th2 cell response is known to play a crucial role in outcome of any infection. Androgens like estrogen have been demonstrated to play a crucial role in negative selection of high affinity auto-reactive B cells in addition to inducing the Th2 response, thereby modulating B cell function.[67,68] Additionally, estrogen enhances CCR5 T cell homing marker thereby inducing the T cell homing.[69] In contrast, testosterone enhances the Th1 response leading to activation of CD8 cells possibly through Androgen receptors (AR) present in the macrophages and lymphocytes which in turn leads to regulation of differential production of cytokines.[70] It also increases anti-inflammatory cytokine such as IL-10 while down-regulating tumor necrosis factor α (TNF-α). In vitro studies have also demonstrated higher Th1:Th2 ratio in men owing to the presence of testosterone.[71,72] Testosterone is also known to

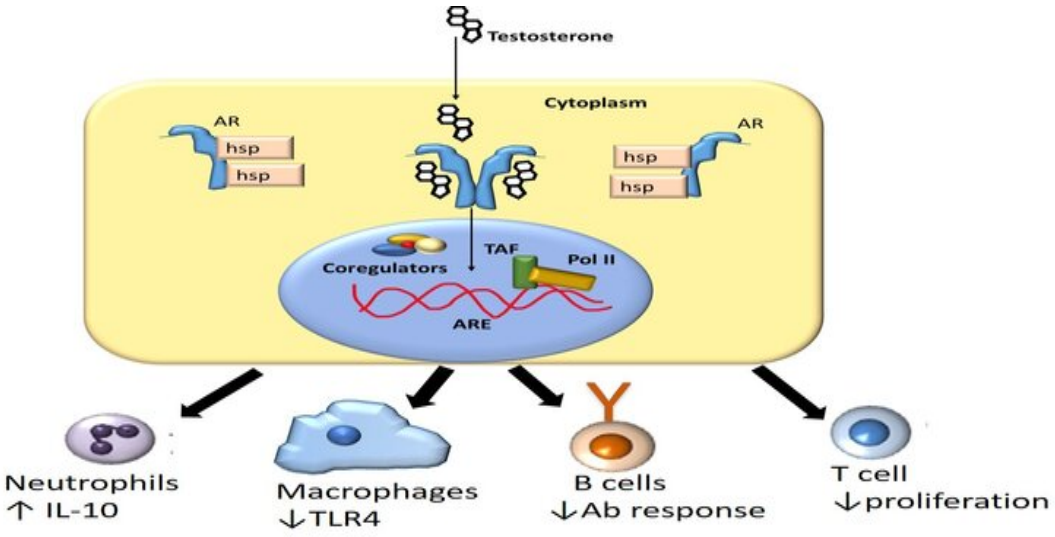


Figure 2. Mechanism of action of testosterone: When testrosterone combines with the androgen receptor (AR) in the cytoplasm, the AR dissociates from the heat shock proteins (HSPs) and chaperone proteins and translocates to the nucleus. Along with the other co-regulators in the nucleus, it binds to androgen response elements (AREs) to regulate target gene expression. Testosterone may exert its immunoregulatory role by acting on various immune cells including neutrophils, macrophage, B cells and T cells.

decrease the expression of pattern recognition receptors (PRR) like Toll like receptor 4 (TLR 4) on monocytes and macrophages;[73] a receptor that acts as a trigger for inflammation and innate immunity.[75]

The contrasting effects of estrogen and testosterone in sepsis have also been demonstrated in various studies. It has been demonstrated that estradiol confers protection against sepsis following hemorrhagic shock in trauma-hemorrhage-induced lung and hepatic injury. The protective effects of estradiol can be attributed to its ability to decrease TLR4-dependent release of pro-inflammatory cytokines like IL-6, TNF-α, macrophage inflammatory proteins 1a and 2, monocyte chemoattractant protein-1 and keratinocyte-derived chemokine in addition to induction of inducible nitric oxide synthesis (iNOS) expression, neutrophil influx and tissue damage.[75] Contrastingly, it has also been observed that higher levels of testosterone and its derivatives cause immunosuppressive effects in trauma-hemorrhage resulting in sepsis in mice. Using a bacterial model of prostrate inflammation, Scalerandi et al. have demonstrated that in testosterone treated mice, the neutrophil accumulation co-related with serum testosterone levels.[76] Additionally, DTH has similarly been associated with increased IL-10 levels and decreased splenocyte proliferation; macrophage function in addition to decreased release of IL-1, IL2, IL-3 , IL-6 and IFN-γ in splenocytes and peritoneal macrophages.[77-79] The down regulation of major histocompatibility complex (MHC) class II receptor on splenic and peritoneal macrophages following trauma-hemorrhage further contributes to immune suppression.[80]

Role of testosterone in pathogenesis of tuberculosis

The macrophages, neutrophils and dendritic cells have been known to be the key players in conferring innate immunity to tuberculosis. Macrophages play a crucial role in phagocytosis, killing of *M.tb*, antigen presentation, granuloma formation, secretion of inflammatory cytokines including IFN-γ, TNF-α, IL-1β, IL-6 in addition to secreting chemokines such as CCL2, CCL3, CCL7, CXCL2 and CXCL10.[81] More recently, macrophages in general have been classified as being of the M1 or M2 types, depending on their functionality. The M1 macrophage play a proinflammatory role by increasing the expression of nitric oxide synthase (iNOS) and secreting IFN-γ and TNF-α. M2 macrophage on the other hand play and anti-inflammatory role via IL-10 cytokine.[82] It has been demonstrated that castrated men as well as castrated mice exhibited significantly increased IFN-γ, TNF-α, IL-2, iNOS and IL-17 based pro inflammatory response than that observed in intact mice. IFN-γ is a major cytokine that activates M1 macrophages thereby facilitating in the control of TB infection in humans as well as mouse.[83] On the other hand, ovary removal in females did not have any effect on their susceptibility to TB, thereby indicating the role of testosterone in increased susceptibility of males to *M.tb* infection.[84]

Becerra-Diaz et. al. demonstrated that androgen (DHT) reconstitution led to reduced lung inflammation in castrated mice having allergic lung inflammation, although it enhanced M2 polarization of alveolar macrophages (Figure 3).

