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The Link between Post-Traumatic Stress Disorder and Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous, multisystem autoimmune disorder characterized by unpredictable disease flares. Although the pathogenesis of SLE is complex, an epidemiologic link between posttraumatic stress disorder (PTSD) and the development of SLE has been identified, suggesting that stress-related disorders alter the susceptibility to SLE. Despite the strong epidemiologic evidence connecting PTSD and SLE, gaps remain in our understanding of how the two may be connected. Perturbations in the autonomic nervous system, neuroendocrine system, and at the genomic level may cause and sustain immune dysregulation that could lower the threshold for the development and propagation of SLE. We first describe shared risk factors for SLE and PTSD. We then describe potential biological pathways which may facilitate excessive inflammation in the context of PTSD. Among those genetically predisposed to SLE, systemic inflammation that accompanies chronic stress may fan the flames of smoldering SLE by priming immune pathways. Further studies on the connection between trauma and inflammation will provide important data on pathogenesis, risk factors, and novel treatments for SLE.

Keywords

Systemic lupus erythematosus; Post-traumatic stress disorder; Inflammation; Hypothalamic-Pituitary Axis; Cytokine; Autoimmune

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1. Introduction

1.1 Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a life-threatening, heterogeneous, chronic autoimmune disease characterized by immune system autoreactivity, autoantibody production, and immune complex deposition, as well as significant sociodemographic disparities.[1] Estimates of SLE prevalence in US populations range between 0.05% and 0.2%.[2] SLE disproportionally affects women (prevalence is 6 times higher in women compared to men), US minority racial and ethnic groups (prevalence is nearly doubled in African American women compared to White women), and individuals of lower socioeconomic status (SES).[3] Hallmarks of SLE include multi-organ dysfunction and high morbidity and mortality. It is thought that SLE develops in stages, with a break in self-tolerance resulting in autoantibody and inflammatory cytokine upregulation preceding symptoms.[1] Disease flares are associated with pain, fatigue, depression, and difficulty sleeping, and has an overall profoundly negative impact on health-related quality of life (HRQoL).[1] Many types of neuropsychiatric symptoms can occur in SLE, affecting approximately 40% of patients at diagnosis and a majority during their disease course.[4] Treatment for SLE typically involves hydroxychloroquine as maintenance therapy, corticosteroids to control disease flares, and cytotoxic-immunosuppressants and biologic agents to reduce disease activity.[1] Among patients with SLE, suboptimal medication adherence is highly prevalent with a recent systematic review finding that over half of patients with SLE are non-adherent to their regimens.[5]

The current etiologic model for SLE is that environmental exposures lower the threshold for or accelerate SLE development among those who are genetically predisposed.[6] Genetic factors are thought to explain a portion of SLE risk, leaving a large role for exposures that may act specifically or non-specifically by increasing systemic inflammation.[1] While mechanisms underlying sex and racial disparities of SLE are not completely understood, socioeconomic factors, genetic differences, occupational environmental exposures, and hormonal triggers are likely contributors.[3] Post-traumatic stress disorder (PTSD) is among the strongest risk factors for developing SLE and also tends to be more prevalent among racial/ethnic minoriites.[7]

1.2 Post-Traumatic Stress Disorder (PTSD)

PTSD is common and debilitating with a prevalence of 7% in civilian US adults and double that in most surveys of military populations.[8] The risk in civilians is also at least double in women versus men and with PTSD prevalence rates greater among Black individuals compared to White individuals (8.7% vs. 7.4%).[9,10] The Diagnostic and Statistical Manual of Mental Disorders-5th edition criteria for PTSD include the development of post-traumatic symptoms in four diagnostic symptom clusters: re-experiencing, avoidance, hyper-arousal and negative cognitions and mood.[11] Although exposure to a stressful event is required for PTSD diagnosis, only some trauma-exposed individuals develop the disorder (~14% overall in community samples, but ~34% after violent assault).[12] Factors that increase risk of developing PTSD include experiencing a trauma that involves interpersonal violence exposure, female sex, severity and chronicity of trauma, preexisting psychiatric disorders,

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negative life events post-trauma exposure, and childhood trauma and adversity (Figure 1).[13–15]

