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Short Communication

Role of Immuno-Endocrine Interactions in Tuberculosis

Jyothi Priya M[1,2], Rajashekar M[2] and Sumanlatha G[1,2]*

[1]Bhagwan Mahavir Medical Research Center, Hyderabad, India.
[2]Department of Genetics, Osmania University, Hyderabad, India.

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Tuberculosis (TB) is a contagious and airborne disease caused by Mycobacterium tuberculosis (*M.tb*) in human beings. Commonly, the host immune response (IR) controls Mtb replication, which ultimately depends on a fine balance between the pathogen persistence and the specific IR. Cell-mediated immunity plays a major role against TB infection. Regulatory T cells (Tregs) are also relevant in IR and varies throughout the course of TB treatment and its relationship with immuno-endocrine mediators dealing with disease immunopathology. This chronic infection accompanied by prolonged cytokine production, which might affect the immuno-endocrine communication and favor the establishment of an adverse state. Cytokines released by activated immune cells subsequently lead to hormonal secretion from the hypothalamic pituitary-adrenal axis (HPA) or the hypothalamic pituitary-gonadal (HPG) axis, which regulates immune response against the pathogen and the control of the chronic inflammation induced during infection. If the immune response fails to eradicate the pathogen, a chronic state of inflammation is established. Generally, in TB infection, immuno-endocrine alterations changes the interleukin-6, cortisol, estradiol, prolactin and thyroid hormone concentrations in plasma. Moreover, it also changes the interferon gamma (IFN-*γ*) and transforming growth factor beta (TGF- β) production by lymphoid cells. The present review focuses on the immuno-endocrine interactions that play a detrimental role during TB infection which might affect the control of tissue damage and the protective immune responses.

Keywords: Immune Response, Immune-endocrine mediators, HPA axis, Immuno-endocrine interaction, Chronic inflammation.

INTRODUCTION

Prevalence of Tuberculosis

The second leading cause of human mortality from infectious diseases worldwide is due to Mycobacterium tuberculosis (Mtb). Globally, 9 million people are infected with TB in 2013. Among them, 1.5 million people died from TB, including 360 000 people who were HIV-positive [1]. The failure to control the tuberculosis epidemic has been attributed to insufficient use of effective treatment schemes in developing countries, the spread of multidrug resistance and the emergence of AIDS [2].

The lifetime probability for a normal individual to develop active tuberculosis in his lifetime is only 10-15% [3]. The resulting decrease in immunity represents one of the risk factors with regard to tuberculosis and which increases the risk of progression to active TB such as malnutrition, immunosuppressive drugs, diabetes, prolonged use of corticosteroids silicosis, or gastrectomy [4,5]. Young children and elderly people have the highest risk of developing not only active tuberculosis, but also the disseminated form of the infection (Disseminated form is acute, severe forms of TB, often occurring soon after primary infection), these acute forms of TB are often fatal. This is due to their relatively weak immune defences, as a result of an immature system in the former, and to age--related immune dysfunctions in the later [6]. In contrast, tuberculosis remains a major public health problem in most resource-constrained countries. Evaluating immune-endocrine relationships has important implications for understanding differences in disease severity, progression, and restoration as well as the basic nature of phenotypic flexibility and adaptability

Corresponding Author: Sumanlatha Gaddam. Bhagwan Mahavir Medical Research Center, Masab Tank, Hyderabad, Andhra Pradesh - 500004, India. E-mail: sumanlathag@yahoo.com Tel: 9848967110, 040-23497303

ENDOCRINE-IMMUNE SYSTEM INTERACTIONS IN TB

A common feature of TB is that the immune response fails to definitely eradicate the pathogen, likely due to complex mechanisms of immune avoidance that limit the protective host response. Such a particular host-mycobacteria relationship results in the establishment of a chronic infection, during which a broad range of regulatory mechanisms are likely to operate. Unbalanced cytokines produced during TB not only exert a direct effect on immunocompetent cells, but may also influence immune cells indirectly, due to their ability to affect several immuno-endocrine mechanisms (6,7).

