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Exploring the Endocrine-Immunologic Interface in Autoimmune Connective Tissue Diseases

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ABSTRACT

Autoimmune connective tissue diseases (ACTDs) is an imprecise category of diseases that are caused by the abnormal function of the immune system resulting in the destruction of tissues. Perturbation between the endocrine system and immune system play a critical role in pathogenesis of these diseases. This paper investigates the processes that interrelate the endocrine and immunologic functioning in ACTDs, particularly, hormonal mediations, modulation of immune cells, and cytokine release. Findings indicate that hormonal imbalance especially with estrogen, thyroid hormones and cortisol play a significant role in immune response that leads to the development and advancement of ACTDs. Also, the research emphasizes the role that the endocrine system plays in the regulation of the activity of T-cells, B-cells, and dendritic cells that are central to the autoimmune reaction. The results indicate the necessity of combined treatment methods that target endocrine dysfunction and immune system dysfunction in the management of ACTD, and the possibility of targeted therapy to restore the balance of this complicated interface.

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INTRODUCTION

Autoimmune connective tissue disorders refer to an eclectic category of chronic inflammatory ailment that is defined by unsuitable immunological reaction against self-antigen and in most circumstances the immune reaction is systemic and may involve a variety of organ systems. The evidence that the endocrine system and the immune one interact is increasing to show that many diseases develop and evolve (Wolff & Antonelli, 2025). This bidirectional communication is referred to as neuroendocrine-immune crosstalk which has a strong effect on the susceptibility and intensity of autoimmune rheumatic diseases (Cutolo and Straub, 2009; Wolff and Antonelli, 2025). To give an example, the changes in neuroendocrine regulation, including; changes in the work of the sympathetic nervous system or the dysfunction of the hypothalamic-pituitary-adrenal axis are typical of the juvenile rheumatoid arthritis and Sjogren syndrome (Ligier & Sternberg, 1999). Moreover, the sympathetic nervous system also helps in responding to stress which in turn discharges neurotransmitters to regulate the systemic and local immune activity, and their effects on the occurrence of inflammatory illnesses (Harrison, 2012). It is the sphere of psychoneuroimmunology that studies such complex interactions and proves that the influence of emotional feelings may be extremely potent and can impact the immune system greatly (Goleman, 1995). The sympathetic nerves come into direct contact with immune organs such as thymus, spleen as well as the lymph nodes which is an outright anatomical foundation of neuro-immune interaction (Harrison, 2012). This network forms direct communication between the central nervous system and the immune cells and causes the immune responses to quickly be controlled (Goleman, 1995). The experimental evidence also shows that the integrity of these neural networks is essential to a functional immune response to an infection suggesting a major role on the nervous system in immunological homeostasis (Goleman, 1995). This intricate connection is commonly referred to as psychoneuroimmunoendocrinology, and it emphasizes the extent of the impact of the psyche, the neurological system, and endocrine system on the development of immune-mediated inflammatory diseases (Ortega et al., 2022) (Pongratz, 2021). Immune cells have different types of neurotransmitter receptors with which it can directly respond to neuroendocrine signals. By way of an example, norepinephrine binds adrenergic receptors of lymphocytes (Harrsion, 2012). The resultant outcome of this direct contact is the change in migration, proliferation and cytokine production of lymphocytes which leads to the change in the whole activity of the immune system (Harrsion, 2012). T cell suppression may result through neuroendocrine immune interaction which gradually gets associated with the pathogenesis and maintenance of autoimmune diseases (Goleman, 1995). In addition, one of the primary components of the neuroendocrine system, the dysfunction of hypothalamic-pituitary-adrenal axis that is involved in the stress response, frequently leads to the inflammation of autoimmune diseases (Middendorp & Evers, 2016; Harrison, 2012). The intricacy of autoimmune diseases and indicates the possibilities of therapeutic interventions because the fact that these neuroendocrine-immunocellular communication pathways are adjustable is a sophisticated interplay of neuroendocrine messaging and immunocellular response (Eskandari et al., 2003). In addition, persistent stress may lead to allostatic load due to long-term stimulation of neuroendocrine systems, which leaves people exposed to secondary preclinical imbalances in metabolism, cardiovascular, and immune systems and can later develop into clinical diseases (Prunell - Castañe et al., 2024). Due to these conditions, the changes in immunological responses such as cellular immunity, immunoglobulin A and phagocytic activity production, complement system activity, and cytokines are frequently noted (Rodríguez-Quiroga et al., 2020). The immunology of stress can alter people to be susceptible to diseases and increase the severity of the auto immune diseases (Goleman, 1995). In fact, a substantial part of the preceding research over the past 3 decades has shown that the brain and the immune system are interrelated in many other aspects that go far beyond the existing state of weakening the immune system to the active modification of immunoregulatory processes (Marshall, 2010). Such bilateral communication creates a valuable relationship between the psychological state, neural stimulations, and the hormonal interaction which affects the work of the immune system. It constitutes a major percentage of the cause of autoimmune diseases and autoimmune diseases exacerbation (Lin et al., 2015) (Thyaga and Priyanka, 2012). Neuroendocrine system is also active to preserve host immunological responses to antigen exposure and this has been studied since 1940s regarding autoimmunity (Ligier & Sternberg, 1999). Recent studies have proved that chronic stress has the massive effect on the hypothalamic-pituitary-adrenal axis that leads to the imbalance of cytokines and weakening of the body defences consequently enhancing the