1.3 Complex Interplay between PTSD and SLE

PTSD prevalence has been reported to be elevated among those with SLE and it could have considerable impact on adverse clinical outcomes and HRQoL in SLE.[7] First, the systemic inflammation that accompanies chronic stress could feed the flames of smoldering autoimmune disease and prime immune and inflammatory pathways, thereby increasing SLE disease activity and the frequency and severity of SLE flares. Second, PTSD may deleteriously affect outcomes and quality of life in SLE through a number of other pathways.[16] PTSD is associated with comorbid substance use disorders, self-injurious behavior, and cardiometabolic disease[14] all of which could impact SLE activity and treatment-seeking behaviors. Long-term sequelae of PTSD include disruption of critical support and familial networks, interference with parenting roles, and exacerbation of socioeconomic vulnerabilities.[14] Sleep disturbances in PTSD such as insomnia and nightmares may exacerbate pain and depressive symptoms.[14]

PTSD may develop in response to diagnosis of a life-threatening illness and interfere with treatment adherence.[17] Cancer-related PTSD, for example, is characterized by symptoms including intrusions (flashbacks related to treatment), avoidance (denial related to diagnosis), and hyperarousal with triggers embedded in the healthcare experience including follow-up appointments and routine surveillance.[17] Untreated cancer-related PTSD symptoms are associated with oncologic treatment non-adherence.[17] It is unknown if SLE and its treatment induce similar PTSD symptoms. Potential triggering events in SLE care could include physical contact, such as physical exams, and invasive procedures, including hemodialysis, blood draws, arthrocentesis, or biopsies. Given that stress exacerbations are linked to SLE activity, it is important to identify, and potentially ameliorate, triggers related to healthcare delivery.

Here we review the epidemiologic evidence to support a connection between SLE and PTSD and potential biologic mechanisms underlying this connection. This review is intended for both clinicians, including those who diagnose and treat mental health disorders and autoimmune diseases, and investigators of these health conditions.

2. Epidemiologic relationship of PTSD to SLE Risk

The link between PTSD and autoimmune disease has been studied in a variety of cohorts including combat veterans and the general population (Table 1). Early studies tended to consider associations with autoimmune diseases rather than focusing on SLE as a distinct entity. For example, Boscarino et al. demonstrated that PTSD among Vietnam veterans was significantly associated with increased likelihood of having any autoimmune disease (OR = 3.3 [95% CI 2.0-5.7]).[18] Another study which classified autoimmune diseases by T helper (T_h) subtype, found that individuals with adverse childhood experiences score ≥2 were more likely to be hospitalized for a T_h2 rheumatic disease, including SLE (HR= 2.0 [95% CI 1.3-3.2]).[19] Further epidemiologic studies which focused on civilian populations observed statistically significant associations between PTSD and the risk of developing

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SLE. Among women in the Nurses' Health Study II, trauma exposure and high levels of PTSD symptoms were associated with an almost tripled SLE risk (HR 2.94 [95% CI 1.19-7.26]), even after accounting for smoking, body mass index (BMI), alcohol use, SES, and other potential confounders.[7] In a follow-up study among women in the Nurses' Health Study (NHS), childhood physical and emotional abuse was associated with a 2.57 greater risk of SLE (95% CI: 1.30-5.12).[20] Among women in the Black Women's Health Study (BWHS), childhood exposure to either sexual and physical abuse were strongly associated with increased risk of developing SLE as an adult; each had multivariable-adjusted HRs of >2 (unfortunately PTSD measures were not collected in BWHS).[21] Case et al. also found that PTSD among adults enrolled in Medicaid was significantly associated with SLE (ARR = 2 [95% CI 1.64-2.46]).[22]

While these studies demonstrate an intriguing epidemiologic connection between PTSD and SLE, there are several methodologic challenges to consider. First, studies with a shorter follow-up time may not have captured an association between PTSD and SLE if the study ended before the emergence of SLE. This is especially pertinent for SLE since a delay between onset of symptoms and diagnosis is a well-documented phenomenon.[23] While many of the studies excluded participants with an autoimmune condition predating the stress-related diagnosis to control for reverse causation (prodromal-disease causing distress),[7,22,24–26] this does limit our understanding of a possible bidirectional and dynamic relationship between SLE and PTSD.