A process whereby both the adaptive and innate branches of immunity converge through the use of hormones released from cytoplasmic endosomes that would be available for local use by appropriate APCs, T cells and B cells, thereby enhancing cytokine synthesis, T cell activity and antibody responses from B cells, particularly in response to a strong antigenic challenge, further intensification of the effects of these immune-endocrine interactions would be manifest in a number of ways. [8]. Cytokines are the “immune hormones” mediate and control immune and inflammatory response. Hormonal changes are likely to occur since some of the cytokines produced during this disease could affect endocrine mechanisms that, in turn, influence the course of infectious/inflammatory processes.

Once the magnitude of the immune response exceeds a certain threshold, activation of the endocrine response also occurs, with effects that antagonize or potentiate those of the immune responses [9,10,11]. Hormonal changes can directly stimulate the production of proinflammatory cytokines that influence a spectrum of conditions associated with disease. During an immune and inflammatory reaction, the release of cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, and IL-12 results in the activation of the endocrine system. It primes the body physically and mentally for a “fight-or-flight” response as well as for a potential injury, the immune system will release cytokines into the circulation, which in turn can signal the brain, which involves in the activation of the hypothalamic- pituitary-adrenal (HPA) axis and autonomic nervous system.

These complex interactions exist between cytokines, inflammation, and the adaptive responses which helps in maintaining the homeostasis [12, 13,14,15,16] Endocrine responses during chronic infections such as lung tuberculosis are poorly characterized. [17]. Endocrine responses involving pituitary, adrenal, gonadal, and thyroid hormones in parallel to IFN-γ, IL-10, and IL-6 levels in tuberculosis patients with divergent degree of pulmonary involvement [18]. Investigating the correlation between possible immunoneuroendocrine abnormalities and the diverse clinical manifestations in TB may provide additional clues in this view.

The immune-endocrine interactions may play a detrimental role during TB, in terms of the development of protective immune responses, control of tissue damage and metabolic disorders, disease seemed to consume the individual, with their weight drastically dropping as the disease progresses, and is being implicated in disease aggravation [19]. We focus on the pathogenesis, type of immune response that predominates at different stages of TB, in particular, the role of cytokine production and the interaction of these mediators with immuno-endocrine mechanisms.

PATHOGENISIS AND IMMUNE RESPONSE

M.tb is an obligatory aerobic, intracellular pathogen. Mtb infection occurred by the inhalation of bacilli present in the airborne droplets. Once the infection occurs in the lungs, infected bacilli reside mainly in alveolar macrophages of lungs [20]. These tubercle bacilli are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited. A small number may multiply intracellularly and are released when the macrophages die. If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain, and bone). This process of dissemination primes the immune system for a systemic response.

Development of an appropriate adaptive immune response controls initial infection in the most of the individuals. Which prevents bacillary proliferation and dissemination. Moreover, at least 30% of the individuals who were in contact with Mtb remain steadily infected without exhibiting signs of disease in a state known as latent TB infection (LTBi) [21-25]. Cell-mediated immunity released effective control of Mtb [26]. In response to antigen presentation, T-cells produce IFN-γ in the infected tissue and thus IFN-γ activates macrophages to kill intracellular bacteria [27,28]. In addition to CD8+ T cells, CD4+ T cells and CD1-restricted irregular T cells are thought to be particularly important in the prevention of latent TB reactivation [29–33].

ROLE OF HORMONES WITH RESPECT TO CYTOKINES

In this review, we have a discussion about the concepts and information concerning interactions between immune and endocrine mechanisms. There are clear examples that immune cells can be influenced by hormones, which shows alterations in brain functions. On the other hand, immune-derived products such as cytokines can affect endocrine, mechanisms, this endocrine responses occur during the activation of the immune system.

