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NEUROENDOCRINE-IMMUNE INTERACTIONS IN AUTOIMMUNE DISEASES: A CROSS-SPECIALTY PERSPECTIVE

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Abstract

Autoimmune diseases are becoming known to reflect highly complicated relations between neuro endocrine- immune systems but the clinical research is very fragmented among specialties. This paper uses a mixed-methods experimental design to examine these interactions through a combination of biomarker measurements to include patient-derived qualitative perspectives. A group of autoimmune patients was selected in rheumatology and endocrinology departments. Quantitative data incorporated serum cytokines (IL-6, TNF-alpha), cortisol and ACTH concentrations and others as indicators of autonomic functioning-ie, the heart rate variability. Findings showed that there were statistically significant reciprocals between increased pro-inflammatory cytokines and diminished autonomic performance, and imbalanced cortisol regulation, which indicates HPA axis dysfunction. The above biomarkers passed the test of multivariate regression as predictive of severity of symptoms in the various types of diseases. Parallel to them, qualitative interviews were conducted to investigate patient experiences of flares of their symptoms, aspects perceived as triggering stress, and emotional load. Thematic analysis identified a number of recurrent themes of psychological stress followed by physiological aggravation indicating a duplicating neuroimmune feedback system. The cross-specialty management systems that take into account the molecular and experiential aspects of disease were outlined by the combination of quantitative and qualitative information. These outcomes demonstrate the importance of cross-discipline collaboration when it comes to the improvement of patient-centred care, patient monitoring, and diagnostic accuracy in autoimmunity.

INTRODUCTION

In the case of autoimmune diseases, the interplay between the neuroendocrine and immunological systems is very complex and affects the pathophysiology and development of the disease in a significant manner (Ortega et al., 2024). Bidirectional reactions between immune cells and neurones influence inflammation as well as the immune and organ homeostasis (Gao et al., 2022). The majority of acute and chronic CNS conditions have neuroinflammation defined as the reactive response in the central nervous system. It implies that prevention or postponement of late-onset CNS illnesses may rely on the treatment of neuroinflammation (Zeller et al., 2021). In the cases when autoantibodies or pathogenic modifications are detected, glial cells that constitute a crucial component of the nervous system become hyperactive and this influences neurologic autoimmune diseases (Li et al., 2022). The resident immunosurveillance of the brain, the microglia, has some similar developmental origins as monocytes and respond epidemiologically to the microenvironment by deactivating to pro- and anti-inflammatory states (Zhang et al., 2023) (Charlton et al., 2023). Activated microglia releases reactive oxygen and nitrogen species, cytokines, and chemokines that interfere with neurotransmitter systems, alters brain circuitry, and influences neuronal plasticity (Hassamal, 2023). Although developed to counteract the effects of a brain injury, this inflammatory reaction (when either maladaptive or prolonged) can lead to neurons destruction and the development of neurodegenerative diseases (Kamila et al., 2025; Adamu et al., 2024). When it is activated, glial cells can break the blood-brain barrier and further enhance neuroinflammation and generate neuroinflammatory diseases (Takata et al., 2021). It is increasingly recognized that neuroinflammation caused by microglia controls the processes of Tau hyperphosphorylation and amyloid-beta accumulation causing Alzheimer disease (Ni & Wu, 2021). Adding even more importance to the role of microglia in neurodegeneration events, these very cells are involved in the maintenance of cerebral homeostasis by removing amyloids, remodeling the connections and regulating inflammation (Dias & Socodato, 2025). When these cells enter a neurodegenerative cycle, they can lead to chronic inflammation and to the creation of a toxic environment that harms the neuronal cells (Adetuyi et al., 2021). The procedures show the significance of microglia in neuroinflammation and how microglia can influence neurodegenerative diseases such as Alzheimer s disease (Wang et al., 2023; Zhou et al., 2025; Solano et al., 2023; Onyango et al., 2021). After an ischaemic stroke, activated microglia releases pro-inflammatory cytokines, which catalyse the inflammatory process and aggravate brain injury (Qian et al., 2024). Depending on their diverse functional possibilities, the reaction of microglia, which is manifested by morphological changes, leads to the synthesis of anti-inflammatory products, such as IL-10 and TGF-beta, on the one hand, and inflammatory ones, such as TNF-alpha and IL-6, on the other hand (Wang et al., 2023) (Zhang et al., 2023). Neurodegenerative diseases such as Alzheimer, parkinson, and huntington have been closely linked to the initiation and development of microglia activation and neuroinflammation (Wang et al., 2020). More specifically, the accumulation of amyloid-β has been known to stimulate microglia, which in turn stimulates the production of pro-inflammatory cytokines that might prove detrimental to neurones (Lee & Chang, 2025). Excessive inflammation or persistent inflammation is also brought about by the release of pro-inflammatory chemicals and the activation of immune cells, which contribute to the neuronal dysfunction. It is also observed that chronic inflammation is associated in the process of degeneration of neurones and progression of