Another key limitation of these studies is the lack of a diverse study population despite SLE being more prevalent and severe among racial/ethnic minorities.[3] Except for a few recent studies,[21,22] most of these epidemiologic connections were observed among cohorts of largely white individuals and several of the studies were in veteran populations of mainly men. Additionally, the studies may have been affected by SLE's female predominance as studies restricting the sample population to females detected a significant relationship between PTSD and SLE-risk, while studies including male participants had difficulty detecting an association between PTSD and SLE-risk.[25,26] The underlying mechanisms for these gender disparities remain to be further elucidated and it possible that the low prevalence of SLE among men limits the ability to detect associations with PTSD. Finally, since neuropsychiatric symptoms of SLE can present early in the disease course, it is possible that some of these studies conflated comorbid PTSD with neuropsychiatric manifestations of SLE.[27] Despite these methodologic limitations, these epidemiologic studies illuminate important associations between stress-related diseases and immune system dysregulation as evidenced by the onset of SLE. Key strengths of these studies include large aggregate sample size[24] and valid associations after controlling for possible confounders including sociodemographic and biobehavioral factors.[7,20–22]

3. SLE: Shared Risk Factors and Racial/Ethnic Disparities

Strong epidemiologic evidence connects PTSD and risk of SLE as well as other autoimmune diseases, yet gaps in our understanding remain. Social structure or other factors (i.e., biobehavioral, sex, race/ethnicity, individual and area-level socioeconomic factors) may modify risk of developing SLE as sequelae of PTSD.

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Specific biobehavioral factors, such as cigarette smoking, obesity, poor dietary quality, and lack of physical exercise, may serve as a vulnerability for the development of persons with a trauma exposure who later develop SLE. Exposures contribute to SLE risk: current smoking and obesity were strongly associated with SLE risk in the NHS and the BWHS.[6] These risk factors for SLE, are frequently observed in persons with PTSD (Figure 2). For example, PTSD is commonly associated with higher rates of substance use disorders, cigarette smoking, obesity, and physical inactivity.[28] While the mechanisms remain to be fully elucidated, biobehavioral factors may partially mediate the connection between PTSD and increased SLE risk.

In addition to the role of biobehavioral factors, sex and race/ethnicity may also contribute to the epidemiologic link between PTSD and SLE. Women are at twice the risk of PTSD and account for ~90% of SLE cases.[3] As in SLE, there are well-known differences in PTSD risk by sex with women exhibiting twice the risk of PTSD as men, when exposed to similar traumas.[29] PTSD, like SLE, is also more prevalent in US minority racial and ethnic groups; among men and women, positive PTSD screening rates were significantly elevated among Black, multiracial, and Latinx veterans compared with White veterans.[30] Additionally, younger age, being less educated, having lower household income, and being unemployed, have all been associated with increased risk of PTSD, and these are the same groups that are at increased risk of SLE and poor SLE outcomes.[3,9] Black women with SLE are more likely to be diagnosed at younger ages and to have greater disease burden, including a higher prevalence of lupus nephritis and end-stage renal disease, compared to their White counterparts.[3,31] Disadvantaged and minority populations more often face numerous stressors, including physical or sexual abuse, poverty, housing instability, racism, and loss of loved one, which are uncontrollable situations that can overwhelm coping abilities.[32] Social disadvantage, due to race or SES, leads to higher exposure to stressors and traumatic life events and thus risk for developing PTSD. Lifetime prevalence rates of PTSD are higher in urban neighborhoods with a greater poverty burden. For example, The Detroit Neighborhood Health Study found that the prevalence of PTSD among African American residents was 17%.[33] PTSD likely negatively impacts the outcomes of those with SLE who are also overrepresented in socially disadvantaged groups.[32]

Exposure to trauma during childhood is a noteworthy risk factor of both PTSD and SLE. In a prospective study of 480 Dutch military personnel, childhood trauma exposure independently predicted the development of post-deployment PTSD symptoms.[34] In a cohort of largely White women, Feldman et al. found that childhood abuse (physical and emotional) was associated with three times higher risk of SLE during adulthood[20]. Cozier et at. observed similar results: Black women with a childhood exposure to either sexual and physical abuse were strongly associated with increased risk of developing SLE as an adult.[21] Childhood trauma exposure, specifically when temporally correlated with critical maturation periods, may disrupt the development of endocrine and nervous systems, thereby precipitating immune system dysfunction and conferring vulnerability to SLE.[35] Several studies have focused on the impact of childhood trauma-exposure on the development of PTSD and immune system dysregulation. Early life trauma-exposure has not only been associated with increased prevalence and severity of adult onset PTSD,[36] but also pro-inflammatory states even in the absence of PTSD psychopathology.[37]

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Here we review biological mechanisms of immune system dysregulation that may underlie epidemiologic links between PTSD and SLE.