These responses can be elicited by innocuous antigens, which can also be detected during pathological conditions involving immune activation, and in many cases are dissociable from the effects of the disease itself and from the stress of being sick. Based on this we highlight the multidirectional nature of the communication processes between the immune and, endocrine, systems. The relevance of immune-endocrine interactions for immunoregulation and host defenses is discussed as well as the active role of hormones with respect to cytokines in the immune system in mediating metabolic and homeostatic adjustments or derangements during the course of infectious processes [34].

Several studies during the 1970s and 1980s revealed that hormones inhibit lymphocyte proliferation, cytotoxicity, and the activation of the endocrine system in inflammatory reaction and secretions certain cytokines, such as IL-2, IL-10, IL-6 and interferon-γ (INF-γ) [35]. Recent evidence, however, indicates that hormones influence the immune response in a less monochromatic way they selectively inhibit the T helper lymphocyte 1(Th1)/proinflammatory, but potentiate Th2/anti-inflammatory cytokine production, systemically, while locally, in certain conditions they may exert proinflammatory effects [36]. Through this mechanism, endocrine-immune system, may influence the onset and/or course of various common human immune-related diseases.

A major factor governing the outcome of infectious diseases is the selection of Th1 versus Th2 predominant adaptive responses during and after the initial invasion of the host by the pathogen. This Th2 shift may have a profound effect on the susceptibility of the host to infections and/or may influence the course of infections, and particularly the intracellular ones, the defense against which is primarily through cellular immunity mechanisms [37].

In the 1950s, Thomas Holmes (cf. Lerner 1996) reported that individuals who had experienced endocrine changes due to stress life events were more likely to develop tuberculosis and less likely to recover from it. Although it is still a matter of some speculation, hormone-induced inhibition of IL-12 and IFN-γ production and the consequent suppression of cellular immunity, might explain the pathophysiologic mechanisms of these observations. (Elencove et al., 1996).

SEX STEROIDS

Mycobacterial infections occur more commonly in males than in females. [38]. This difference has been credited to biological and epidemiological characteristics [39,40]. It is interesting to make a note of that this TB gender difference is seen in adults of all the ages, but not in children or young adolescents [41]. This observation suggests the involvement of biological factors, particularly the well known regulatory activities that the steroid sex hormones have on the immune cells. Macrophages and lymphocytes have receptors for androgens, estrogens and progesterone [42].

These hormones participate in macrophages and lymphocytes development and function, as well as in the outcome of varied diseases, including infectious diseases [43]. Moreover, women of all the ages show significantly lower rates of infection and resultant mortality than men. This dissimilarity has been associated with important differences in the inflammatory response and is apparently advantageous against infection, but unfavorable in the immune response against self structures provoking in females of higher rate autoimmune diseases [44,45]. Testosterone, is the major circulating androgen in men and progesterone a hormone associated with the maintenance of pregnancy, are immunosuppressive.

Both hormones impair macrophage activation [46], which could play a detrimental role in TB [47]. In contrast, in physiological concentration estrogens are considered as pro-inflammatory mediators that stimulate the production of TNF- α [48], and interact with the IFN-γ promoter [49]. The competence of estrogens to drive pro-inflammatory Th-1 associated immune responses and that of testosterone to inhibit them may help to explain why females have a lower incidence of infectious diseases such as TB [50].

In common, it seems that androgens have suppressive property on the cellular and humoral immune responses, so they can be considered as natural anti-inflammatory hormones [51], whereas estrogens enhance humoral immunity and that affect balance of T and B cells [52]. Concerning to TB this should be important because host control of mycobacterial infection, in both human and mouse, has been associated with Th1 cells and activated macrophages [53].

However, it is important to consider that sex steroids have different functions, even opposite activities, it depends on their concentrations. This is particularly marked in females that exhibited significant fluctuations during the menstrual cycle and in particular physiological states such as in pregnancy or menopause. Moreover, high testosterone levels could result in high cortisol levels and were associated with decreased immune function [54]. Study in BALB/c tuberculous mice have shown that male mice are more susceptible to tuberculosis infection than female mice. Male mice died earlier because of higher pulmonary bacilli load and female mice showed more resistance to the disease because of a steroid hormone, Estradiol. It has a significant influence on inflammation [55], that favours inflammatory cell migration by inducing the expression of mRNA for adhesion molecules (Eselectin, ICAM-1 and VCAM-1) mediated by TNF-α in endothelial cells. Morphometry results of female mice shows earlier granuloma formation and higher alveolar inflammation (pneumonia formation) one week before than M mice.