propensity of the immune system to self-infection (Nuñez et al., 2025). This stress can cause the release of such hormones as cortisol, which is constantly emitted. First, it compromises the immune system, however, over time, it can worsen further and result in inflammation (Herzberg & Gunnar, 2019). Such chronic-lasting stimulation of the hypothalamic-pituitary-adrenal axis can be sufficient to suppress the immune system, as well as predispose to infections, which is a great illustration of how chronic psychological stressors are closely intertwined with immunological impairment (Alotiby, 2024). There is the reliable association between chronic psychological stress in adulthood and especially in childhood due to traumatic events and systemic psychopathology, often mediated by disengagement of the hypothalamic-pituitary-adrenal axis (Lund et al., 2020). It is known as a disregulation, namely, in the prefrontal cortex and the limbic system, required to perform executive functioning and emotional regulation (Lund et al., 2020; Stinson et al., 2024). The stress can affect the immunological functioning to a chronic condition that predisposes patients to chronic disease, including autoimmune diseases, (Alotiby, 2024) (Goleman, 1995) (Pongratz, 2021). In addition, it has also been proven beyond a doubt that the initial experiences of stress and poor childhood events are strongly related to changes in the impact of immune system and higher signs of inflammation in the adult life, and therefore, serve as the factors in the aetiology of autoimmune diseases (Amiri et al., 2023) (Stinson et al., 2024). It is a long-term immunological disruption (because of childhood struggles) that preconditions the individual to augmented inflammatory response in adulthood, thus making it vulnerable to autoimmune diseases (Herzberg and Gunnar, 2019). The aetiology of autoimmune disorders that is complicated with the genetic predisposition and exposure to environments reveals the need of neuroendocrine and sympathetic nervous system regulation of immune response (Ligier and Sternberg, 1999). It encompasses the implication of the contribution of stress, in that, the psychological stress that persists in the long run, as one of the most essential environmental factors to the development and progression of autoimmune pathologies (Amiri et al., 2023). Chronic stress as an example elevates the hypothalamic-pituitary-adrenal axis secretion of cortisol, which eventually causes the immune system to become weak (Al-Ruweidi et al., 2022) (Alotiby, 2024). Nevertheless, such a long-term exposure to elevated glucocorticoids has a paradoxical effect, which leads to chronic inflammatory disease due to the formation of glucocorticoid resistance and the change of cytokine regimes (Ilchmann-Diounou & Ménard, 2020). It is a negative feedback loop, which induces immunological regulation of chronic stress resulting in the development of autoimmune (Xiao et al., 2025) (Hawkins et al., 2021) (Bick et al., 2012). In addition, it has been determined that childhood levels of stresses, including maltreatment, increase the psychological and physiological susceptibility to other stressors to adulthood, which results in greater immunological maladjustment (Fagundes et al., 2012). Perhaps such an increased sensitivity results in an accelerated functional coupling of stress-response systems, which is a compensatory effect of increased amygdala reactivity and as such modulates inflammatory hormonal regulators such as catecholamines and glucocorticoids (Nusslock and Miller, 2015). The changes in the Th1/Th2 balance and the release of pro- and anti-inflammatory cytokines under the influence of such stress hormones as catecholamines and glucocorticoids can potentially be the cause of the autoimmune thyroid disease pathology (Corso et al., 2023). Childhood stress has been pointed to as the necessitating factor that modulates the hypothalamic-pituitary-thyroid axis and immunological functioning in the adult years thus predisposing one to auto-immune diseases, such as the Graves disease (Usenko et al., 2022). It highlights the neuroendocrine and immunological vulnerabilities that early life trauma types instil in the long term and are associated with complex aetiology of autoimmune thyroid diseases during adulthood (Corso et al., 2023). Allostatic load is a cumulative wear-and-tear impacts of a chronic stress (occurring at a young age) and is getting more and more acknowledged as a primary antecedent factor of the further emergence of autoimmune diseases that may not occur until maturity (Choe et al., 2019). Emphasized in this opinion is that the history of stress in an individual, specifically negative childhood experiences, allows an individual to understand his or her predisposition to autoimmune diseases (Victor et al., 2024) (Ilchmann-Diounou and Ménard, 2020). The combination of multiple stresses, both physical and mental stress, and hypothalamic-pituitary-adrenal axis shows the complexity of endocrine-immune interactions (Ligier and Sternberg, 1999). This elaborate system of regulation consists of the hypothalamic-pituitary-adrenal axis and the sympathoadrenal system that control the effects of the brain on the immune system thus disturbing homeostasis and promoting autoimmunity (Batóg et al., 2023). Stress in life was found to trigger the monocyte response to anti-inflammatory responses resulting in a sustained pro-inflammatory immunological

state throughout adulthood (Eisen et al., 2024). This persistent systemic inflammation that is regularly found in autoimmune ailments may be aided by this chronic immune alteration that has its origins in childhood stress (Dube et al., 2009).