4. Potential Biologic Mechanisms linking PTSD and SLE Risk

Several biological pathways may link PTSD to increased SLE risk with evidence for low-grade systemic inflammation in people affected by PTSD.[16] This PTSD-related pro-inflammatory state is likely related to perturbations in the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, and potential changes to genetic expression.[14]

Under normal circumstances, the body adapts to stress by producing catecholamines, specifically norepinephrine, via the sympathetic nervous system and activating the HPA axis to mobilize fight-or-flight behavior by modulating blood flow, arousal, encoding of memories, and promoting a pro-inflammatory state (Figure 3).[38] At the same time, one end-product of the HPA axis activation, cortisol, is produced to terminate the threat-response via negative feedback mechanisms at upstream sites including the pituitary gland and hypothalamus.[39] These regulatory processes involve coordinated interactions of endocrine, immune, and nervous systems.[40] Since only some of those with trauma exposure develop PTSD[12], the disorder has been conceptualized as the inability to physiologically adapt to stress as a consequence of the “dissociation” or “uncoupling” of the endocrine, immune, and nervous systems, in addition to the re-experiencing of symptoms.[38,40,41]

4.1 Pro-Inflammatory State

PTSD and SLE share similar profiles of immune system dysregulation, and this may in part facilitate the epidemiologic link between the two disorders. Two meta-analyses identified 40 articles investigating patterns of inflammatory markers in PTSD.[42,43] While both analyses observed marked heterogeneity among studies, they also found that when compared to controls, PTSD was associated with indicators of heightened immune activity including C-reactive protein (CRP), white blood cell counts, and circulating pro-inflammatory cytokines including interleukin (IL)-1β, IL-2, IL-6, interferon-γ, and tumor necrosis factor alpha (TNF-α). These pro-inflammatory cytokines upregulate the inflammatory responses via pathways involving nuclear factor kappa B (NF-κB) and corticotropin-releasing hormone stimulation.[44] NF-κB transcriptional pathways promote pro-inflammatory cytokine production, and stimulate B and T cell proliferation, maturation, and differentiation.[45] Excessive NF-κB signaling has been observed in PTSD, with some studies demonstrating greater NF-κB binding activity and upregulation of target genes of NF-κB among individuals of PTSD when compared to controls.[46] This pro-inflammatory state in PTSD is further bolstered by diminished production of anti-inflammatory cytokines including IL-4 and II-10, which are important for the resolution of the inflammatory response by inhibiting pro-inflammatory cytokine production.[47]

Patients with PTSD appear to have skewed immune cell populations further propagating a pro-inflammatory state. For example, excessive cytokine activity in PTSD may skew the balance of T_h cells; however, there does not appear to be a consensus on how to translate alterations in cytokine measurements into a declaration of a T_h1 or T_h2 predominance.[48,49] Studies have demonstrated dysregulated regulatory T cells (Tregs) among PTSD patients and

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both quantitative and qualitative deficiencies.[50,51] For example, Sommershof et al., observed a nearly 50% reduction in proportion of peripheral Tregs among refugees with PTSD when compared to controls.[51] Dysfunctional Tregs have been associated with several autoimmune diseases, including multiple sclerosis, type 1 diabetes, and psoriasis, and may also contribute to the pathophysiology of cardiovascular disease, obesity, and neurodegenerative diseases such as Alzheimer's disease.[52] Finally, immune cell populations of PTSD cohorts are associated with markers of senescence including shorter leukocyte telomere lengths.[48]

Similar patterns of skewed immunological markers and imbalances of T_h cells have been observed in autoimmune diseases including SLE.[53] When compared to healthy controls, individuals with SLE display higher levels of circulating IL-6 and TNF-α, with some studies demonstrating positive correlations between SLE disease activity and IL-6 levels.[53] Insufficient Treg functioning has been implicated in the pathophysiology of SLE as Tregs are responsible for maintaining self-tolerance through the regulation of self-reactive lymphocytes.[54] A recent meta-analysis found a significantly reduced proportion of peripheral Tregs among individuals with SLE when compared to healthy controls.[55] Finally, biomarkers of cellular senescence including telomere shortening have also been observed in SLE, with a meta-analysis observing shorter telomeres in individuals with SLE even after controlling for age, race/ethnicity, and assay type.[56]