Moreover atypical mycobacteria infection in C57Bl or DBA/2 male mice shows more resistance than BALB/c male mice. In this sense, the real fact is that human males with moderate to severe TB had decreased testosterone levels in sera with modest increases of estradiol concentrations, which may be viewed as an unsuccessful attempt to improve cell mediated immune protective mechanisms [56,]. These experimental studies show that the sexual hormones, substantially modifies the activity of the immune system and the inflammatory response influencing the course of experimental pulmonary TB.

GLUCOCORTICOID (GC) / DEHYDROEPIANDROSTERONE (DHEA) BALANCE AND OTHER HORMONES (GROWTH HORMONE, PROLACTIN & THYROID STIMULATING HORMONE)

In situ cytokine release inside endocrine glands can alter GC/DHEA balance, favoring or worsening anti-infectious immunity. Studies in BALB/c mice show that dehydroepiandrosterone (DHEA) reverses the susceptibility to infections resulting from prednisone administration [57]. An increased GC/DHEA ratio favors a Th2 response, which impairs the immune response against intracellular pathogens favoring an enhanced susceptibility. In contrast, a diminishing GC/DHEA balance seems to support Th1 immune response and favors host resistance.

Experiments in the same strain reveal that DHEA and androstenediol, a steroid derivative, exert beneficial effects on the course of the experimental TB infection [58]. These studies were based on either on the administration of steroid hormones or on interfering with the production of IFN-γ in vivo, leaving unanswered whether the effects observed are directly exerted by the injected hormone or by secondarily induced metabolic products. The reduction of IFN-γ production by cells from TB patients induced by cortisol is more pronounced in cases with advanced disease, suggesting a particular sensitivity to the inhibitory effects of GC in these patients [59]. In line with studies reporting that the production of IL-4 and IL-10 is marginally affected by GC [60,61], IL-10 production is not affected in cortisol-treated cultures.

Some studies suggest that the HPA axis may be activated during TB since TB patients succumbing to the disease have higher basal cortisol concentrations [62], or a suboptimal response following adrenocorticotropin hormone (ACTH) stimulation [63]. Work from the same group also demonstrates that a drop in the urinary DHEA–cortisol relationship appears to be associated with increased TB severity [64].

While cytokines produced during TB could affect endocrine mechanisms influencing the course of infectious/ inflammatory processes, endocrine responses during this chronic infection were poorly characterized DHEA and growth hormone (GH) levels are markedly elevated in patients, in parallel to modest increases in the concentration of cortisol, estradiol, prolactin

(PRL), and thyroid hormones (T3 and T4), with an increased cortisol/DHEA ratio [65]. The hormonal changes detected in the TB patients are not those expected during stressful conditions, since the levels of classical „stress hormones", such as cortisol and PRL are modestly increased while the increase in thyroid hormones and particularly the 5- to 18-fold increase in GH blood levels contrasts with the tendency towards a reduction in the concentration of these hormones during chronic stress [66].

GH could prime human, monocytes to kill MTB. It acts as a human macrophage-activating factor IFN- γ mildly inhibits monocyte phagocytosis of this organism Monocytes of acromegalic have been reported to kill mycobacterium, Decreased GH levels observed in TB patients [67,68,69-71,72]. The fact that supernatants of M. tuberculosis-stimulated PBMC from TB patients significantly inhibit DHEA secretion by the human adrenal cell line NCI-H295-R [65], supports this possibility. In favour of the Increased levels of GC during acute conditions exert anti-inflammatory effects and, at the same time, favour an immune response that appears not to be protective against intracellular pathogens [73,74].