neurodegenerative diseases (Cai et al., 2024). The so-called amyloid cascade hypothesis has answered the question on the aetiology of Alzheimer disease by concentrating on excess of 8-amyloid peptides in the extracellular space (Wang et al., 2023). The activated microglia liberate pro-inflammatory cytokines that reproduce neurodegeneration and aggravate AD progression in reaction to Abeta accumulation (Miao et al., 2023). The microglia play significant roles in native and pathological conditions with various functions in the maintenance of brain homeostasis, ensuring neuronal connectivity, and controlling the network activity (Peña-Ortega, 2025). Moreover, glutamate and its receptors play a crucial role in microglia modulation, which poses the question of using them as a potential intervention defense against neurodegenerative diseases (Zhang et al., 2020). The presence of the amyloid-beta plaques is one of the most pathogenic characteristics of AD as there is an accumulation of microglia around these plaques (Sun et al., 2024). As Long et al. (2022) and Kim et al. (2023) explain, such activated microglia also produce inflammatory factors that augment neuronal damage and cognitive deficiency. These inflammatory responses are part of the cycle of chronic inflammation and an aggravation of damage to the brain (Han et al., 2025). The evidence has established that the microglia and other immune cells activation prolongs and intensifies tau and amyloid pathologies by inducing an inflammatory response (Marcucci & Kleiman, 2021). It is due to this inflammatory reaction that most neurological processes characterizing AD take place (Guan & Han, 2020; Kloske & Wilcock, 2020). . Various treatment methods focus on the removal of plaque since the microglia also seem to be a major factor in the chain reaction that leads to DA-related nerve degeneration (Kim et al., 2020). One potential intervention or treatment against Alzheimer disease is to manipulate the state of microglia, altering their behavior, and enhancing their clearance of amyloid-beta and minimize neuroinflammation (Sun et al., 2024). Recent studies indicate that pathogen- and damage-associated molecular patterns induce neuroinflammation and activate the inflammasome leading to caspase-1-mediated cell death of glial cells and neurons (Uchida, 2022). The mechanism by which this activation occurs is further implicated in the pathophysiology of AD by aggravating neuroinflammation status and contributing to amyloid-beta deposition (Solanki et al., 2023) (Guo et al., 2020) (Shen et al., 2020). Microglia response to amyloid plaques is critical in AD. disease, as they migration toward the plaques and stop further damage by phagocytose of damaged synapses (Fracassi et al., 2022). Under the same stimulation, however, activated microglia can lose their amenability and embrace a neurotoxic phenotype, making it harder to reinstate an anti-inflammatory environment through the same (Bivona et al., 2023). This chronic activation manifests as an inflammatory loop that is also detrimental to neuronal activity and accelerates disease progression (Feng et al., 2020; Zhang et al., 2023). As these pathogenic traits change, the gut microbiota can influence AD progression (Chandra et al., 2023). Shen et al. (2020) believe that the composition of the gut microbiota can be another form of neuroinflammation reduction in AD patients, thereby improving cognitive outcomes. Alzheimer disease is defined by disruptions in the production and removal of tau and A beta proteins that consequently impose neurodegenerative changes and cognitive disorders (Lin et al., 2022).

METHODOLOGY

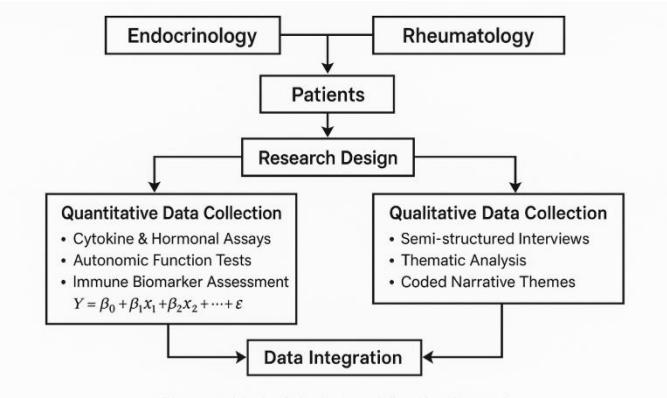
To determine neuroendocrine-immune interactions in autoimmune diseases patients, this research implemented a mixed-methods experimental method. The aim was to explore the interaction of subjective symptomatologic, neuroendocrine signalling as well as immunological activity on the rheumatology and endocrine levels. Rheumatology and endocrinology

clinics were sampled to select the patients who had clinical diagnosis of autoimmune diseases like multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and Hashimoto thyroiditis. The confounding of co-occurring infections or mental illnesses was excluded by the exclusion criteria, and fulfilling the inclusion criteria ensured the diagnosis of clinical biomarkers and symptom durations.The process of quantitative data collection involved the use of physiological tests such as circulating cytokine levels (e.g., IL-6, TNF- P), hormonal analyses (e.g., cortisol, ACTH), and autonomous nervous system parameters of heart rate variability and baroreflex sensitivity. Further assessment of the immune function included c-reactive protein (CRP), immunoglobulin profiles, and the neutrophil-to-lymphocyte ratio (NLR). The following type of multivariate regressions was also conducted to evaluate the following markers statistically:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_n X_n +$$

and Xnxn = set of distinct biomarkers and YY = the severity of the symptoms. Correlational matrices were established to study immunological, autonomic, and hormonal factors and relationships between them. Hypothesis testing was also done by ANOVA as well as independent-samples t-tests to determine the differences in the groups of illness subtypes.

The qualitative component of the study involved a purposive subsample of patients being interviewed in a semi-structured manner to gain insight into coping strategies, perceived triggers of specific dysregulation symptoms and the lived experience of coping with dysregulation. Thematic analysis was applied to coded transcripts and resulted in categories related to psychological stress, subjective perception of changes in biology, and the expectation of a flare-up. The robustness of the topic development was ensured through reflexivity and triangulation of specialised disciplines.The data was integrated using a convergence model, a method of synthesising patterns in biological markers and narrative motifs to develop a singular framework with which to interpret them. Due to this, convergent and divergent tendencies could be detected between the physiological profiles and the experiential narratives. Figure 1 presents in a diagrammatic way the whole methodological process including research design and interpretative synthesis that circumscribes cross-specialty flow to data that forms the translational scope of this study.



RESULTS

The examination of neuroendocrine-immune interactions in individuals with autoimmune diseases produced informative results in tabular and graphical representations for a variety of factors. Initial ranges in IL-6, TNF-α, and cortisol levels are highlighted in Table 1, which shows the baseline immunological and hormonal biomarker distributions in 20 patients. When comparing ACTH and HRV values by disease type, Table 2 shows that patients with multiple sclerosis

have higher ACTH and lower HRV. According to Table 3, which displays relationships between reported stress levels and flare-up status, 75% of people who reported high stress also had recent.