Additionally, enhanced IL-4 stimulated M2 macrophage polarization by dihydorotestosterone is also observed.[85] It can therefore be suggested that increased M2 responses that resulted in reduced pro inflammatory responses and are less protective could be attributed to higher susceptibility of males to TB. Apoptosis of infected macrophages is crucial to control tuberculosis infection. Apoptosis limits cell death and bacterial growth and enhances Th1 response. Necrosis on the other hand promotes bacterial growth.[86,87]

Neutrophils have been known to facilitate phagocytosis, granuloma formation, tissue damage and T cell inhibition. The phagocytic activity of neutrophils and macrophages is higher in females than males.[88] It has been demonstrated that only a small

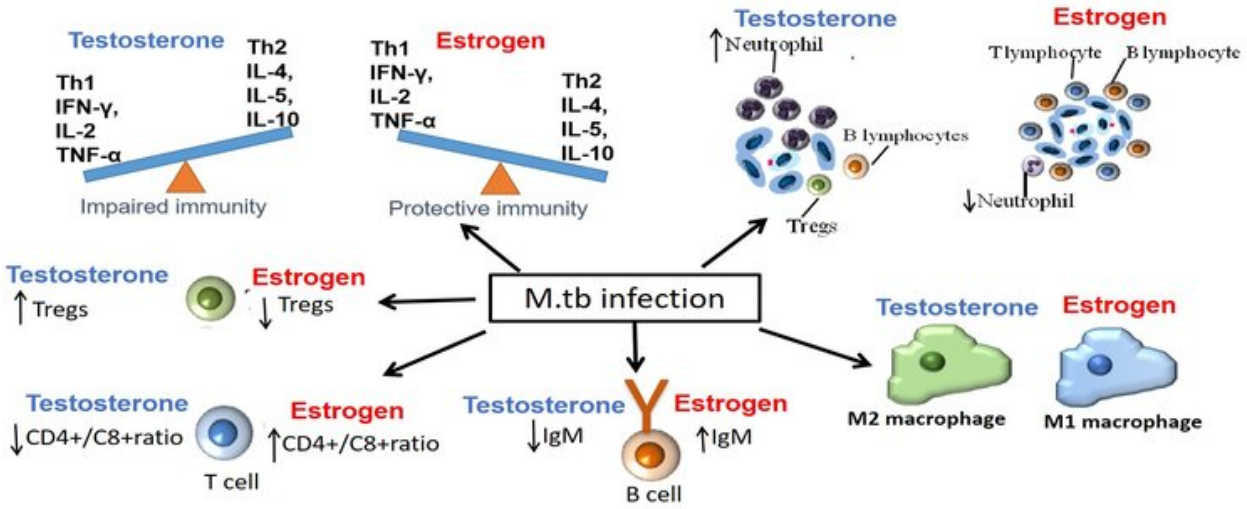


Figure 3. Role of testosterone and estrogen in tuberculosis: The immunosuppressive role of testosterone following *M.tb* infection may be attributed to the higher Th2 response, increased neutrophil influx leading to disorganized granuloma, activation of less protective M2 macrophage, decreased IgM response and CD4+/CD8+ ratio and increased Treg cells activation. Whereas, the immunoprotective role of estrogen in tuberculosis can be due to higher Th1 response, decreased neutrophil and increased lymphocyte influx leading to organized granuloma, activation of more protective macrophage, increased CD4+/CD8+ ratio and decreased Treg activation

number of neutrophils are recruited to the site of infection in the case of resistant mice such as B6.[89-91] On the other hand, significantly higher number of neutrophils in susceptible mice such as DO mice is associated with tissue pathology.[91] Similarly, neutrophil abundance has also been associated with severe tuberculosis in humans.[92-94] Gideon et. al. studied the interaction of *M.tb* and neutrophils of cynomolgus macaque monkeys in vitro, wherein infection of *M.tb* induced the expression of TNF, IL-4, and IL-10 by neutrophils. Granuloma neutrophils also expressed a combination of these cytokines. They also demonstrated that neutrophils stimulated by *M.tb* antigens, inhibited antigen-specific IFN-γ production by T cells.[95]

Studies have shown that a Th1/Th2 balance is crucial in controlling tuberculosis infection.[96,97] Th1 mediated protective immune response to TB is induced by IL-12, IFN-γ and TNF-α whereas the Th2 mediated immune response induced by IL-4 antagonizes protective cytokines thereby contributing to disease pathology.[98] As discussed above, the Th2 cytokines activate M2 macrophages which are a lesser bactericidal state of the macrophages.[99] Additionally, Th2 cytokines decrease the intracellular degradation of mycobacteria by inhibiting autophagy.[100]