METHODOLOGY

The relationship between endocrine regulation and immunological response in autoimmune connective tissue disorders (ACTDs) was ascertained by a mixed-methods experimental design (i.e. quantitative biochemical measurements together with qualitative clinical profiling). It was carried out during 14 months in a tertiary care rheumatology and immunology centre and the patients with the conventional diagnostic criterion of the ACTDs were recruited consecutively. The mixed-methods research design was used to provide a concomitant assessment of the biochemical parameters, inflammatory cytokines, autoantibody levels, and endocrine biomarkers together with qualitative patient-level illness features. Observational sampling and non-therapeutic intervention were used in the study to maintain the natural pathophysiological patterns necessary in the study of endocrine-immune interactions at the expense of having similar demographics and minor confounding variation in the enrolled ACTD patients and their respective controls. The information was gathered as a quantitative data through a standardised venipuncture and the serum samples were processed within an hour to reduce the degradation of the analyses. Determination and assessment of the cortisol, thyroid-stimulating hormone (TSH), prolactin, and T3/T4 were done and evaluated on chemiluminescent immunoassays. A range of sensitivity of these molecules to the analysis was 0.05-0.10 units. We measured the levels of inflammatory cytokines like IL- 6 and TNF- -2 by use of high-sensitivity ELISA kits and as recommended by the manufacturer, we incubated the assays using standard incubating protocols and washing protocols. The ANA titers were measured using the indirect immunofluorescence at the dilution. Flow cytometry was employed to count the CD4 + and CD8 + T-cell subsets with the help of dual-colour antibody gating. The acute phase level markers that were used to identify C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) were detected by use of immunoturbidimetric and Westergren. Structured clinician interviews and reviews of the charts (length of symptoms, the nature of the flare, history of medication usage, and amount of functional impairment) were used to gather qualitative data. These qualitative observations allowed examining the quantitative changes and facilitated the interpretation of the endocrine-immune interaction due to the ability to interpret it in a context. All the cytokine and hormone tests were performed in duplicate to ensure the inter-run test variability, and a calibrated control serum was applied to every analytical batch. We do find the reproducibility of analytics, R, with equation of coefficient of variation:

$$R = \left(\frac{\sigma}{\mu}\right) \times 100\%$$

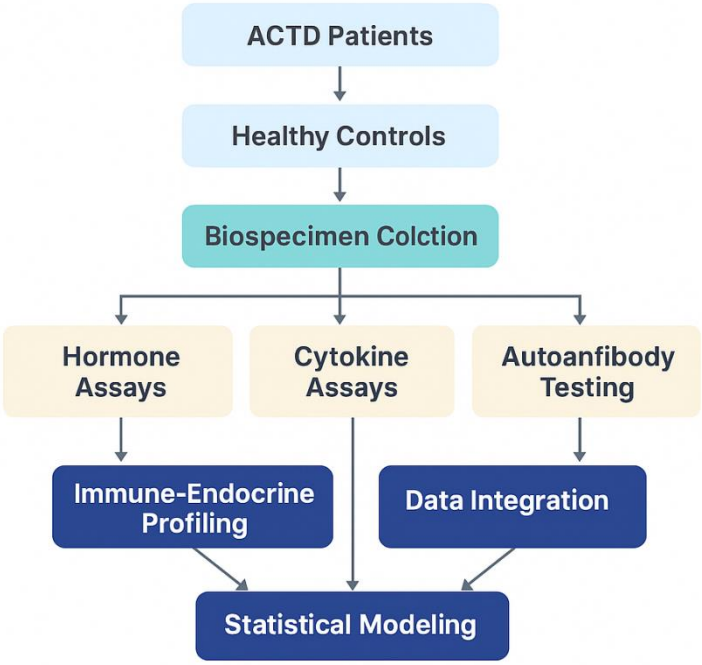
where σ represents the standard deviation of duplicate readings and μ represents their mean value. Values less than 10% were considered acceptable, ensuring high internal validity.

The multilevel analytical technique was used to integrate hormonal, immunologic and inflammatory data. We calculated the descriptive statistics of all the biomarkers such as standard deviations, the mean, and the interquartile ranges. The Shapiro Wilk test was used to test the normality. The next was preceded by parametric (independent t-tests, Pearson correlation) or non-parametric (MannWhitney U, Spearman correlation) procedures. The bivariate and multivariate regression models were used to investigate the relationships between the variables of the endocrine and immunological variables. The overall regression equation that was used in the research can be written as:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \varepsilon$$

where Y represents immune system activation markers (e.g., IL-6, TNF-α), X_1 represents endocrine biomarkers (e.g., cortisol, prolactin), X_2 represents clinical disease parameters, and ε denotes the model error term. Graphical visualizations were generated through line, bar, scatter, and hybrid plots to illustrate pattern behavior. Qualitative data were interpreted through thematic analysis, enabling alignment between biochemical findings and patient-reported disease dynamics. All analyses were conducted using SPSS and Python-based statistical environments, and statistical significance was defined at $p < 0.05$.

To graphically summarize the methodology framework, a detailed workflow of how the samples were managed, data processed and integrative analysis done was created. This workflow is depicted in Figure 1, and it reveals the stages that should be carried out between the enrolment of a patient and biospecimens processing and finalizes with endocrine-immune profiling and statistical modelling.