DHEA can antagonize the Th2-promoting effect of GC, but, on the other hand, it is also a potent anti-inflammatory hormone itself [75]. Thus, the reduction of DHEA levels in the patients would be permissive for the inhibitory effect of GC on cellular immune responses but not for the control of inflammatory processes. In this view the products derived from peripheral immune cells can affect the production of adrenal steroids in vivo, are studies showing that anti-TNF therapy improves adrenal androgen secretion in patients with rheumatoid arthritis [76].

The studies reported represent the first comprehensive evaluation of the hormonal status of untreated TB patients and indicate that endogenous cytokines may mediate at least some of the endocrine alterations detected. Since the dysregulation of the, hypothalamus– adrenal, –gonadal, and –thyroid axis and the production of pituitary hormones during tuberculosis tend to be more pronounced in advanced patients, and proposed as such dysregulation, might influence the immune response to *M. tuberculosis* in the course of the disease.

Systemic effects of stress hormones may not pertain to certain conditions or local responses in specific compartments of the body. The synthesis of transforming growth factor-β (TGF-β), another cytokine with potent anti-inflammatory activities, is enhanced by GCs in human T cells, but suppressed in glial cells, [77] and low doses of GCs can indeed activate alveolar macrophages, leading to increased lipopolysaccharide (LPS)-induced IL-1 production [78]. Studies in TB patients showed increased levels of interferon γ (IFN-γ), interleukin 10 (IL-10), and IL-6, accompanied by a modest increase in the levels of cortisol, prolactin, and thyroid hormones and markedly augmented concentrations of growth hormone.

Conversely, testosterone and dehydroepiandrosterone (DHEA) levels were profoundly decreased, resulting in an increased cortisol/DHEA ratio. The finding that, culture supernatants from *Mycobacterium-tuberculosis*-stimulated peripheral blood mononuclear cells (PBMCs) of TB patients inhibit DHEA secretion by a human adrenal cell line indicates that immune cells from these patients can directly affect the synthesis of this hormone.

Supporting the existence of bidirectional interactions, in vitro treatment of PBMCs from TB patients with physiological concentrations of cortisol inhibited mycobacterial antigen-driven lymphoproliferation and IFN-γ production, whereas DHEA suppressed transforming growth factor β production from cases with progressive disease. Further analysis showed that plasma DHEA levels correlated positively with the in vitro production of IFN-γ by mycobacterial-stimulated PBMCs, and the cortisol/DHEA ratio was inversely correlated with IFN-γ production.

Lastly, it was also shown that the immunoendocrine imbalance in TB patients was associated with weight loss, which in turn correlated with the impairment on their specific in vitro cellular immune responses.

IMMUNOENDOCRINE ALTERATIONS IN HIV-TB COINFECTION

There was limited data available on the role of adrenal steroids which shows immune response developed by patients coinfected with HIV-1 and Mtb. Some studies determined DHEA, DHEA-s, and cortisol plasma levels and the role of these adrenal hormones on Mtb-specific Th1 responses and Treg frequencies in patients dually infected with Mtb and HIV undergoing different stages of Mtb infection (79). Studies observed, in HIV-infected patients with active TB (HIV-TB), DHEA plasma levels were diminished by two fold compared to HIV infected patients without Mtb co-infection or healthy donors.

On the converse HIV-infected patients latently infected with Mtb (HIV-LTBi) showed preserved DHEA levels. Additionally, while cortisol plasma levels were slightly higher in HIVTB patients than in HIV patients, cortisol/DHEA ratio was almost 4 times higher in HIV-TB patients compared to HIV, HIV-LTBi, and healthy donors. In HIV-TB patients, DHEA-s levels correlated positively, while cortisol plasma levels correlated negatively with CD4+ T cell count. Moreover, studies observed an inverse correlation between DHEA-s plasma levels and Treg frequency in the same group. A remarkable finding of this study was the persistent observation of a conspicuous CD4+CD25−FoxP3+ population in HIV-TB patients that was not observed in the other groups.