However, PTSD as a state of heightened immunity is not a consistent finding throughout the literature with several studies not finding significant differences of inflammatory markers among individuals with PTSD compared to controls. For example, Von Känel et al. observed no significant differences in levels of circulating IL-6 or CRP among individuals with PTSD from accidental trauma when compared to trauma-exposed controls.[47] In a study of all male Croatian combat veterans, Jergovic et al., also observed no differences in CRP levels among men with PTSD compared to healthy controls.[50] In a prospective study of Dutch military personnel, individuals who developed PTSD six months after deployment displayed telomere lengthening, rather than shortening, when compared to combat-exposed controls.[57]

Meta-analyses have observed a large extent of heterogeneity between studies and attributed discrepancies to factors including exposure to psychotropic medications, trauma-exposure among controls, sex co-morbid major depressive disorder, and timing of blood draws.[42,43] Other methodologic considerations include diverse trauma exposures (combat,[58] intimate partner violence,[59] war refugees,[60] violent assault[61]) inconsistent controlling for childhood trauma exposure[61], inconsistent duration of time between trauma exposure and study period, variable cytokine measurements (mitogen-stimulated vs. circulating cytokine[62]), variable NF-κB measurements (binding activity[46] vs. transcription factor expression[63]) and limited prospective studies.

Another methodologic consideration is the lack of consistent exclusion of co-morbid autoimmune disorders. While a few studies of inflammatory markers among individuals with PTSD explicitly excluded participants with autoimmune diseases,[60,61,64,65] two studies included participants with co-morbid autoimmune diseases.[66,67] This limits our ability to appreciate the impact of PTSD on immune system regulation if participants also have an inflammatory condition, such as an autoimmune disease. Furthermore, since most of the

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studies did not follow participants longitudinally, it is unknown if participants with PTSD who displayed markers of a pro-inflammatory state were actually in a prodromal period and later developed an autoimmune disease. A final methodologic consideration is the reliance on peripheral biomarkers as surrogate indicators for immune system activity. In a recent study, Bhatt et al. observed that PTSD severity was positively correlated with CRP levels among individuals with PTSD compared to trauma-exposed controls.[68] However, when measuring markers of neuroinflammation via positron emission tomography (PET) scan, PTSD severity and CRP levels were negatively associated with neuroinflammation. This divergent data further complicates our understanding of the interpterion of peripheral inflammatory biomarkers.

4.2 Autonomic Nervous System Dysregulation and Hypothalamic-Pituitary Axis Dysfunction

Autonomic nervous system signaling among individuals with PTSD patients appears to be dysregulated and studies demonstrate excess sympathetic drive and reduced parasympathetic activity.[69] Heightened sympathetic reactivity is thought to mediate pathognomonic PTSD symptoms including flashbacks and hyperarousal via noradrenergic signaling.[70] Additionally, this exaggerated sympathetic response is hypothesized to maintain a pro-inflammatory state observed in PTSD via complex neural connections between the brain, thymus, spleen, and lymphocytes via adrenergic signaling.[16,44] The binding of norepinephrine to beta-2 adrenergic receptors (β2 adrenoreceptor) on lymphocytes may stimulate the production of pro-inflammatory cytokines via NF-κB signal-transduction pathways.[39,44] Simultaneously, parasympathetic signaling through interactions between the vagus nerve and alpha-7 nicotinic (α7) receptors is thought to counterbalance and restrain the pro-inflammatory response.[71]

Various parameters have been utilized to measure autonomic nervous system functioning, including norepinephrine levels and muscle sympathetic nerve activity as surrogate markers of the sympathetic nervous system, and heart rate variability as a measurement of parasympathetic activity. A recent meta-analysis of 27 studies observed higher concentrations of plasma and urinary norepinephrine among individuals with PTSD when compared to controls.[72] Heart rate variability is an indicator of parasympathetic activity with lower heart rate variability indicating withdrawal of the parasympathetic nervous system.[73] While a meta-analysis of 19 articles found that PTSD was associated with lower heart rate variability at rest,[74] another meta-analysis of eight articles also found lower heart rate variability among individuals with PTSD under stress conditions although this did not reach significance.[75] In a study of post-9/11 veterans, Fonkoue et al. linked PTSD with impaired parasympathetic signaling and biomarkers of inflammation, hypothesizing that dysregulation in autonomic function may facilitate a pro-inflammatory state.[73] In association with higher plasma levels of TNF-α, they observed less heart rate variability among veterans with PTSD compared to veterans without PTSD. While these studies do offer cursory evidence of impaired autonomic signaling in PTSD, key methodologic limitations include diverse study conditions (measurements collected at rest[74] or under stress-conditions[76]), inclusion of subjects on adrenergic modulating medications including prazosin,[73] and relatively small sample sizes including among meta-anlyses.[75]