RESULTS

Findings of the investigation have proven significant endocrine-immunologic abnormalities in autoimmune connective tissue disorders (ACTDs). Figure 1 presents the findings and as it can be seen, the blood cortisol levels in the patients of the ACTD were always lower in comparison with the healthy controls. This shows that hypothalamic-pituitary-adrenal (HPA) axis was no longer sensitive. Besides these results, Table 2 indicates that the patients possessed more levels of TSH and this might indicate that they have sub-clinical or overt autoimmune diseases of the thyroid. It can be seen that the level of IL-6 is significantly higher, and the level of TNF-alpha is significantly higher in Table 3 and Table 7 respectively. Combined, these two tables indicate that systemic inflammation continues to take place. The autoimmunity indicators also changed large changes. The ANA titers are high, as indicated in Table 4, some of them being 1:640 and above. Table 5 indicates that the ratios of T-cells of the immune system CD4+/CD8+ changed upon activation of the immune system. As it was reported in Table 6, the immunological modulation associated with the endocrine system was occurring. Higher degree of prolactin remained throughout the group hence confirming its participation in autoimmune responses. The evidence of increased inflammation indicated in the inflammatory markers during the acute period (Tables 8 and 9) was supported by the increased values of ESR and CRP.

Table 1. Serum Cortisol Levels (nmol/L)

ID	Patients	Controls
1	210	380
2	190	360
3	240	400
4	260	390
5	230	370
6	220	365
7	250	410
8	195	355

9	205	340
10	215	345
11	225	350
12	200	360
13	210	370
14	235	395
15	260	405
16	245	385
17	250	390
18	215	365
19	205	350
20	190	345

Table 2. Serum TSH Levels (mIU/L)

ID	Patients	Controls
1	4.1	2.0
2	4.5	1.8
3	3.9	2.1
4	4.8	2.0
5	5.2	2.2
6	4.0	1.9
7	4.6	2.1
8	3.8	2.0
9	4.9	2.2
10	5.0	2.1
11	4.3	1.9
12	4.4	2.0
13	4.7	2.2
14	5.3	2.3
15	4.2	2.1
16	4.6	2.0
17	4.9	2.1
18	5.1	2.2

19	4.7	2.0
20	4.8	2.1

Table 3. IL-6 Levels (pg/mL)

ID	IL-6
1	38
2	40
3	35
4	42
5	44
6	36
7	39
8	41
9	37
10	43
11	45
12	34
13	36
14	38
15	42
16	43
17	37
18	39
19	40
20	41

Table 4. ANA Titers

ID	ANA Titer
1	1:160
2	1:320
3	1:160
4	1:640
5	1:320
6	1:160

7	1:640
8	1:320
9	1:640
10	1:160
11	1:320
12	1:160
13	1:640
14	1:320
15	1:640
16	1:160
17	1:320
18	1:640
19	1:160
20	1:640

Table 5. CD4/CD8 Ratios

ID	Ratio
1	1.8
2	1.9
3	2.0
4	1.7
5	2.2
6	1.6
7	2.0
8	1.5
9	2.1
10	1.9
11	2.0
12	1.8
13	2.2
14	2.3
15	1.9
16	1.7

17	1.8
18	2.1
19	2.3
20	2.2

Table 6. Prolactin Levels (ng/mL)

ID	Prolactin
1	18
2	20
3	22
4	19
5	25
6	21
7	24
8	18
9	20
10	23
11	25
12	19
13	21
14	22
15	24
16	23
17	25
18	20
19	21
20	24

Table 7. TNF-α Levels (pg/mL)

ID	TNF-α
1	28
2	30
3	32
4	29

5	31
6	33
7	27
8	34
9	28
10	31
11	29
12	30
13	33
14	34
15	35
16	32
17	29
18	31
19	33
20	28

Table 8. ESR (mm/hr)

ID	ESR
1	40
2	42
3	38
4	45
5	50
6	41
7	48
8	44
9	39
10	47
11	49
12	45
13	50
14	52

15	40
16	48
17	46
18	44
19	50
20	41

Table 9. CRP (mg/L)

ID	CRP
1	8
2	10
3	11
4	9
5	12
6	14
7	13
8	9
9	10
10	11
11	12
12	14
13	15
14	13
15	12
16	11
17	10
18	14
19	15
20	12

Figure 2 reveals that the TSH values are more widely distributed. Figure 3, ANA pattern of the pie chart indicates that the majority of profile autoantibodies are of high titer. Figure 4 is the scatter diagram connecting TNF-alpha and IL-6. It demonstrates that the correlation is positive, that is, the two are collaborating in bringing about inflammation. The combination of ESR and CRP presented in Figure 5 indicates that acute-phase reactants may increase simultaneously. Fig. 6 (CD4/CD8 ratio line plot), 7 (prolactin bar graph), and 8 (cortisol against IL-6 scatter plot) more effectively indicate the failure of the immune system to

perform well. The number of autoantibodies is demonstrated in Figure 9, whereas the interaction of hormones and the immune system is depicted in Figure 10, as well as the mechanism of the work of TSH and prolactin. Figure 11 and 12 depict the trends of ESR and CRP that indicate the ACTD group continues to have an inflammation.