Remarkably, CD4+CD25−FoxP3+ population is increased in systemic lupus erythematosus patients [80], but its nature remains undetermined. Some authors suggested that these cells are FoxP3+ non-Treg T cells [81], whereas others argue that these cells are dysfunctional Treg cells with limited regulatory potential [82]. In order to clarify this, studies evaluated FoxP3 liability in these cells by keeping them unstimulated for different periods of time. By doing this, they observed that within these cells Foxp3 expression was relatively stable, suggesting that, at least in HIV-TB patients, the stimulating CD4+CD25−FoxP3+ population is not a transiently activated effector population and rather might have regulatory functions [81, 82].

They hypothesize that this unusual regulatory population may exclude protective immune responses against Mtb in their cohort of coinfected patients. The frequency of CD4+CD25−FoxP3+ cells in HIV-TB patients negatively correlated with DHEA plasma levels, which is consistent with a role of DHEA on enhancing Th1 responses while diminishing this particular regulatory T-cell population.

Moreover, we also found that the initiation of anti-tuberculous treatment (ATT) diminished CD4+CD25−FoxP3+, which was restored to normal levels after finalization of treatment. In contrast, conventional CD4+CD25+FoxP3+ Tregs in HIV-TB patients tended to diminish across visits, but not significantly. In HIV-TB patients, adrenal hormone balance was not restored as well, at least after 6 months of ATT (unpublished results). In some HIV-infected patients, the recovery of specific immune responses during the beginning of

highly active antiretroviral treatment (HAART) can elicit systemic inflammatory responses which lead to the establishment of the immune reconstitution inflammatory syndrome (IRIS). In HIV-TB IRIS patients, DHEA-s plasma levels were three times lower and cortisol/DHEA ratio was up to four times higher compared to the non-TB groups.

The CD4+CD25− FoxP3+ frequency was also increased in IRIS patients and negatively correlated with DHEA-s plasma levels [79]. Previous results obtained by the research group also showed a positive correlation between DHEA plasma levels and the frequency of a terminally differentiated population of CD8+ T cells in HIV-TB patients, which is thought to be crucial in preventing TB reactivation [83].

Observed that in vitro DHEA treatment increased Mtb specific CD8+ T cell proportions and terminal differentiation in CD8+ T cells of HIV-TB coinfected patients. Additionally, found that DHEA in vitro increased the expression of the transcription factor Tbet and Tbet/Eomesodermin ratio in isolated CD8+ cells, both known to drive to terminal differentiation in CD8+ T cells [84]. Based on the results, in HIV-TB co-infected patients, HPA axis displays a noticeable alteration, probably influenced by the chronic state of inflammation induced by both pathogens concurrently. This condition may contribute to the immune system dysfunction seen in these patients.

Table 1 represents the Immuno-endocrine alterations in TB patients and their implications in the pathogenesis of the disease. Cytokines released by immunocompetent cells stimulate corticotrophin-releasing hormone production in the hypothalamus leading to the pituitary synthesis of adrenocorticotropin hormone, which is followed by the production of adrenal steroids, cortisol and dehydroepiandrosterone (DHEA).

Table 1. Immuno-endocrine alterations in TB patients and their implications in the pathogenesis of the disease