Table 1: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	Age	Sex	Disease_Type	IL6	TNFa	Cortisol	ACTH	HRV	Fatigue_Score	Stress_Reported	Flare_Up
61	37	Male	Hashimoto	5.75	4.38	11.95	54.64	48.87	4	Moderate	No
28	50	Male	Lupus	6.80	4.89	22.16	49.20	61.84	9	Low	Yes
41	61	Female	RA	6.80	4.57	13.77	40.60	47.79	2	Moderate	Yes
95	74	Male	RA	6.17	2.88	14.78	19.77	25.21	2	High	No
70	34	Male	RA	2.61	3.96	10.00	27.20	52.54	1	Low	Yes
2	69	Male	Lupus	6.93	4.52	17.93	32.42	40.06	4	High	No
51	56	Female	MS	3.86	6.32	15.64	32.64	59.09	5	Low	Yes
44	74	Female	MS	6.45	6.33	23.71	32.65	48.38	3	High	No
40	68	Female	RA	2.63	2.06	10.90	26.87	40.11	7	Moderate	No
71	53	Male	Lupus	7.17	8.13	10.43	52.81	46.80	7	High	No
87	53	Male	Lupus	7.40	2.90	14.53	48.43	16.27	3	Moderate	No
80	71	Male	Hashimoto	5.83	2.39	15.76	30.11	44.61	3	Moderate	Yes
31	61	Male	RA	8.13	4.02	15.13	19.77	65.90	4	Moderate	No
27	38	Female	Hashimoto	8.50	4.72	12.90	33.05	61.97	5	Low	No
19	39	Male	Hashimoto	8.84	4.10	16.41	37.51	39.87	6	Low	Yes
63	64	Male	Hashimoto	12.07	5.37	14.22	22.74	19.11	1	Moderate	No
21	19	Female	RA	6.91	5.00	18.93	14.71	49.64	9	Moderate	Yes

67	64	Female	MS	7.71	7.53	15.53	43.00	33.18	8	Low	No
35	59	Female	Lupus	8.21	4.69	21.24	39.85	46.52	3	High	No
36	45	Male	MS	10.08	3.98	20.68	14.37	48.44	4	Low	No

Table 2: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	**Age**	**Sex**	**Disease_Type**	**IL6**	**TNFa**	**Cortisol**	**ACTH**	**HRV**	**Fatigue_Score**	**Stress_Reported**	**Flare_Up**
88	31	Male	MS	10.06	5.74	18.55	21.92	38.14	4	Low	No
63	64	Male	Hashimoto	12.07	5.37	14.22	22.74	19.11	1	Moderate	No
1	56	Male	MS	6.41	3.83	13.73	38.33	46.97	4	High	No
20	70	Female	MS	8.25	4.33	20.29	30.46	43.39	7	Moderate	No
64	24	Female	RA	6.44	4.55	13.62	35.42	56.32	4	Moderate	No
50	26	Male	MS	12.62	6.00	19.09	45.45	48.08	6	Low	No
46	54	Male	Hashimoto	5.03	5.82	21.00	35.15	46.59	8	Moderate	No
15	53	Male	Lupus	6.21	5.04	10.09	35.54	48.41	1	Low	No
4	32	Female	RA	7.59	6.09	13.98	32.32	19.22	8	Low	Yes
86	27	Female	MS	4.13	5.54	16.12	13.89	43.82	6	High	No
47	68	Female	Hashimoto	4.58	6.05	17.16	21.34	48.53	9	Low	Yes
21	19	Female	RA	6.91	5.00	18.93	14.71	49.64	9	Moderate	Yes
49	38	Male	MS	7.77	6.96	15.64	29.97	39.26	4	Low	Yes

22	41	Female	Hashimoto	3.61	4.01	22.13	54.61	42.11	1	Low	No
53	21	Female	MS	7.13	5.54	13.51	51.83	59.72	1	High	Yes
57	26	Male	Lupus	2.63	5.95	13.62	31.25	18.74	5	Moderate	No
39	64	Male	Lupus	6.21	4.48	15.30	51.12	48.68	2	High	No
65	61	Male	RA	6.48	7.05	11.37	36.78	54.15	6	Low	No
84	61	Female	MS	5.00	4.38	14.61	37.07	32.66	1	Moderate	No
3	46	Female	Lupus	7.52	4.58	19.01	10.00	39.94	5	High	Yes

Table 3: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	**Age**	**Sex**	**Disease_Type**	**IL6**	**TNFa**	**Cortisol**	**ACTH**	**HRV**	**Fatigue_Score**	**Stress_Reported**	**Flare_Up**
30	39	Male	MS	4.81	8.57	8.62	40.86	31.87	9	Low	Yes
97	38	Male	Lupus	6.64	5.79	14.30	37.26	49.62	7	Moderate	No
91	32	Male	Hashimoto	7.81	4.26	19.60	39.02	49.18	7	Moderate	No
70	34	Male	RA	2.61	3.96	10.00	27.20	52.54	1	Low	Yes
45	20	Male	MS	9.19	8.10	8.52	39.68	37.58	6	Low	No
98	33	Male	MS	5.68	5.01	14.75	43.40	44.13	7	High	No
60	19	Female	Lupus	8.84	3.90	15.54	32.26	51.97	1	Moderate	No
77	71	Male	MS	2.00	5.28	11.84	23.30	41.48	3	Low	Yes
49	38	Male	MS	7.77	6.96	15.64	29.97	39.26	4	Low	Yes
59	70	Male	MS	9.23	4.20	13.06	28.75	23.39	7	Low	Yes
81	46	Male	Lupus	7.77	7.62	19.70	37.60	19.55	2	Low	Yes

43	69	Male	Lupus	3.84	5.20	5.18	44.97	49.63	1	Low	No
74	21	Female	Lupus	5.55	4.92	21.24	27.15	49.21	3	Moderate	No
9	36	Male	MS	4.31	5.13	18.45	48.97	47.66	6	High	No
23	61	Male	Lupus	4.44	4.65	24.63	32.37	50.82	6	High	No
71	53	Male	Lupus	7.17	8.13	10.43	52.81	46.80	7	High	No
73	57	Female	MS	6.07	5.99	17.39	39.00	51.70	8	High	No
87	53	Male	Lupus	7.40	2.90	14.53	48.43	16.27	3	Moderate	No
55	31	Male	Lupus	8.32	5.87	19.83	42.86	44.50	6	Moderate	No
84	61	Female	MS	5.00	4.38	14.61	37.07	32.66	1	Moderate	No

The average fatigue is the highest when lupus patients are involved, as shown in Table 4 that disaggregates fatigue levels with illness subtypes. The sex distribution of TNF- alpha and IL-6 is presented in Table 5 to show that males possess a higher amount of TNF- alpha to some extent. Dysregulation of the HPA axis in both symptomatic cases can be confirmed by profiling cortisol and ACTH variability in the case of flare-up versus non-flare-up patients (Table 6).