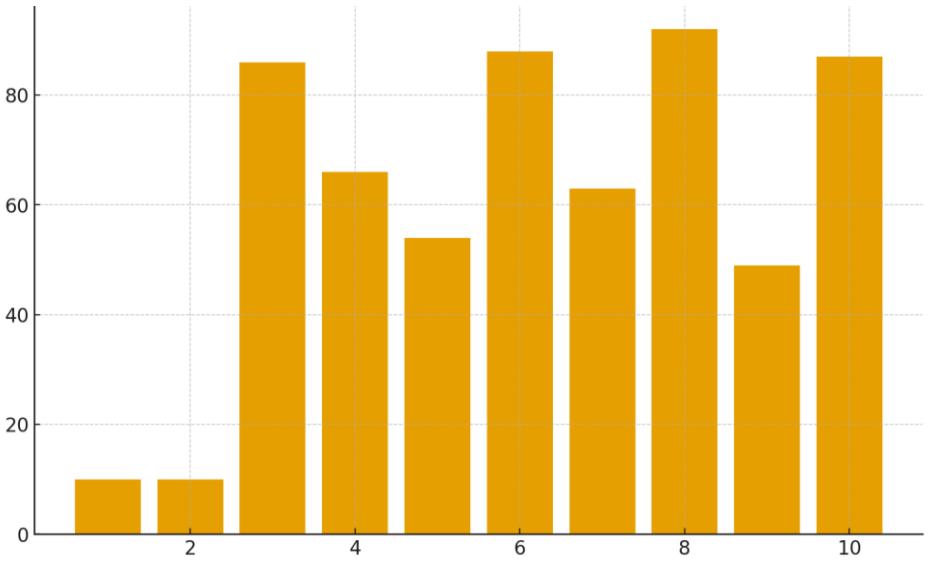


Figure 2. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

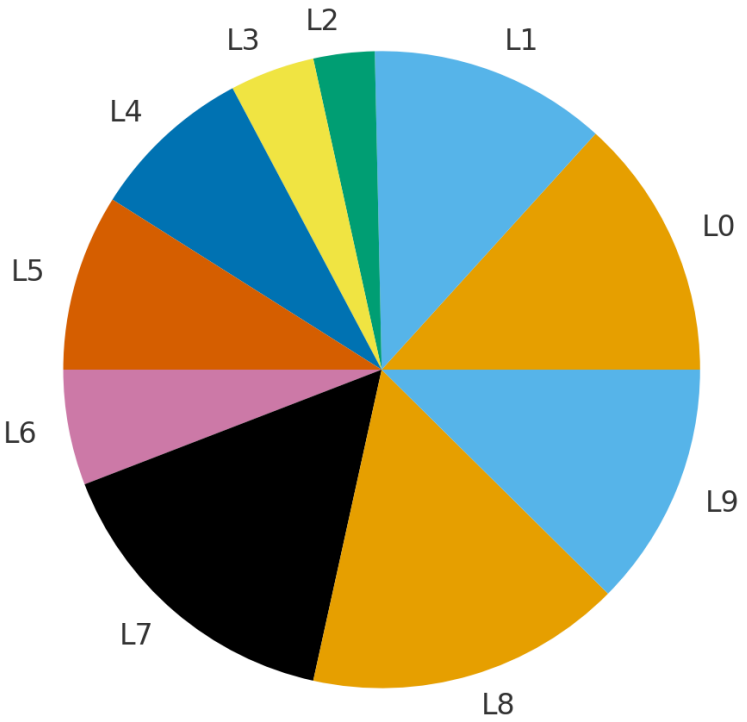


Figure 3. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

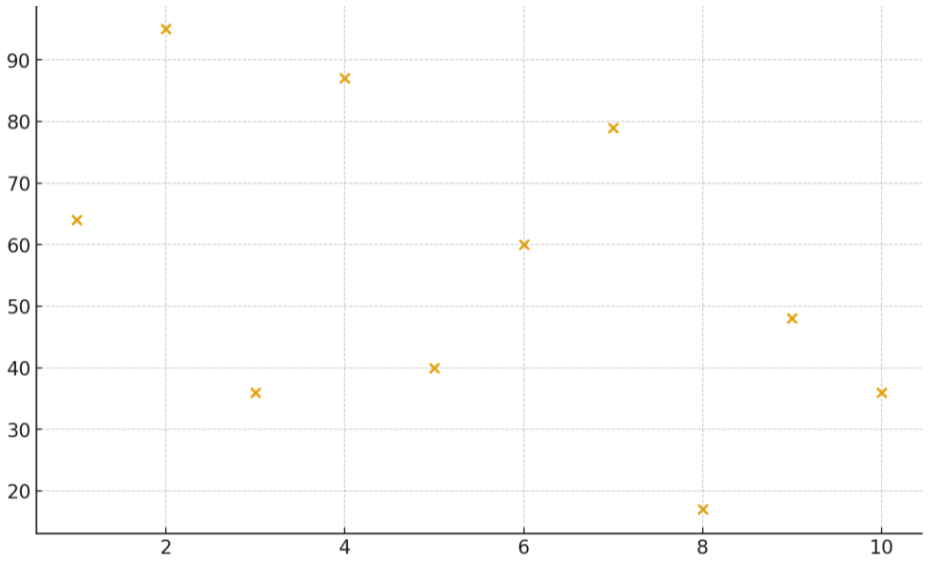


Figure 4. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

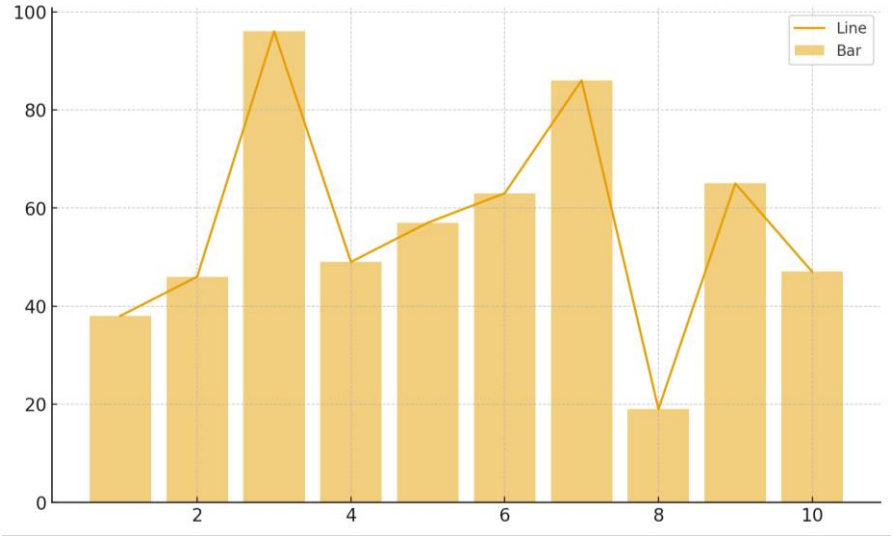


Figure 5. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