Testosterone is believed to downregulate Th1 response while estrogen is known to upregulate it. Bini et. al. observed that female and castrated male mice expressed significantly higher levels of TNF-α, IFN-γ, IL12, iNOS and IL17 in comparison to non-castrated males during the first month of infection. These findings emphasize on the possible role of testosterone in dampening the Th1 response and thereby aggravating disease pathology. They also observed that serum testosterone increased significantly during late infection in male mice. However, orchidectomy at day 60 post-infection not only led to significant decrease of bacilli burdens but also significantly higher expression of TNF-α, IL-2 and IFN-γ. Hence, it was observed that higher susceptibility of male mice to tuberculosis can be altered by castration, emphasizing the possible role of testosterone as a tuberculosis susceptibility factor.[84] Additionally, estrogen is known to inhibit production of IL-10 while testosterone increases secretion of IL-10. Malkin at al. in their single blind, placebo-controlled crossover study of testosterone replacement (Sustanon100) vs. Placebo in men with symptomatic androgen deficiency observed that testosterone induced a decrease in TNF-α and IL-β levels and an increase in IL-10 levels.[101]

CD8+ T cells have been known to play a significant role in immune response to tuberculosis, by way of cytotoxic activity. Studies on the sex differences in immune response carried out in multiple ethnic groups have demonstrated that females (both children and adults) have higher CD4+ T cell counts and higher CD4/CD8 ratios than age-matched males.[94,102-105] Predictably, males were demonstrated to have higher CD8 T+ frequencies.[94,103-105] Additionally, in vitro studies following PBMC stimulation showed marked increase in counts of CD4+ T cells, CD8+ T cells and proliferating T cells in peripheral blood of females than in males.[94,102,106] Wolday et al. in their study of CD4/CD8 ratio on the incidence of tuberculosis (TB) in patients that were on anti-retroviral therapy (ART) observed the independent association of low CD4/CD8 ratio with increased risk of incident TB despite viral suppression. They therefore suggested that CD4/CD8 ratio can serve as a biomarker for identifying patients at risk of TB in patients on ART.[107] It can, thus be concluded that low CD4+/CD8+ ratio in males in addition to decreased counts of CD4+ T cells, CD8+ T cells and reduced T cell proliferation in PBMCs of males compared to females may be a crucial factor governing higher male susceptibility to tuberculosis.

B cells contribute to immune response against tuberculosis infection by involving in presentation of antigens to T cells and the consequent production of cytokines and *M.tb*-specific antibodies.[108] Studies on sputum smear and culture-positive tuberculosis patients have shown that total IgM was lower and IgE was higher in males; although IgG did not show any significant difference between the sexes. Additionally, analysis of IgG antibody levels to purified antigens, proteins as well as *M.tb* restricted epitopes of these antigens did not show any gender bias. Mendoza et al. studied IgG and IgM levels in healthy controls, tuberculosis patients and their contacts using ELISA plates coated with extracellular proteins of H37Rv, such as ESAT6 and CFP-10. They concluded from this study that IgM and IgG positive sera from contacts of infected patients suggest they could be infected with *M. tb*. The presence of antigen specific IgG but not IgM in healthy individuals could be interpreted as immunological memory that the tuberculosis infection was in the process of resolving; whereas no antigen specific IgM or IgG detectable levels indicated no infection with *M. tb*.[109] Since IgM levels in males are lower than in females following stimulation, it indicates that the primary humoral immune response might be playing a crucial role in females to resolve the infection at an early stage.

Effect of tuberculosis on testosterone

While males are more susceptible to MTB infection, it has also been widely observed that during genital as well as pulmonary tuberculosis, sexual dysfunction is seen in both males and females. The common factor appears to be the cytokines that are elaborated during tuberculosis. Studies in both mice and humans have demonstrated a significant reduction in testosterone levels as the disease progresses, due to an adverse effect of cytokines such as IL-6 and IL-1β on the hypothalamic-pituatary-adrenal axis. [110,111] This effect on the reproductive system was also found to have an impact on various reproductive tissues and organs in the case of mice. These include reduced weight and epithelial atrophy of seminal vesicles and prostate glands leading to impaired spermatozoid development.[111] Additionally, the cytokines released during tuberculosis also affects the male reproduction. The pro-inflammatory cytokines like IL-6 released in testes during advanced active tuberculosis not only decreases testosterone production but also increases estrogen synthesis by conversion of estrogen from testosterone.[112,113] Contrastingly, low levels of IL-1 cytokine during the late phase of tuberculosis could lead to reduced steroidogenesis and spermatozoid production.[111]

In a very detailed study conducted with human subjects, del Rey et al. concluded that the endocrine changes observed during tuberculosis are mediated by the endogenous cytokines and are not 'stress' related as a consequence of infection. This was further supported by the in vitro studies using an adrenal cell line which failed to produce DHEA in response to supernatants obtained from patients PBMCs activated with MTB antigens. However, they do contend that there is no direct evidence that the hormonal changes contribute to TB pathogenesis.[110] The beneficial effects of DHEA have been demonstrated by Hernandez-Pando et al in a murine model of pulmonary infection, where it was shown that administration of DHEA changes the course of the disease for the better.[114]

Studies have demonstrated that the serum testosterone levels continue to decrease significantly as the infection proceeds from moderate to advanced stage.[111] Hence it can be suggested that the presence of testosterone during the early phase of tuberculosis infection gives rise to anti-inflammatory cytokines that lead to Th2 response thus contributing to establishment of infection. [84,101] Whereas chronic inflammation during late phase of infection leads to a delayed type of hypersensitivity reaction that causes tissue damage.[115-117] Hence it can be suggested that the decrease of testosterone levels in the advanced stages of disease might contribute to delayed type of hypersensitivity leading to the healthy tissue damage thus contributing to pathogenesis of the disease.

SUMMARY

Although our knowledge regarding the factors responsible for increased susceptibility of males to tuberculosis infection compared to females is limited, studies have shown testosterone to play an active role in this gender bias. Testosterone plays an immunosuppressive role in tuberculosis. Following *M.tb* infection, testosterone modulates both the innate and adaptive immune responses. It increases the neutrophil influx to the site of infection thus contributing to disease pathology. Additionally, proliferation and activation of macrophages to M2 macrophage instead of the protective M1 macrophage also affects the disease outcome. The Th2 arm of the immune response is also activated by testosterone leading to release of anti-inflammatory cytokines like IL-4, IL-5 and IL-10 that not only antagonises the protective pro inflammatory cytokines like IFN-γ and TNF-α but also aggravates tissue damage.