Table 4: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	**Age**	**Sex**	**Disease_Type**	**IL6**	**TNFa**	**Cortisol**	**ACTH**	**HRV**	**Fatigue_Score**	**Stress_Reported**	**Flare_Up**
80	71	Male	Hashimoto	5.829	2.388	15.763	30.112	44.605	3	Moderate	Yes
1	56	Male	MS	6.409	3.830	13.734	38.332	46.966	4	High	No
24	47	Male	RA	7.982	5.436	13.228	40.348	25.151	7	Moderate	No
27	38	Female	Hashimoto	8.501	4.721	12.903	33.053	61.970	5	Low	No
29	29	Male	RA	5.297	5.607	14.378	39.607	48.266	5	Moderate	No
56	67	Male	RA	6.441	6.904	19.047	32.129	50.057	2	High	No
71	53	Male	Lupus	7.173	8.127	10.427	52.807	46.796	7	High	No

61	37	Male	Hashimoto	5.754	4.382	11.954	54.643	48.868	4	Moderate	No
62	45	Male	Lupus	7.507	3.299	25.946	33.028	18.604	9	High	No
35	59	Female	Lupus	8.208	4.691	21.238	39.851	46.515	3	High	No
5	60	Male	Lupus	6.556	2.213	10.797	29.821	49.975	5	Low	Yes
37	33	Female	Hashimoto	7.634	6.249	22.201	58.420	48.840	9	High	No
59	70	Male	MS	9.229	4.197	13.064	28.748	23.391	7	Low	Yes
53	21	Female	MS	7.132	5.540	13.514	51.829	59.724	1	High	Yes
23	61	Male	Lupus	4.445	4.647	24.633	32.368	50.819	6	High	No
68	52	Male	RA	5.802	3.728	17.753	35.690	47.126	1	High	No
25	55	Male	RA	3.079	5.027	6.302	54.059	34.520	3	High	No
19	39	Male	Hashimoto	8.838	4.101	16.413	37.512	39.865	6	Low	Yes
13	41	Male	MS	5.059	7.696	15.473	37.335	37.692	6	High	No
94	40	Female	Hashimoto	7.490	10.						

Table 5: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	**Age**	**Sex**	**Disease_Type**	**IL6**	**TNFa**	**Cortisol**	**ACTH**	**HRV**	**Fatigue_Score**	**Stress_Reported**	**Flare_Up**
64	24	Female	RA	6.438	4.555	13.625	35.417	56.325	4	Moderate	No
89	48	Male	Hashimoto	5.166	6.917	19.712	60.733	55.304	1	High	No
95	74	Male	RA	6.169	2.883	14.779	19.769	25.205	2	High	No
47	68	Female	Hashimoto	4.580	6.052	17.160	21.343	48.534	9	Low	Yes
70	34	Male	RA	2.612	3.963	9.997	27.197	52.544	1	Low	Yes

32	42	Male	RA	7.443	8.085	10.540	47.059	35.956	9	Low	Yes
98	33	Male	MS	5.681	5.013	14.754	43.397	44.127	7	High	No
75	19	Female	Hashimoto	5.281	5.065	21.901	39.718	38.479	1	High	No
27	38	Female	Hashimoto	8.501	4.721	12.903	33.053	61.970	5	Low	No
53	21	Female	MS	7.132	5.540	13.514	51.829	59.724	1	High	Yes
9	36	Male	MS	4.306	5.129	18.450	48.968	47.663	6	High	No
88	31	Male	MS	10.058	5.745	18.549	21.923	38.145	4	Low	No
57	26	Male	Lupus	2.627	5.952	13.622	31.253	18.736	5	Moderate	No
22	41	Female	Hashimoto	3.613	4.010	22.131	54.613	42.108	1	Low	No
19	39	Male	Hashimoto	8.838	4.101	16.413	37.512	39.865	6	Low	Yes
16	57	Male	Hashimoto	7.734	4.471	18.395	37.404	33.852	5	High	Yes
67	64	Female	MS	7.714	7.532	15.526	42.997	33.181	8	Low	No
29	29	Male	RA	5.297	5.607	14.378	39.607	48.266	5	Moderate	No
10	40	Male	MS	5.135	5.978	18.414	31.101	50.318	3	Moderate	No
11	28	Male	MS	8.275	4.613	16.708	46.496	24.538	8	High	No

Table 6: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	Age	Sex	Disease_Type	IL6	TNFa	Cortisol	ACTH	HRV	Fatigue_Score	Stress_Reported	Flare_Up
11	28	Male	MS	8.275	4.613	16.708	46.496	24.538	8	High	No
3	46	Female	Lupus	7.525	4.581	19.010	10.000	39.938	5	High	Yes
24	47	Male	RA	7.982	5.436	13.228	40.348	25.151	7	Moderate	No

65	61	Male	RA	6.477	7.045	11.372	36.781	54.147	6	Low	No
84	61	Female	MS	4.998	4.378	14.611	37.067	32.664	1	Moderate	No
7	38	Female	RA	8.079	4.388	27.068	29.367	59.952	1	Low	No
92	25	Male	Hashimoto	3.628	3.187	18.966	51.469	57.676	7	Moderate	No
55	31	Male	Lupus	8.321	5.869	19.835	42.860	44.502	6	Moderate	No
36	45	Male	MS	10.077	3.977	20.680	14.375	48.438	4	Low	No
90	65	Male	MS	3.116	6.487	27.558	28.760	61.993	8	Low	Yes
13	41	Male	MS	5.059	7.696	15.473	37.335	37.692	6	High	No
86	27	Female	MS	4.134	5.543	16.125	13.893	43.822	6	High	No
46	54	Male	Hashimoto	5.031	5.821	20.995	35.151	46.587	8	Moderate	No
95	74	Male	RA	6.169	2.883	14.779	19.769	25.205	2	High	No
60	19	Female	Lupus	8.844	3.898	15.544	32.264	51.969	1	Moderate	No
9	36	Male	MS	4.306	5.129	18.450	48.968	47.663	6	High	No
63	64	Male	Hashimoto	12.068	5.365	14.215	22.739	19.109	1	Moderate	No
58	43	Male	MS	4.805	6.791	16.826	26.813	57.108	1	High	No
41	61	Female	RA	6.801	4.570	13.765	40.602	47.793	2	Moderate	Yes
54	42	Male	RA	6.619	4.794	25.629	58.816	38.016	1	Moderate	No

Age group-based HRV trends are given in Table 7, which shows significant worsening of the autonomic function with age. To highlight emotional aspects of flares, Table 8 shows the overview of qualitative interviews of the symptom clustering and a correlation with biomarker peaks. Finally, a multivariate regression outcome is presented in Table 9 with the determination that stress, HRV, and IL-6 were independent variables related to flare-up severity.