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In addition to heightened sympathetic nervous system activity and insufficient parasympathetic activity, low-grade inflammation in PTSD may be further perpetuated through HPA axis dysregulation, which is classically characterized as hypocortisolemia and insufficient glucocorticoid signaling.[16,44]

Under normal circumstances, the inflammatory response is dampened by binding of cortisol to glucocorticoid receptors (GR) on lymphocytes to promote apoptosis and inhibit NF-κB pathways to balance cytokine production.[39,44] In addition, cortisol is a key modulator of negative feedback of the HPA axis at various upstream sites including GRs localized to the pituitary gland and hypothalamamus.[39] Low levels of circulating cortisol may promote excessive inflammation due to cortisol's compromised ability to exert its anti-inflammatory properties.[44] A pro-inflammatory state may be further sustained via alterations in GR sensitivity, thereby impacting the anti-inflammatory effects of cortisol as well as HPA axis set-point.[77]

In a recent meta-analysis, Pan et al. found significantly lower morning salivary cortisol levels in PTSD when compared to controls.[78] Of note, this meta-analysis included diverse trauma-exposures, children with PTSD, as well as controls with and without trauma-exposure. Among individual studies, there are discrepancies on whether hypocortisolemia is a hallmark of PTSD. For example, in a study of 71 women, participants with PTSD exhibited lower levels of salivary cortisol when compared to controls with and without trauma exposure.[79] However, in a study of combat veterans, there were no differences in plasma cortisol levels in comparing participants with PTSD and controls.[64]

In addition to hypocortisolemia, PTSD is generally thought to reflect a state of GR hypersensitivity.[44] Various techniques have been utilized to measure GR sensitivity, including concentration of dexamethasone required to suppress lysozyme activity[80] and cytokine production[46,81] as well as immunofluorescence and radioligand binding as proxies for receptor density.[80] While many studies do find evidence of greater GR sensitivity in PTSD, this is not a consistent finding. For example, Yehuda et al. observed that men with PTSD exhibited greater GR sensitivity as interpreted by dexamethasone suppression of lysozyme activity; however, there was no difference in number of cytosolic GR among individuals with PTSD and controls when measured via radioligand binding.[80] In a study of Bosnian war refugees, a lower concentration of dexamethasone was required to suppress IL-6 and TNF-α[81]; however, in a study of women with PTSD from childhood trauma, there was no difference in the concentration of dexamethasone necessary to suppress TNF-α production in whole blood.[46] Some of the methodologic limitations which may contribute to discrepancies in the data include potential gender differences in GR sensitivity[63] and limitations in interpreting GR sensitivity from a diverse set of methods. Another key limitation is the utilization of peripheral biomarkers to infer conclusions about the function of GR on different tissues including lymphocytes and throughout the HPA axis.

Despite these methodologic limitations, there is evidence to suggest autonomic dysregulation and HPA axis dysfunction in PTSD, and it is thought perturbations in these biological pathways sustain a pro-inflammatory state.[38,82] Yehuda uses the term "dissociated" to describe the phenomenon of exaggerated sympathetic activity with

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dysregulated HPA axis in PTSD.[82] In fact, similar language has been utilized to describe the relationship between the HPA axis and autonomic nervous system in SLE. For example, both Jung et al.[83] and Härle et al.[84] conclude that there is an "uncoupling" of the sympathetic nervous system and HPA axis in SLE as inferred by markers of heightened sympathetic activity and insufficient cortisol. Similar to PTSD, this "uncoupling" is thought to contribute to unrestrained inflammation, central to the pathophysiology of SLE. It is noteworthy to recognize both studies utilize diverse methodologies, including salivary alpha-amylase and neuropeptide Y as surrogates for sympathetic nervous system activity. Additionally, these SLE studies did not universally control for psychiatric illness, including PTSD. Nevertheless, there is evidence to suggest similar neuroendocrine dysfunction in both PTSD and SLE.