The increased *M.tb* antigen specific IgM immune response in females also emphasizes on the role of primary immune response in resolving the infection at an early stage. In conclusion, further detailed studies connecting the dots on the role of testosterone in male susceptibility to tuberculosis may help us gain better understanding in the development of future therapies and may prove crucial in evaluating the effectiveness of vaccines and diagnostic tests.

REFERENCES

1. J. W. Wilson, D. W. Foster, H. Kronenberg, and P. R. Larsen. "Principles of endocrinology" in William Textbook of Endocrinology. WB Sounders Company, **1998**; pp 1–10.
2. E. Cabrera-Muñoz, O. T. Hernández-Hernández, I. Camacho-Arroyo. Role of estradiol and progesterone in HIV susceptibility and disease progression. *Med. Chem*, **2012**, 12 (11), 1049–1054.
3. S. A. Ahmed, E. Karpuzoglu, and D. Khan. Effects of sex steroids on innate and adaptive immunity," In Sex Hormones and Immunnity To Infection; S. L. Klein and C. W. Roberts, Eds.: Springer, Berlin, Germany, **2010**; pp. 19–51.
4. D. T. Hughes, V. Sperandio. Inter-kingdom signalling: communication between bacteria and their hosts. *Nat. Rev. Microbiol*. **2008**, 6(2), 111–120.
5. Y. Zhao, H. Ying, J. Demei, J. Xie. Crit Rev Tuberculosis and sexual inequality: the role of sex hormones in immunity. *Crit. Rev. Eukaryot. Gene Expr*. **2012**, 22(3), 233-41.
6. C. J. Malkin, P. J. Pugh, R. D. Jones, et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J. Clin. Endocrinol. Metab.* **2004**, 89(7), 3313–3318.
7. J. Baillargeon, R. J. Urban, W. Zhang, et al. Testosterone replacement therapy and hospitalization rates in men with COPD. *Chron. Respir. Dis*. **2018**, 147997231879300.
8. E. Armocida, M. Martini. Tuberculosis: a timeless challenge for medicine. *J Prev Med Hyg*, **2020**, 61(2), E143–E147.
9. World Health Organization. Global tuberculosis report. Geneva: **2020**.
10. S. Mishra, M. Khatri, V. Mehra. Trials and tribulations in tuberculosis research: Can plant based drug(s) be the solution? *Chem. Biol. Lett*, **2017**, 4(1), 33–47.
11. R. L. Hunter. The Pathogenesis of Tuberculosis–The Koch Phenomenon Reinstated. *Pathogens*, **2020**, 9(10), 813.
12. Y. J. Jeong, K. S. Lee. Pulmonary Tuberculosis: Up-to-Date Imaging and Management. *AJR Amer. J. Roentgenol*. **2008**, 191(3), 834–844.
13. R. Domingo-gonzalez, O. Prince, A. Cooper, S. Khader. Cytokines and chemokines in Mycobacterium tuberculosis infection (n.d.). Tuberculosis and the tubercle bacillus, **2016**, Second Edition, 33–72.
14. M.T. Silva. Neutrophils and macrophages work in concert as inducers and effectors of adaptive immunity against extracellular and intracellular microbial pathogens. *J. Leukoc. Biol*. **2010**, 87(5), 805-13.
15. A. Mihret. The role of dendritic cells in Mycobacterium tuberculosis infection. *Virulence*. **2012**, 3(7), 654–659.
16. D. Hertz, B. Schneider. Sex differences in tuberculosis. *Seminars in Immunopathology*, **2019**, 41(2), 225-237.
17. J. Chan, S. Mehta, S. Bharrhan, Y. et al. The role of B cells and humoral immunity in Mycobacterium tuberculosis infection. *Sem. Immunol*. **2014**, 26(6), 588–600.
18. S. Ehlers, U. E. Schaible. The Granuloma in Tuberculosis: Dynamics of a Host–Pathogen Collusion. *Front. Immunol*. **2013**, 3.
19. P. L. Lin, J. L. Flynn. CD8 T cells and Mycobacterium tuberculosis infection. *Sem. Immunopathol.* **2015**, 37(3), 239–249.
20. M. Silva Miranda, A. Breiman, S. Allain, et al. The Tuberculous granuloma: an unsuccessful host defence mechanism providing a safety shelter for the bacteria? *Clin. Dev. Immunol*. **2012**, 1–14.
21. J. E. Grotzke, D. M. Lewinsohn. Role of CD8+ T lymphocytes in control of Mycobacterium tuberculosis infection. *Microbes and Infection*, **2005**, 7(4), 776-88.
22. K. A. Mcdonough, Y. V. Kress, B. R. Bloom. Pathogenesis of tuberculosis: interaction of Mycobacterium tuberculosis with macrophages. *Infection and immunity*, **1993**, 61(7), 2763-73.
23. T. Ulrichs, S. H. E. Kaufmann. New insights into the function of granulomas in human tuberculosis. *J. Pathol*. **2006**, 208, 261–269
24. Russell, D. G. Who puts the tubercle in tuberculosis? *Nat. Rev. Microbiol*., **2007**, 5, 39–47.
25. J. D. MacMicking, G. A. Taylor, J. D. McKinney. Immune control of tuberculosis by IFN-gamma-inducible LRG-47. *Science*, **2003**, 302(5645), 654-9.
26. K. H. Bhat, S. Mukhopadhyay. Macrophage takeover and the host–bacilli interplay during tuberculosis. *Future Microbiol*. **2015**, 10(5), 853–872.