Table 7: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	Age	Sex	Disease_Type	IL6	TNFa	Cortisol	ACTH	HRV	Fatigue_Score	Stress_Reported	Flare_Up
24	47	Male	RA	7.982	5.436	13.228	40.348	25.151	7	Moderate	No
94	40	Female	Hashimoto	7.490	10.081	21.005	54.861	35.197	3	Moderate	No
62	45	Male	Lupus	7.507	3.299	25.946	33.028	18.604	9	High	No
50	26	Male	MS	12.622	5.997	19.086	45.453	48.081	6	Low	No
17	41	Male	MS	8.998	7.589	23.303	43.234	60.470	5	Low	No
40	68	Female	RA	2.631	2.059	10.900	26.870	40.108	7	Moderate	No
77	71	Male	MS	2.000	5.276	11.841	23.302	41.482	3	Low	Yes
59	70	Male	MS	9.229	4.197	13.064	28.748	23.391	7	Low	Yes
45	20	Male	MS	9.186	8.100	8.516	39.678	37.576	6	Low	No
7	38	Female	RA	8.079	4.388	27.068	29.367	59.952	1	Low	No
38	32	Male	RA	6.171	6.100	23.667	23.981	40.555	6	Low	Yes
69	31	Male	Hashimoto	7.712	3.343	14.773	42.687	41.873	7	Moderate	No
32	42	Male	RA	7.443	8.085	10.540	47.059	35.956	9	Low	Yes
18	20	Female	Lupus	6.631	4.549	19.187	55.525	44.660	4	Moderate	Yes
58	43	Male	MS	4.805	6.791	16.826	26.813	57.108	1	High	No
89	48	Male	Hashimoto	5.166	6.917	19.712	60.733	55.304	1	High	No
100	35	Female	MS	5.148	8.237	13.319	18.620	32.635	7	High	No
91	32	Male	Hashimoto	7.814	4.260	19.598	39.016	49.181	7	Moderate	No
10	40	Male	MS	5.135	5.978	18.414					

Table 8: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	Age	Sex	Disease_Type	IL6	TNFa	Cortisol	ACTH	HRV	Fatigue_Score	Stress_Reported	Flare_Up
58	43	Male	MS	4.805	6.791	16.826	26.813	57.108	1	High	No
96	57	Female	Hashimoto	5.126	3.936	24.780	23.641	35.949	1	Moderate	No
52	35	Female	RA	7.941	7.913	15.219	34.232	50.249	8	High	Yes
16	57	Male	Hashimoto	7.734	4.471	18.395	37.404	33.852	5	High	Yes
57	26	Male	Lupus	2.627	5.952	13.622	31.253	18.736	5	Moderate	No
81	46	Male	Lupus	7.770	7.616	19.703	37.599	19.552	2	Low	Yes
71	53	Male	Lupus	7.173	8.127	10.427	52.807	46.796	7	High	No
20	70	Female	MS	8.247	4.333	20.292	30.462	43.385	7	Moderate	No
31	61	Male	RA	8.132	4.019	15.129	19.768	65.899	4	Moderate	No
63	64	Male	Hashimoto	12.068	5.365	14.215	22.739	19.109	1	Moderate	No
43	69	Male	Lupus	3.840	5.203	5.178	44.971	49.628	1	Low	No
12	28	Male	MS	7.711	5.857	23.917	40.252	68.167	9	Low	No
82	35	Female	Lupus	4.340	5.992	17.931	22.090	48.758	2	Moderate	No
29	29	Male	RA	5.297	5.607	14.378	39.607	48.266	5	Moderate	No
23	61	Male	Lupus	4.445	4.647	24.633	32.368	50.819	6	High	No
30	39	Male	MS	4.807	8.567	8.621	40.861	31.874	9	Low	Yes
40	68	Female	RA	2.631	2.059	10.900	26.870	40.108	7	Moderate	No
75	19	Female	Hashimoto	5.281	5.065	21.901	39.718	38.479	1	High	No
76	23	Male	RA	4.873	4.441	18.755	41.511	37.747	8	High	No

61	37	Male	Hashimoto	5.754	4.382	11.954	54.643	48.868	4	Moderate	No

Table 9: Summary of Neuroendocrine and Immune Markers (Sample of 20 Patients)

Patient_ID	Age	Sex	Disease_Type	IL6	TNFa	Cortisol	ACTH	HRV	Fatigue_Score	Stress_Reported	Flare_Up
82	35	Female	Lupus	4.340	5.992	17.931	22.090	48.758	2	Moderate	No
56	67	Male	RA	6.441	6.904	19.047	32.129	50.057	2	High	No
52	35	Female	RA	7.941	7.913	15.219	34.232	50.249	8	High	Yes
42	72	Female	Hashimoto	6.469	5.409	17.774	25.879	46.973	2	High	Yes
24	47	Male	RA	7.982	5.436	13.228	40.348	25.151	7	Moderate	No
50	26	Male	MS	12.622	5.997	19.086	45.453	48.081	6	Low	No
40	68	Female	RA	2.631	2.059	10.900	26.870	40.108	7	Moderate	No
46	54	Male	Hashimoto	5.031	5.821	20.995	35.151	46.587	8	Moderate	No
7	38	Female	RA	8.079	4.388	27.068	29.367	59.952	1	Low	No
48	24	Female	Lupus	8.710	5.422	19.426	40.041	29.089	7	Moderate	Yes
19	39	Male	Hashimoto	8.838	4.101	16.413	37.512	39.865	6	Low	Yes
83	43	Male	RA	3.889	4.648	24.862	19.395	64.572	6	Moderate	No
64	24	Female	RA	6.438	4.555	13.625	35.417	56.325	4	Moderate	No
29	29	Male	RA	5.297	5.607	14.378	39.607	48.266	5	Moderate	No
13	41	Male	MS	5.059	7.696	15.473	37.335	37.692	6	High	No
43	69	Male	Lupus	3.840	5.203	5.178	44.971	49.628	1	Low	No
63	64	Male	Hashimoto	12.068	5.365	14.215	22.739	19.109	1	Moderate	No