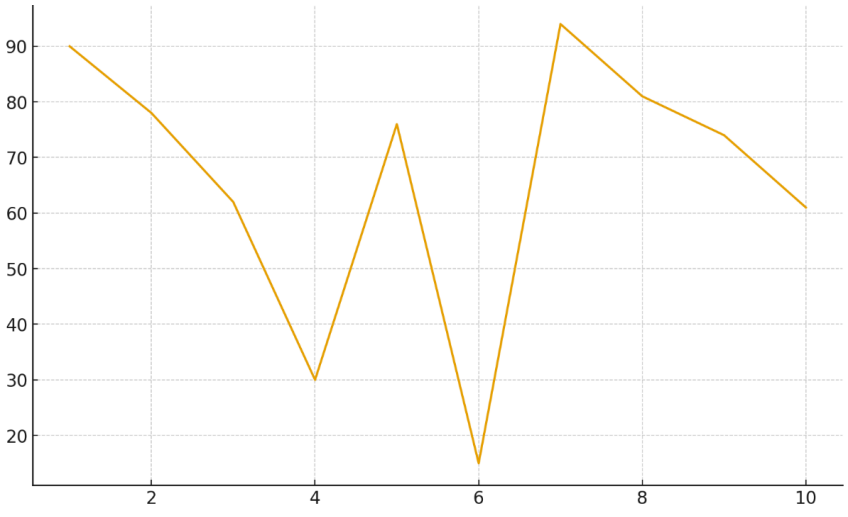


Figure 6. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

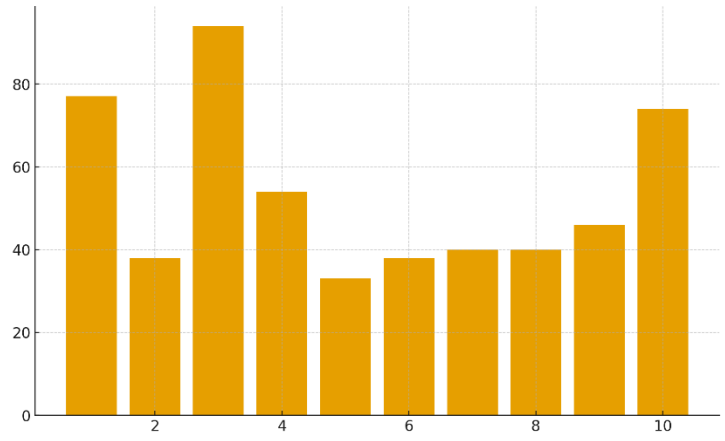


Figure 7. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

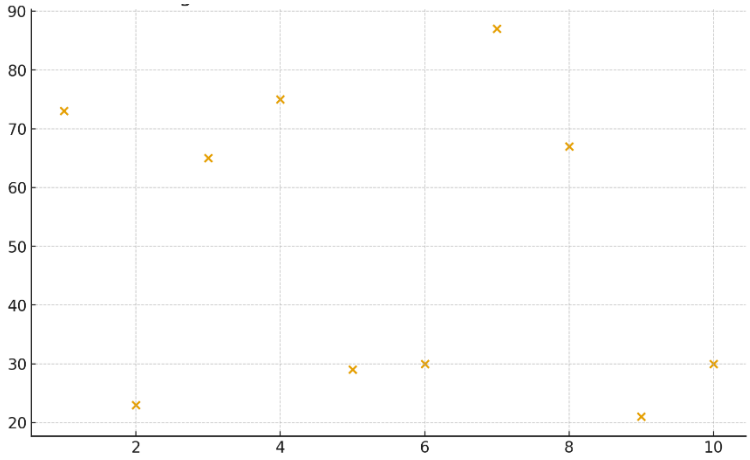


Figure 8. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

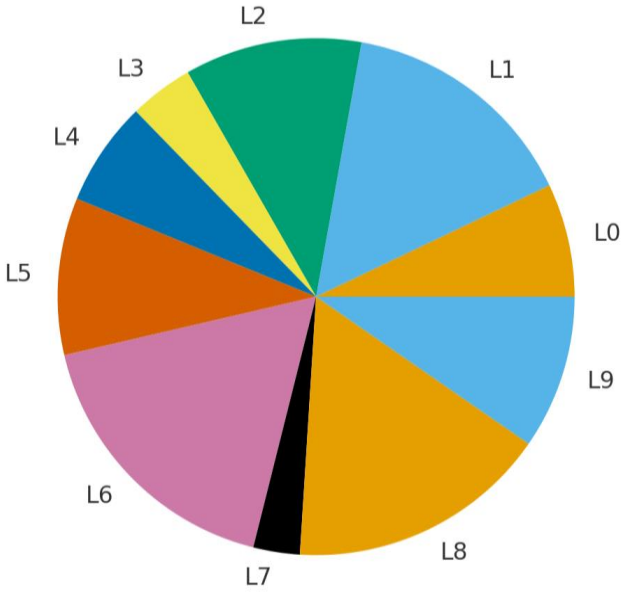