27. K. H. Bhat, A. Das, A. Srikantam S. Mukhopadhyay. PPE2 protein of Mycobacterium tuberculosis may inhibit nitric oxide in activated macrophages. *Ann. N. Y.Acad. Sci*. **2013**, 1283(1), 97–101.
28. N. Rao, R. Shrivastava, G. Pradhan, P. Singh, S. Mukhopadhyay. Phagosome-lysosome Fusion Hijack - An Art of Intracellular Pathogens. *Proc. Indian National Sci. Acad*. **2017**, 83(3), 533-548.
29. S. Ehrt, D. Schnappinger. Mycobacterial survival strategies in the phagosome: defence against host stresses. *Cell. Microbiol*. **2009**, 11(8), 1170–1178.
30. S. H. E. Kaufmann. Protection against tuberculosis: cytokines, T cells, and macrophages. *Ann. Rheum. Dis*. **2002**, 61(Supplement 2), 54–58.
31. T. Prezzemolo, G. Guggino, M. P. La Manna, et al. Functional Signatures of Human CD4 and CD8 T Cell Responses to Mycobacterium tuberculosis. *Front. Immunol*. **2014**, 5.
32. R. Al-Attiyah, N. M. Madi, A. M. El-Shamy, et al. Cytokine profiles in tuberculosis patients and healthy subjects in response to complex and single antigens of Mycobacterium tuberculosis. *FEMS Microbiol. Immunol*. **2006**, 47(2), 254–261.
33. X. Bai, S. E. Wilson, K. Chmura, N. E. Feldman, E. D. Chan. Morphometric analysis of Th(1) and Th(2) cytokine expression in human pulmonary tuberculosis. *Tuberculosis (Edinb)*. **2004**, 84, 375–85.
34. J. Flynn. Immunology of tuberculosis and implications in vaccine development. *Tuberculosis (Edinb)*. **2004**, (4) 93–101
35. J. Turner, M. Gonzalez-Juarrero, D. L. Ellis, et al. In vivo IL-10 production reactivates chronic pulmonary tuberculosis in C57BL/6 mice. *J. Immunol*. **2002**, (169) 6343–51.
36. R. E. Weir, G. F. Black, H. M. Dockrell, et al. Mycobacterial purified protein derivatives stimulate innate immunity: Malawians show enhanced tumor necrosis factor alpha, interleukin-1beta (IL-1beta), and IL-10 responses compared to those of adolescents in the United Kingdom. *Infect. Immun*. **2004**, 72, 1807–11.
37. P. Shrivastava, T. Bagchi. IL-10 Modulates In Vitro Multinucleate giant cell formation in human tuberculosis. *PLoS ONE*. **2013**, 8(10), e77680.
38. V. Rozot, S. Vigano, J. Mazza-Stalder, et al. Mycobacterium tuberculosis-specific CD8+T cells are functionally and phenotypically different between latent infection and active disease. *Eur. J. Immunol*. **2013**, 43(6), 1568–1577.
39. B.M. Saunders, A. A. Frank, I. M. Orme, A. M. Cooper. CD4 is required for the development of a protective granulomatous response to pulmonary tuberculosis. *Cell. Immunol*. **2002**, 216(1-2), 65–72.
40. T. Ulrichs, S. H. E. Kaufmann. New insights into the function of granulomas in human tuberculosis. *J. Pathol*. **2005**, 208(2), 261–269.
41. S. J. Sasindran, J. B. Torrelles. Mycobacterium Tuberculosis Infection and Inflammation: what is beneficial for the host and for the bacterium? *Front. Microbiol*. **2011**, 2.
42. C. Kolappan, P. G. Gopi, R. Subramani, P. R. Narayanan. *Int. J. Tuberc. Lung Dis.* **2007**, 11(9), 999-1003.
43. S. Nhamoyebonde, A. Leslie. Biological differences between the sexes and susceptibility to tuberculosis. *J. Infect. Dis*. **2014**,209, (Suppl):S100–6.
44. M. W. Jiménez-Corona, L. García-García, K. DeRiemer, et al. Gender differentials of pulmonary tuberculosis transmission and reactivation in an endemic area. *Thorax*. **2006**, 61, 348–53.
45. T. Ephrem, B. Mengiste, F. Mesfin, W. Godana. Determinants of active pulmonary tuberculosis in Ambo Hospital, West Ethiopia. *Afr. J. Prim. Health Care Fam. Med*. **2015**, 7.
46. E. P. Hong, M. J. Go, H. L. Kim, J. W. Park. Risk prediction of pulmonary tuberculosis using genetic and conventional risk factors in adult Korean population. *PLoS One*. **2017**, 12.
47. K. C. Horton, P. MacPherson, R. M. G. J. Houben, et al. Sex differences in tuberculosis burden and notifications in low- and middleincome countries: a systematic review and meta-analysis. *PLoS Med*. **2016**, 13.
48. C. D. Nnadi, L. F. Anderson, L. R. Armstrong, et al. Mind the gap: TB trends in the USA and the UK, 2000–2011. *Thorax*. **2016**, 71, 356–63.