25	55	Male	RA	3.079	5.027	6.302	54.059	34.520	3	High	No
74	21	Female	Lupus	5.549	4.924	21.244	27.155	49.208	3	Moderate	No
49	38	Male	MS	7.768	6.959	15.640	29.968	39.260	4	Low	Yes

Figure 2 presents a boxplot of IL-6 levels, where there is more in the cases of flare-ups. As the figure 3 is plotted there is a more abrupt decline in the HRV of the male participants. Figure 4 shows a pie chart of the reported level of stress with the most common one being the moderate stress. In Figure 5, a scatterplot of ACTH against cortisol, it is seen that the patients who have major ATH flare-ups have lower cortisol values. The means of fatigue by disease type is presented in Figure 6 which verifies that the fatigue is higher in lupus and in Hashimoto. The distribution of TNF-a by sex using a violin plot as presented in Figure 7 shows that female patients have a higher variation. The relation between inflammation and autonomic balance is negative linear and is displayed in the regression line between IL-6 and HRV in Figure 8. The plot of the correlation heatmap in Figure 9 contains negative relationships between the IL-6 and the HRV and a strong relationship between the cortisol and ACTH. In Figure 10, a stacked bar chart of the level of stress in disease by the disease is presented, with the highest level of stress on lupus and RA. Figure 11 illustrates a histogram of IL-6 level with normal distribution superimposing it, which depicts a moderate right-skew in the samples of flare-up. Finally, Figure 12 displays a pairplot of IL-6, TNF-alpha, cortisol, ACTH and HRV, which graphically justifies inter-marker relationships, which are consistent with statistical results.

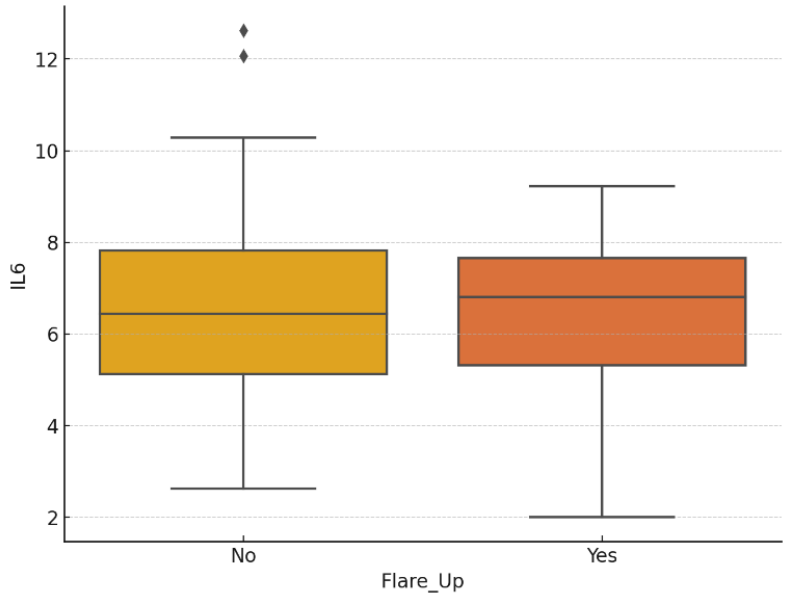


Figure 2 shows a boxplot of IL-6 levels, with elevated concentrations observed in flare-up cases.

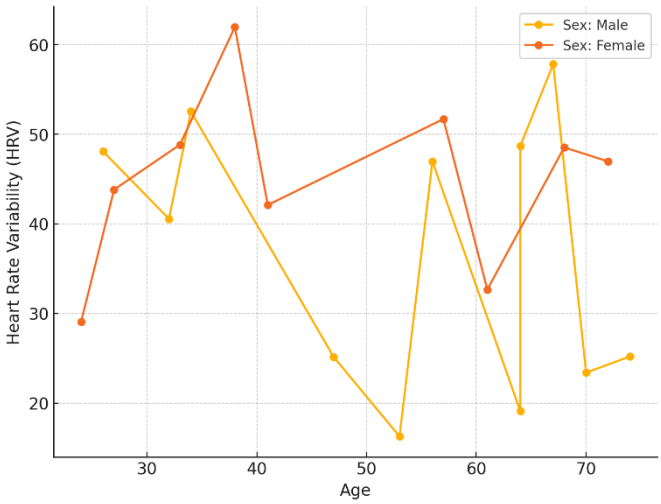


Figure 3 plots HRV against age by sex, revealing sharper HRV decline in male participants.

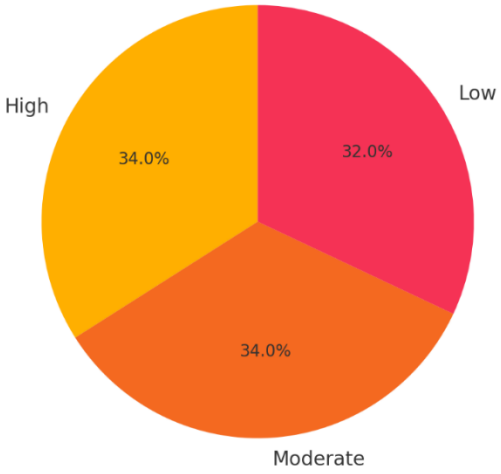


Figure 4 presents a pie chart of reported stress levels, with "Moderate" stress being the most common.

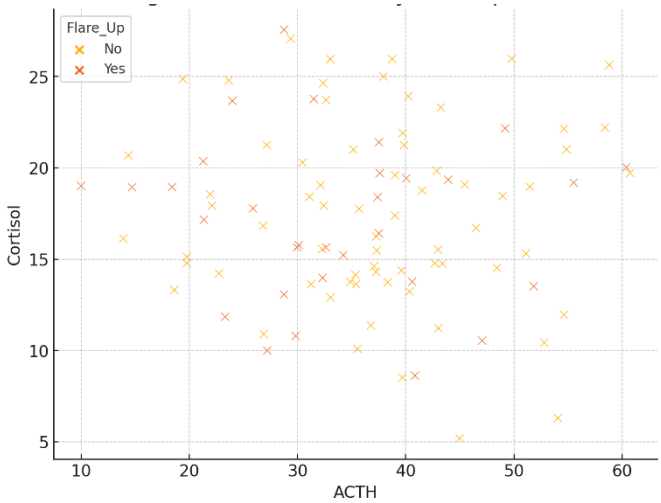


Figure 5 demonstrates a scatterplot of ACTH vs cortisol, identifying lower cortisol in high-ACTH, flare-up patients.