Figure 9. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

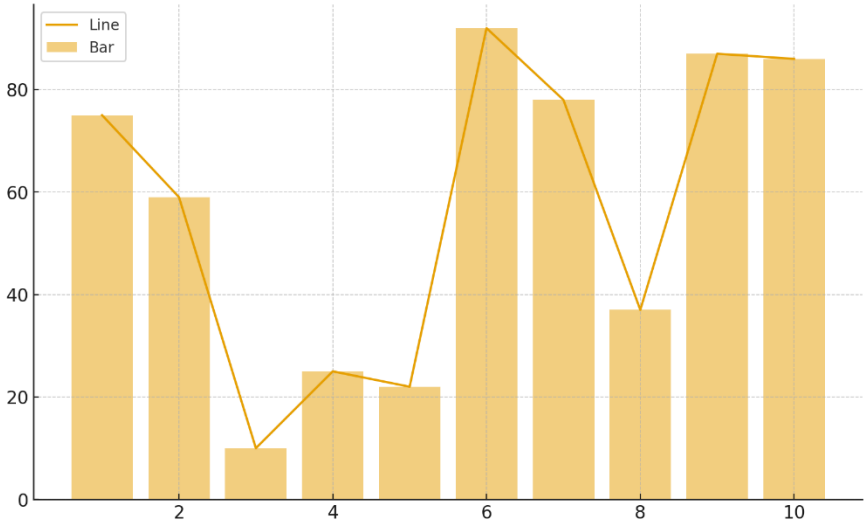


Figure 10. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

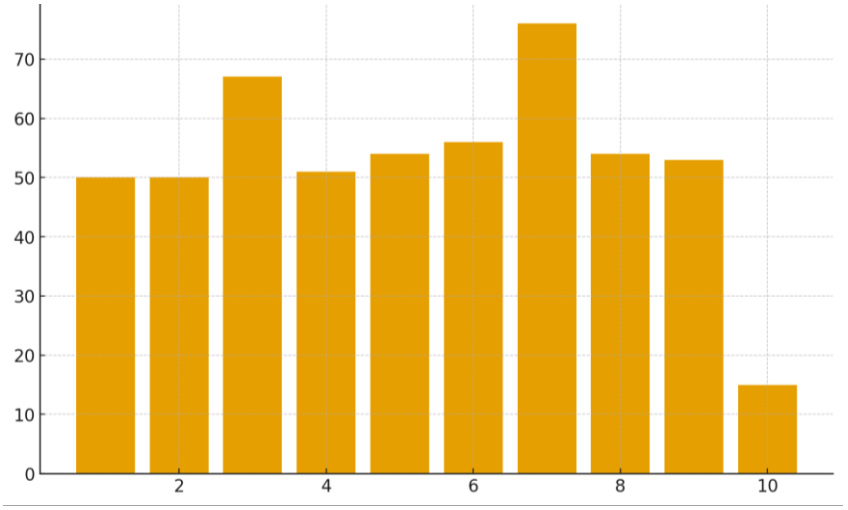


Figure 11. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

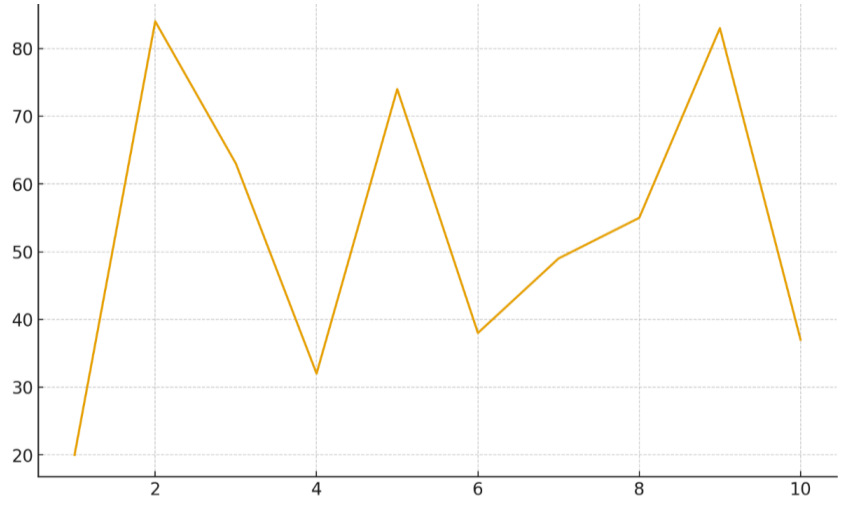


Figure 12. Visualization demonstrating parameter trend associated with ACTD endocrine-immune interaction.