49. R. Bhurayanontachai, K. Maneenil. Factors influencing development and mortality of acute respiratory failure in hospitalized patient with active pulmonary tuberculosis: a 10-year retrospective review. *J. Thorac. Dis*. **2016**, 8,1721–30.
50. M. G. Weiss, J. Sommerfeld, M. W. Uplekar. Social and cultural dimensions of gender and tuberculosis. *Int. J. Tuberc. Lung Dis*. **2008**, 12(7), 829–830.
51. S. J. Rhodes, G. M. Knight, K. Fielding, et al. Individual-level factors associated with variation in mycobacterial-specific immune response: gender and previous BCG vaccination status. *Tuberculosis (Edinb)*. **2016**, 96, 37–43.
52. K. Chavez, R. Ravindran, A. Dehnad, I. H. Khan. Gender biased immune-biomarkers in active tuberculosis and correlation of their profiles to efficacy of therapy. *Tuberculosis (Edinb)*. **2016**, 99, 17–24.
53. J. Brown, K. Clark, C. Smith, et al. Variation in C-reactive protein response according to host and mycobacterial characteristics in active tuberculosis. *BMC Infect. Dis*. **2016**, 16, 265.
54. D. Whiting, G. Hsieh, J. J. Yun, et al. Chemokine monokine induced by IFN-gamma/CXC chemokine ligand 9 stimulates T lymphocyte proliferation and effector cytokine production. *J. Immunol*. **2004**, 172:7417–7424.
55. G. T. Brice, J. L. Graber, S. L. Hoffman, D. L. Doolan. Expression of the chemokine MIG is a sensitive and predictive marker for antigen-specific, genetically restricted IFN-gamma production and IFN-gamma-secreting cells. *J. Immunol. Methods*. **2001**, 257: 55–69.
56. A. Stival, E. Chiappini, C. Montagnani, et al. Sexual dimorphism in tuberculosis incidence: children cases compared to adult cases in Tuscany from 1997 to 2011. *PLoS ONE*. **2014**, 9(9), e105277.
57. A. Pawlowski, M. Jansson, M. Skold, et al. Tuberculosis and HIV co-infection. *PLoS Pathog*. **2012**, 8, e1002464
58. M. M. Addo, M. Altfeld. Sex-based differences in HIV type 1 pathogenesis. *J. Infect. Dis*. **2014**, 209(Suppl 3), S86–S92.
59. I. E. Eder, Z. Culig, T. Putz, C. Nessler-Menardi, G. Bartsch, H. Klocker. Molecular biology of the androgen receptor: from molecular understanding to the clinic. *Eur Urol*., **2001**, 40(3), 241-51.
60. R. A. Davey, M. Grossmann. Androgen Receptor Structure, Function and Biology: From Bench to Bedside. *Clin. Biochem. Rev*. **2016**, 37(1), 3–15.
61. M. R. Gubbels Bupp, T. N. Jorgensen. Androgen-Induced Immunosuppression. *Front Immunol*, **2018**, 9, 794.
62. D. P. Marin, A. P. Bolin, R. C. dos Santos, R. Curi, R. Otton. Testosterone suppresses oxidative stress in human neutrophils. *Cell Biochem Funct*, **2010**, 28, 394–402.
63. J. A. Rettew, Y. M. Huet-Hudson, I. Marriott. Testosterone reduces macrophage expression in the mouse of toll-like receptor 4, a trigger for inflammation and innate immunity. *Biol Reprod*, **2008**, 78:432–437.
64. M. K. Angele, M. G. Schwacha, A. Ayala, I. H. Chaudry. Effect of gender and sex hormones on immune responses following shock. *Shock*, **2000**, 14, 81–90.
65. Y. Weinstein, S. Ran, S. Segal. Sex-associated differences in the regulation of immune responses controlled by the MHC of the mouse. *J Immunol*, **1984**, 132, 656–661.
66. R. Naik, S.A. Shivashankar, P.J. Bindu. Microwave-assisted synthesis of copper nanoparticles: influence of copper nanoparticles morphology on the antimicrobial activity. *J. Mater. Nanosci*. **2020**, 7 (2), 62–67.
67. M. Cutolo, S. Capellino, A. Sulli, et al. Ann N Y.Estrogens and autoimmune diseases. *Acad Sci*., **2006**, 1089, 538-47.
68. M. Grimaldi, V. Jeganathan, B. Diamond. Hormonal regulation of B cell development: 17 beta-estradiol impairs negative selection of high-affinity DNA-reactive B cells at more than one developmental checkpoint. *J Immunol*., **2006,** 176(5), 2703-2710.
69. R. Mo, J. Chen, A. Grolleau-Julius, et al. Estrogen regulates CCR gene expression and function in T lymphocytes. *J Immunol*., **2005**, 174(10), 6023-6029
70. T. Irez, S. Biçer, E. Şahin, S. Dutta, P. Sengupta. Cytokines and adipokines in the regulation of spermatogenesis and semen quality. *Chem. Biol. Lett*., **2020,** 7(2), 131-139.