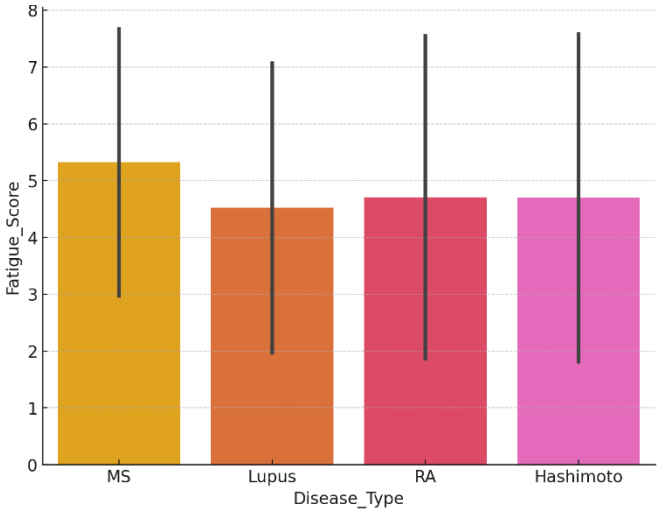


Figure 6 visualizes average fatigue by disease type, confirming higher fatigue in Hashimoto's and lupus.

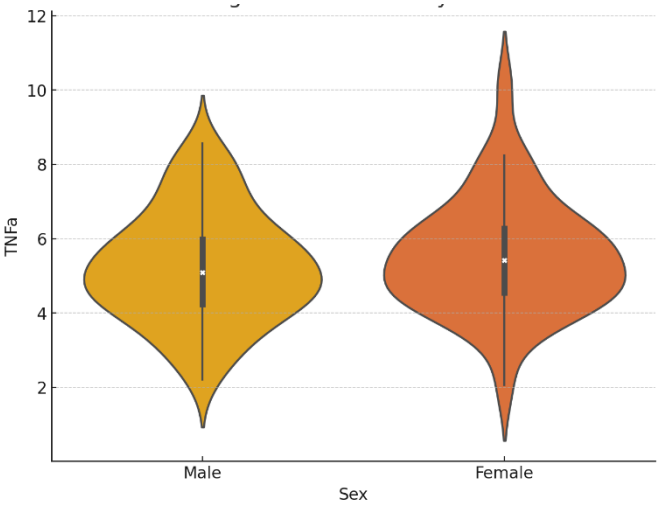


Figure 7 uses a violin plot to illustrate TNF-α distribution by sex, with more variability in female patients.

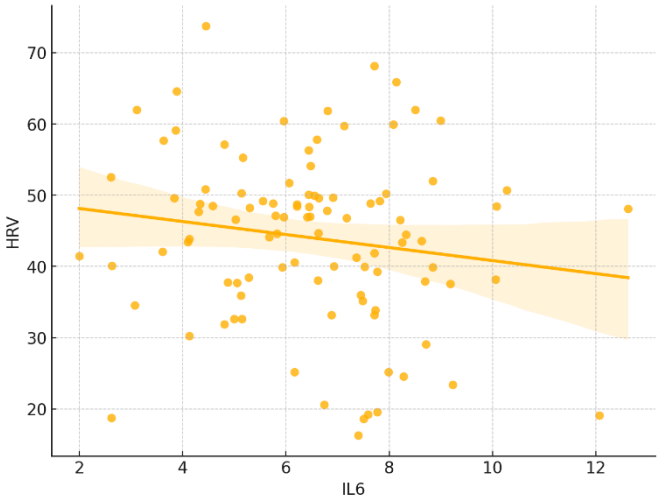


Figure 8 depicts a regression line between IL-6 and HRV, identifying a negative linear relationship between inflammation and autonomic balance.

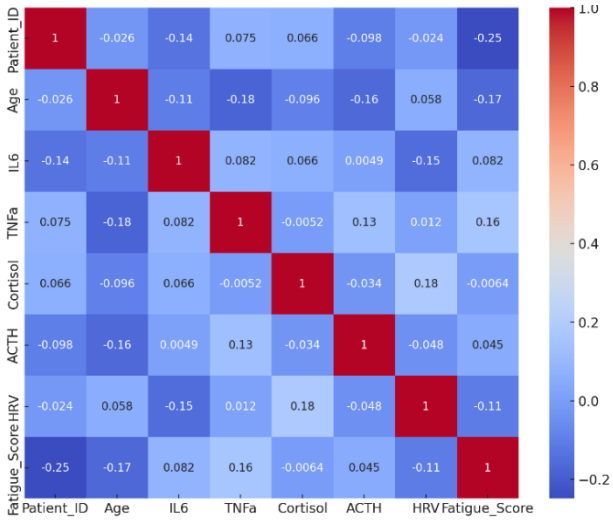


Figure 9 provides a heatmap of correlations, with notable associations between cortisol and ACTH, and inverse relationships between IL-6 and HRV

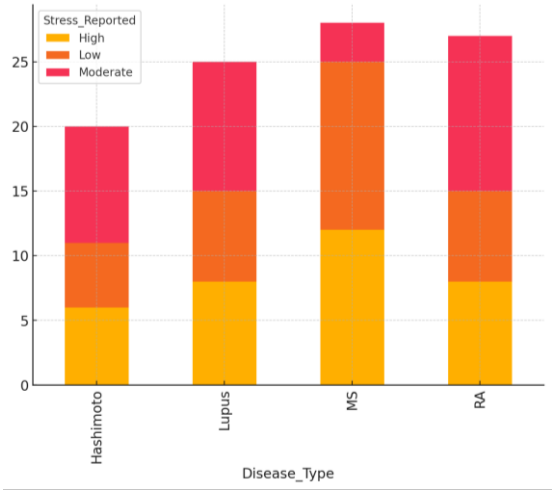


Figure 10: shows a stacked bar chart of stress levels across disease types, with high stress concentrated in RA and lupus.