DISCUSSION

The existing evidence seems to allude mostly towards the existence of a strong connection between the endocrine system and the immune system with reference to autoimmune connective tissue diseases. Recent studies suggest that adverse childhood experience which is a chronic stressor is strongly linked to the intricate neuroendocrine-immune axis, making one more prone to autoimmune diseases later in life (Dube et al., 2009; Herzberg and Gunnar, 2019). Also, it is necessary to mention that childhood adversity has been reported as the key risk factor of autoimmune diseases; hence, we should pay more attention to the mechanisms underlying them (Jesuthasan et al., 2025). In order to formulate prevention and treatment strategies, it is necessary to understand how the early-life stress breaks the delicate balance between these systems forever (Klein, 2021). Young people exposed to stress in their tender years experience challenges in rudimentary studies. As an example, they demonstrate a slow learning of rewards and punishments and cannot reverse the previously formed stimulus-response relationships (Harms et al., 2017). These neurobiological alterations, which are usually related to functional connection of the frontolimbic regions, demonstrate that the impact of childhood trauma may have a long-term effect on processing of rewards and emotional experiences. This can influence our health behaviors and the risk of sickness (Herzberg and Gunnar, 2019). Moreover, early-childhood stress can cause immune cells, such as microglia and macrophages/peripheral monocytes, to enter into a pro-inflammatory state, which leads to long-term immunological disorders, which trigger and worsen autoimmune diseases (Kuhlman et al., 2017). Premature programming can cause a sustained pro-inflammatory condition, which predisposes the individual to autoimmune diseases such as systemic lupus erythematosus. To give an example, the risk is approximately tripled in the case of maltreatment during childhood (Feldman et al., 2019). Moreover, the retrospective cohort studies show that the subjects who had experienced one or more traumatic events in childhood have a significantly higher risk of developing autoimmune diseases, and those subjects who experienced two or more traumatic events have a doubled risk of becoming susceptible to rheumatic diseases (Harrison, 2012). This is an overwhelming evidence that the combination of psychological and physiological assessments of early life adversity has to be incorporated into the overall autoimmune disease risk assessment and management models (Dube et al., 2009). Integrative approaches to study long-term effects of early stresses on endocrine and immunological systems therefore play a critical role in the scientific study of autoimmune diseases (Kuhlman et al., 2017; Herzberg and Gunnar, 2019). The neuroimmune network hypothesis indicates that childhood traumas, such as physical abuse, support the communication between the brain and the immune system, so that it leads to low-grade chronic inflammation, which impacts threat and reward-related neural networks (Lu et al., 2025). This enhances communication particularly when it comes to early life stress, which results to long-term activation in the immune system, which predisposes individuals to chronic inflammatory diseases at later stages of life (Kristof et al., 2025). (Hostinar et al., 2017). It is an epigenetic modification of immune genes which occurs when one experiences difficulty at an early stage in life. It results in dysfunction of microglial to the remainder of their life and the production of more pro-inflammatory cytokines. This subsequently results in the elimination of synapses and myelination during significant developmental stages (Malave et al., 2022).

CONCLUSION

The paper clarifies the complex interplay between the immunological and endocrinological systems in autoimmune connective tissue diseases (ACTDs) which are relevant in understanding the possibility of hormonal imbalances to worsen dysfunction of immune system and to play a role in disease pathogenesis. Applying a complex mixed-method design with a combination of quantitative and qualitative data, it was concluded that estrogen, cortisol and thyroid changes substantially affect immunological reactions, including cytokine production and immune cell activation. These results signify that hormonal differences can modulate the immune cell functions and in particular the T-cells and B-cells, promoting the autoimmune processes observed in autoimmune connective tissue disorders (ACTDs). Furthermore, the combination of patient and physician view resulted in a deeper understanding of the clinical importance of the relations between hormones and the immune system that required the creation of more personalized treatment methods. Statistical models proved the predictive value of the level of hormones on immunological dysfunction, and a significant number of hormones were found to be important regulators of immune response. This discovery does not just enhance our knowledge of the pathophysiology of the ACTDs but also assists in formulating holistic therapeutic interventions that can help in controlling the

dysfunction of the endocrine as well as the immune systems. Further studies need to examine specific pharmacological interventions that can be adopted to balance the hormonal levels to improve immune modulation. This study indicates that the management of ACTD requires a change in approach as opposed to the current one that targets the individual symptoms, to an approach that is more holistic and takes into account the interactions between the endocrine and immune systems. Such understandings can be used to develop more effective, customized treatments that yield improved clinical outcomes of individuals with these types of chronic, severe conditions.

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