71. A. Bouman, M. Schipper, M. J. Heineman, M.M. Faas. Gender difference in the non-specific and specific immune response in humans. *Am J Reprod Immunol.*, **2004**, 52(1), 19-26.
72. J. A. Girón-González, F. J. Moral, J. Elvira, D. García-Gil, F. Guerrero, I. Gavilán, L. Escobar. Consistent production of a higher TH1:TH2 cytokine ratio by stimulated T cells in men compared with women. *Eur J Endocrinol*., **2000**, 143(1), 31-6.
73. S. Dutta, P. Sulagna, P. Sengupta, et al. Role of toll-like receptors in the reproductive tract inflammation and male infertility. *Chem. Biol. Lett*., **2020**, 7(2), 113-23.
74. J. A. Rettew, Y. M. Huet-Hudson, I. Marriott. Testosterone Reduces Macrophage Expression in the Mouse of Toll-Like Receptor 4, a Trigger for Inflammation and Innate Immunity. *Biology of Reproduction*, **2008**, 78(3), 432–437.
75. Y. C. Hsieh, M. Frink, B. M. Thobe, et al. 17Beta-estradiol downregulates Kupffer cell TLR4-dependent p38 MAPK pathway and normalizes inflammatory cytokine production following trauma-hemorrhage. *Mol Immunol.*, **2007**, 44, 2165–2172.
76. M. V. Scalerandi, N. Peinetti, C. Leimgruber, et al. Inefficient N2-Like Neutrophils Are Promoted by Androgens During Infection. *Frontiers in Immunology*, **2018**, 9.
77. M. W. Wichmann, R. Zellweger R, C. M. DeMaso, A. Ayala, Chaudry IH. Mechanism of immunosuppression in males following trauma-hemorrhage: critical role of testosterone. *Archives of Surgery*, **1996**,131(11), 1186.
78. M. K. Angele, M. W. Knöferl, A. Ayala, et al. Testosterone and estrogen differently effect Th1 and Th2 cytokine release following trauma-hemorrhage. *Cytokine*, **2001**,16:22–30.
79. M. K. Angele, A. Ayala, W. G. Cioffi, et al. Testosterone: the culprit for producing splenocyte immune depression after trauma hemorrhage. *Am J Phys*., **1998**, 274(C),1530–1536.
80. S. Mayr, C. R. Walz, P. Angele, et al. Castration prevents suppression of MHC class II (Ia) expression on macrophages after trauma-hemorrhage. *J Appl Physiol.*, **2006**, 101, 448–453
81. S. Nhamoyebonde, A. Leslie. Biological Differences Between the Sexes and Susceptibility to Tuberculosis. *Journal of Infectious Diseases*, **2014**, 209(3), S100–S106.
82. L. Wang, X. Shang, X. Qi, et al. Clinical Significance of M1/M2 Macrophages and Related Cytokines in Patients with Spinal Tuberculosis. *Dis Markers*, **2020**, 2020, 2509454.
83. R. F. Silver, Q. Li, W. H. Boom WH, J. J. Ellner. Lymphocyte-dependent inhibition of growth of virulent Mycobacterium tuberculosis H37Rv within human monocytes: requirement for CD4+ T cells in purified protein derivative-positive, but not in purified protein derivative-negative subjects. *J Immunol*., **1998**, 160:2408–2417.
84. E. I. Bini, D. Mata Espinosa, B. Marquina Castillo, et al. The influence of sex steroid hormones in the immunopathology of experimental pulmonary tuberculosis. *PLoS ONE*, **2014**, 9, e93831.
85. M. Becerra-Diaz, A. B. Strickland, A. Keselman, N. M. Heller. Androgen and androgen receptor as enhancers of M2 macrophage polarization in allergic lung inflammation. *J Immunol*., **2018**, 201, 2923–2933.
86. A O'Garra, P.S. Redford, F. W. McNab, et al. The immune response in tuberculosis. *Annu Rev Immunol*, **2013**, 31, 475-527.
87. M. Divangahi, D. Desjardins, C. Nunes-Alves, H. G. Remold, S. M. Behar. Eicosanoid pathways regulate adaptive immunity to Mycobacterium tuberculosis. *Nat Immunol*, **2010**, 11, 751-758.
88. J. A. Spitzer. Gender differences in some host defense mechanisms. *Lupus*, **1999**, 8, 380–383.
89. E. B. Eruslanov, I. V. Lyadova, T. K. Kondratieva, et al. Neutrophil responses to Mycobacterium tuberculosis infection in genetically susceptible and resistant mice. *Infect Immun*, **2015**, 73, 1744–1753
90. C. Keller, R. Hoffmann, R. Lang, et al. Genetically determined susceptibility to tuberculosis in mice causally involves accelerated and enhanced recruitment of granulocytes. *Infect Immun*, **2006**, 74, 4295–4309
91. V. Yeremeev, I. Linge, T. Kondratieva, A. Apt. Neutrophils exacerbate tuberculosis infection in genetically susceptible mice. *Tuberculosis*, **2015**, 95:447–451
92. S. M. Irwin, E. Driver, E. Lyon, et al. Presence of multiple lesion types with vastly different microenvironments in C3HeB/FeJ mice following aerosol infection with Mycobacterium tuberculosis. *Dis Model Mech*, **2015**, 8, 591–602.
93. A.V.Panteleev, I.Y. Nikitina, I.A. Burmistrova, et al. Severe tuberculosis in humans correlates best with neutrophil abundance and lymphocyte deficiency and does not correlate with antigen-specific CD4 T-cell response. *Front Immunol*, **2017**, 8, 963.
94. P. F. Barnes, J M. Leedom, L. S. Chan, S. F. Wong, J. Shah, L. A. Vachon, G. D. Overturf, R. L. Modlin. Predictors of short-term prognosis in patients with pulmonary tuberculosis. *J Infect Dis*, **1988,** 158,366–371
95. H. P. Gideon, J. Phuah, B. A. Junecko, J. T. Mattila. Neutrophils express pro- and anti-inflammatory cytokines in granulomas from Mycobacterium tuberculosis-infected cynomolgus macaques. *Mucosal Immunology*, **2019**, 12, 1370–1381.
96. M. T. Herrera, M. Torres, D. Nevels, C. N. Perez-Redondo, J. J. Ellner, E. Sada, S. K. Schwander. Compartmentalized bronchoalveolar IFN-gamma and IL-12 response in human pulmonary tuberculosis. *Tuberculosis*, **2009**, 89, pp. 38-47
97. S. Ehlers, U. E. Schaible. The Granuloma in Tuberculosis: Dynamics of a Host–Pathogen Collusion. *Frontiers in Immunology*, **2013**, 3.
98. G. A. Rook. Th2 cytokines in susceptibility to tuberculosis. *Curr. Mol. Med*., **2007**, 7, pp. 327-337
99. S. Gordon, F. O. Martinez Alternative activation of macrophages: mechanism and functions. *Immunity*, **2010**, 32, pp. 593-604
100. J. Harris, S. A. De Haro, S. S. Master, J. Keane, E. A. Roberts, M. Delgado, V. Deretic. T helper 2 cytokines inhibit autophagic control of intracellular Mycobacterium tuberculosis *Immunity*, **2007**, 27, 505-517.
101. D.J. Malkin, P. J. Pugh, R. D. Jones, D. Kapoor, K. S. Channer, T. H. Jones. The Effect of Testosterone Replacement on Endogenous Inflammatory Cytokines and Lipid Profiles in Hypogonadal Men. *The Journal of Clinical Endocrinology & Metabolism*, **2004**, 89(7), 3313–3318.
102. E. Rees, J. Murray J. Silica, silicosis and tuberculosis. *Int J Tuberc Lung Dis*, **2007**, 11, 474–484
103. Philippines National Tuberculosis Prevalence Survey. Department of Health (Philippines), Foundation for the Advancement of Clinical Epidemiology, Inc (FACE), Philippine Council for Health Research and Development. **2016**.
104. World health Organisation. **2016**. Tuberculosis in women. https://www.who.int/tb/challenges/hiv/tb_women_factsheet.pdf
105. J. S. Mathad, A. Gupta. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clin Infect Dis*, **2012**, 55:1532–1549.
106. O.M. Loto, I Awowole Tuberculosis in pregnancy: a review. *J Pregnancy*, **2012**, 379271.
107. D. Wolday, K. Yazezew, D. Legesse, D. S. Siraj, J. A. McBride, M. J. Kirsch, R. Striker. Role of CD4/CD8 ratio on the incidence of tuberculosis in HIV-infected patients on antiretroviral therapy followed up for more than a decade. *PLoS One*, **2020**, 15(5), e0233049.
108. J. Chan, S. Mehta, S. Bharrhan et al. . The role of B cells and humoral immunity in Mycobacterium tuberculosis infection. *Semin Immunol*, **2014**, 26:588–600.
109. A.Y. Arce Mendoza, M. P. Cantú Rodríguez, J. A. Ramírez Vega, A. G. Rosas Taraco, A.Y. Limón Flores. Determination of anti-Mycobacterium tuberculosis IgM and IgG antibodies in individuals in contact with patients with active tuberculosis. *Front. Immunol. Conference Abstract: IMMUNOCOLOMBIA2015 - 11th Congress of the Latin American Association of Immunology - 10o. Congreso de la Asociación Colombiana de Alergia, Asma e Inmunología*, **2015**.
110. A. del Ray, V. E. Mahuad, V. V. Bozza, C. Bogue, M. A. Farroni, M. L. Bay, B. A. Oscar, H. O. Besedovsky. Endocrine and cytokine