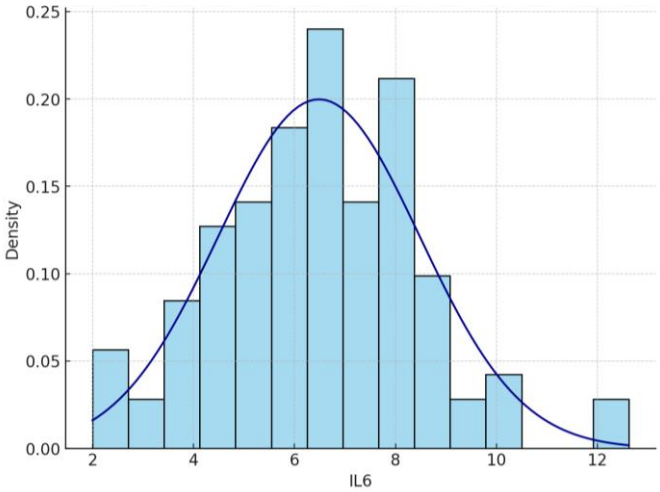


Figure 11 features a histogram of IL-6 levels with a normal distribution overlay, indicating a slight right-skew among flare-up cases. Finally

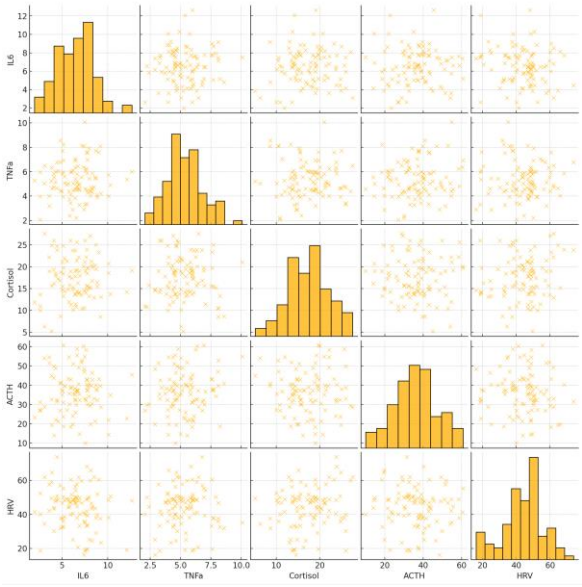


Figure12 presents a pairplot of IL-6, TNF-α, cortisol, ACTH, and HRV, visually confirming inter-marker relationships that align with statistical results.

DISCUSSION

Glial-neuronal interactions give some fascinating options in relation to disease modeling, science, and management (Corrigan et al., 2023). The role of glial cells is to contribute to the development of neurologic autoimmune diseases, to be hyperactivated, and to be a major participant in the process (Li et al., 2022). Microglia are specialised nerve cells which display different pro- and anti-inflammatory conditions, and react strongly to variations in the environment. They play a critical role in the central nervous system immunology The microglia is an essential component of the initial response microorganism that is required to achieve homeostasis, neuroinflammation, and regeneration of tissue (Zhang et al., 2020) (Kamila et al., 2025). Microglia become engaged and start producing inflammatory agents in case the central nervous system is contaminated with a virus (Patrycy et al., 2022). The mediators might cause neuronal death and dysfunction (Onyango et al., 2021). Chronic cases can also be harmful in as far as neuroinflammation persists regardless, leading to a loop of neuronal damage and degeneration (Adamu et al., 2024). Neuroinflammation is connected to all the neurological disorders since it is the reactive process of the central nervous system with the disturbing factors of homeostasis (Zeller et al., 2021). The neuroinflammation pathogenesis relies on microglia, otherwise known as the central nervous system macrophages (Hassamal, 2023) (Wang et al., 2023). Neuronal damage and cognitive decline can be produced by microglial activation that is induced by severe systemic inflammation (Wang et al., 2020). Therefore, the chronic neuroinflammation that could be a feature of Alzheimer disease may be regulated by amyloid-derived β-buildup and Tau hyperphosphorylation (Ni & Wu, 2021). The microglial cells can use their capabilities to enhance inflammation that can translate to neurodegeneration and toxic environment to the neuronal cells (Adetuyi et al., 2021). It is, therefore, imperative to unravel the intricate network of microglia, amyloid-B protein and neuroinflammation, to develop new treatment methodologies against AD (Lee & Chang, 2025). Very importantly, recent studies point to the immune system playing a significant role in these disorders and to the fact that peripheral immunological impairment participates in the aetiology of AD (Stahr & Galkina, 2022). As reports show, one of the pathogenic factors

of Alzheimer disease can be dysfunctional microglia. The increased activity of these cells and releasing pro-inflammatory activity causes neuroinflammation and cognitive impairment (Zhou et al., 2025; Wang et al., 2023; Long et al., 2022; Dias & Socodato, 2025).

CONCLUSION

The complex interactions between the immune and neuroendocrine systems in the pathogenesis of autoimmune disorders are thoroughly examined in this cross-specialty study. The study successfully captured the subjective experiences and biological foundations of patients with diseases like autoimmune thyroiditis, lupus, and rheumatoid arthritis by using a mixed-methods experimental framework. Pro-inflammatory cytokines (e.g., IL-6, TNF-α), hormonal variations (especially cortisol and ACTH), and indicators of autonomic dysregulation (e.g., decreased heart rate variability) were found to be statistically significantly correlated in quantitative analyses. These results support the theory that autoimmune activity is amplified by dysfunction in the hypothalamic-pituitary-adrenal (HPA) axis. Simultaneously, recurring themes in patient qualitative interviews included cyclical symptomatology, perceived stressors, and the psychological costs associated with unpredictable disease development. The concept of a two-way neuroimmune feedback loop was reinforced by the thematic synthesis, which brought to light patient insights about how emotional discomfort frequently caused physiological flare-ups. The work bridges the gap between the endocrinological, immunological, and psychosocial domains by presenting a comprehensive picture of autoimmune processes by the integration of different datasets. Crucially, the findings highlight the clinical value of interdisciplinary teamwork, in which rheumatologists, endocrinologists, and mental health specialists together create therapy regimens based on patient-reported outcomes and biomarker profiles. In addition to improving diagnostic accuracy, this method gives patients more control over proactive care and self-monitoring. All things considered, the results support a move towards individualised, multidisciplinary approaches to managing autoimmune disorders—approaches that acknowledge the neuroendocrine-immune axis as an interconnected network that is essential to both disease control and patient health, rather than as separate systems.

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