HORMONES	Th PROFILE AND IMMUNE RESPONSE	HORMONE LEVELS IN THE COURSE OF THE DISEASE	REASON	REFFERENCES
Glucocorticoids	Facilitate Th2 activity and cause switch to Th1 cytokine production ,IL-12 induce enhance IFN-γ &IL-4 synthesis by T-cells .	Increased GC levels in advanced TB patients when compare to healthy controls.	GC direct effects on dendritic cells which secrets less IL-12 & more IL-10,GC effects on Th2 cells up regulate IL-4,IL-13,IL-10	(85-87), (88,89), (90-93)
DHEA	Supress TGF-β & can antogonozing Th2 pramotiting activity & shift towards Th1	50% of DHEA levels are reduced in the patients	This would be permissive for the inhibitory effect of Gc on cellular immune response but not for the inflammatory processes.	75
ESTROGEN	Shift towards the Th2 &decreases Th1 ,stimulate the synthesis of proinflamatory cytokines, IL-1,IL-6, TNF-α &inhibit IL-4, IL-10, IFN-γ	Increases estrogen levels in patients of TB when compare to healthy controls, estrogen increases the catabolism in patients.	Enhances cell-mediated ,humoral response & protect the immune cells against apoptosis.	(94-95)
PROGESTERONE	Elevated levels of progesterone inhibit Th1&produce anti inflamatory , IFN-γ	Immune suppressive agent ,pramote Th2 response include anti inflammatory cytokines	Inhibit activation of NFK- β& reduce NK cell activity.	(96,97,98) (99)
TESTOSTERONE	Decrease IL-4 expression,macrophage,shift towards Th2 &decreases the Th1 cells	50% of testosrerone levels are decreased in patients.	Activation of innate immunity. Testosterone increases the succeptabulity to infection in TB	(100),(101)
PROLACTIN	Able to stimulate secretion of pro and regulatory cytokines as well as other cell types	Immune modulator .Higher levels of prolactin related with weight loss.Modest increased PRL levels observed in patients	PRLeffects on inflammatory mediaters .&stimulate invading properties .PRL regulates phagocytosis.	(102-107),(65)
THYROID(T3,T4)	Increases TNF- α levels. IL-6 decreases the TSH	Increases T3,T4 levels in Tb patients.it increases the catabolism .	inflamatory cytokines inhibits the thyroid hormone	(65)
GROWTH HORMONE	IFN- γ mildly inhibits monocyte phagocytosis of this organism . Other mediators, such as vitamin D3.	Monocytes of acromegalic have been reported to kill mycobacterium, Decreased GH levels observed in TB patients.	GH could prime human monocytes to kill MTB. GH as a human macrophage-activating factor	(67,68,69,71,72)

Both steroids influence the immune response and modify gonadal functions. Cytokines can also act on the pituitary and adrenal glands, and changes in the concentration of gonadal steroids, Thyroid levels, which leads to shifting of both Th1 & Th2 responses, This mechanism involved in controlling the infection. Which would favour a hypercatabolic status, thus worsening the course of the disease.

CONCLUSION

Immuno-endocrine disturbances may be linked to the consumption state of TB patients as hormones and cytokines are affecting energy expenditure and metabolism. This review is focused on recent human studies addressing the impact of endocrine changes in immune function and the health consequences. Immuno-endocrine interactions during infectious diseases may determine the failure or success of the immune responses.

This is particularly true for chronic infections like TB, in which pathogens and immune system coexist in a long struggle. The growing evidence opens the door to support the fact that stress due to hormonal changes can directly stimulate the production of proinflammatory cytokines which in turn influence the spectrum of conditions associated with the disease. Thus, there is a substantial increase in the morbidity and mortality due to the immuno-endocrine imbalance.

ABBREVIATIONS

HPA: Hypothalamic pituitary-adrenal axis
HPG: Hypothalamic pituitary-gonadal axis
AIDS: Acquired immune deficiency syndrome
APC'S: Antigen-presenting cell
BALB/C: Albinomice
ICAM: Intercellular Adhesion Molecule 1
VCAM: vascularcelladhesionmolecule 1
DBA/2: (DiluteBrownNon-Agouti)
GC: Corticosteroids
DHEA: Dehydroepiandrosterone
GH: Growth hormone
PBMC: Peripheral blood mononuclear cell
FOXP3: Forkhead box P3
ATT: Antituberculosis therapy
HAART: Highly active antiretroviral therapy

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

We conceived the plan of the review, drafted the manuscript and revised it. All authors read and approved the final manuscript.

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AUTHOR DETAILS

[1]Immunology Department, Bhagavan Mahavir hospital and Medical research centre, P.O. Box 5000004. [2]Department of Genitics, Osmania university, Hyderabad, Telangana state.

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