responses in humans with pulmonary tuberculosis. *Brain, Behavior, and Immunity*, **2007**, 21(2), 171–179.
111. B. Ramos Robles, R. A. Valdez, U. J. Hernández, B. Marquina Castillo, D. Mata Espinosa, J. Payan Barrios, R. H. Pando, M. C. Romano. Immunoendocrine abnormalities in the male reproductive system during experimental pulmonary tuberculosis. *Tuberculosis*, **2018**, 109, 109–116.
112. J. M. Garcia, H. Li, D. Mann, D. Epner, T. G. Hayes, M. Marcelli, R. G. Cunnigham. Hypogonadism in male patients with cancer. *Cancer*, **2006**, 106, 2583-2591.
113. M. Hermann, J. Scholmerich, R. H. Straub. Influence of cytokines and growth factors on distinct steroidogenic enzymes in vitro: a short tabular data collection. *Ann NY Acad Sci*, **2002**, 966, 166-86.
114. R. Hernandez-Pando, M. De La Luz Streber, H. Orozco, K. Arriaga, L. Pavon, S. A. Al-Nakhli, G. A. Rook. The effects of androstenediol and dehydroepiandrosterone on the course and cytokine profile of tuberculosis in BALB/c mice. *Immunology*, **1998**, 95(2), 234–241.
115. M. P. Hedger. Immunophysiology and pathology of inflammation in the testis and epididymis. *J Androl*, **2011**, 32, 625-640.
116. M. Shrivastava, P. Sharma, R. Singh. Identification of potential CYP51 inhibiting anti-Aspergillus phytochemicals using molecular docking and ADME/T studies. *Chem. Biol. Lett.* **2021**, 8 (1), 18–21.
117. S.P.S. Sri. V, M. George. In vitro anticancer and antitubercular activities of cellulose-magnetite nanocomposite synthesized using deep eutectic solvent as a dispersant. *J. Mater. Nanosci.* **2021**, 8 (1), 1–10.

AUTHORS BIOGRAPHIES

Dr. Parul Shrivastava is working as an Assistant Professor in ITM Vocational University Vadodara. She did her post-graduation in Medical Microbiology from Baroda Medical College, Vadodara, Gujarat. Later she did a Diploma in Genetic Engineering from M.S. University, Vadodara and went on to pursue her Ph.D. in Microbiology (Immunology) on immune response to tuberculosis from Department of Microbiology and Biotechnology Center, M. S. University, Vadodara. Her main fields of interest include medical microbiology, biotechnology and cellular immunology.

Dr. T. Bagchi is a retired academician who is currently an entrepreneur in the area of biotechnology skill development. He was earlier at the Central University of Gujarat (CUG), India where he was the Dean, School of Nano Sciences. Prior to joining CUG, he was at the M.S. University of Baroda, Vadodara, India where he served as the Head, Department of Microbiology, and the Coordinator of the Biotechnology Programme there. He has extensive interests in infectious diseases, probiotics, cellular immunology, and application of nanotechnology.