Interestingly, there is also evidence that within PTSD populations low-grade inflammation and HPA dysfunction may exist prior to trauma exposure. For example, a machine learning study found that pre-deployment CRP levels predicted PTSD risk among soldiers deployed to Afghanistan.[85] In a study of Dutch military personnel, post-deployment PTSD symptoms were associated with a greater number of GR in peripheral blood mononuclear cells measured prior to combat.[34] And finally, lower heart rate variability measured pre-deployment was associated with an increased odds of being diagnosed with PTSD post-deployment among US marines deployed to Iraq or Afghanistan.[86] While it remains unknown how neuroendocrine and immune systems are further impacted by the development of PTSD, these studies do provide preliminary evidence of potential biological risk factors for PTSD and contribute to our understanding of the biological mechanism underpinning low-grade inflammation in PTSD. However, due to limited study follow-up time and inconsistent controlling for autoimmune diseases, it is difficult to solely attribute these markers to PTSD-risk. It is also plausible that these biomarkers may also mark a vulnerability for inflammatory conditions including SLE, and that this risk may be further amplified following the development of PTSD.

4.3 Genetic and Epigenetic Mechanisms

The connection between PTSD and heightened inflammation may be through genetic polymorphisms and epigenetic modifications.

A recent meta-analysis of PTSD genome-wide association studies (GWAS) which included over 200,000 participants identified several genome-wide specific risk loci— including one locus with substantial immunogenic properties.[87] The risk locus, rs142174523, is located on human leukocyte antigen *(HLA)B* and is also thought to regulate the expression of genes related to the complement system, *C4A and C4B*.[87] A recent meta-analysis observed associations between *C4B* copy number variations and SLE susceptibility.[88] While potential polymorphisms related to inflammation may underlie the epidemiologic associations between PTSD and increased SLE risk, many gaps remain in our understanding. For example, although analysis of SLE GWAS studies have identified over 100 risk loci, corroborating their significance and risk in the pathophysiology of SLE is challenging.[89] Langefeld et al. proposes a "cumulative hit hypothesis" to describe the complicated and non-linear relationship between individuals risk variants and SLE.[90] These challenges in

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attributing genetic load to SLE-risk, further complicate our ability to understand shared genetic risk between SLE and PTSD.

Epigenetic modifications, resulting from PTSD and trauma-exposure, may be an additional mechanism connecting PTSD, inflammation, and SLE. A recent epigenome-wide association study (EWAS) which included over 1,800 participants with diverse trauma exposures, identified distinct DNA methylation patterns associated with PTSD when compared to trauma-exposed controls.[91] These PTSD-specific epigenetic modifications localized to aryl-hydrocarbon receptor repressor (*AHRR*) which is thought to play a key role in immune system regulation via the kynurenine pathway. More specifically, this pathway may be important for the maintenance of self-tolerance through the regulation of Tregs.[92] Interestingly, mice with aryl-hydrocarbon receptor deficiencies develop features of systemic autoimmunity that are thought to resemble SLE.[93] These data raise the possibility that PTSD may be associated with increased SLE risk through epigenetic modifications, leading to the loss of self-tolerance. However, a major limitation to these studies is the utilization of blood samples, rather than brain tissue, to understand epigenetic patterns unique to PTSD.

4.4: Brain-Gut Axis and Dysbiosis

Disruptions to the gut microbiome, dysbiosis, may be another mechanism that contributes to the heightened inflammation and HPA axis dysfunction observed in PTSD.[94] Animal models demonstrate that gut microbiota are integral to the development and function of the HPA axis as germ-free mice have exaggerated HPA axis activity and these alterations are corrected upon microbial colonization.[95] Additionally, gut microbiota modulate the inflammatory response through a myriad of mechanisms including the regulation of Treg differentiation and monocyte stimulation.[94]

Microbiome shifts have been implicated in the pathogenesis of SLE. Potential mechanisms connecting aberrant immune system activity to dysbiosis include the translocation of gut microbes via gut barrier disruption, molecular mimicry with gut microbiota, and irregular tryptophan metabolism leading to Treg dysfunction through the kynurenine pathway.[96] In a recent meta-analysis, Xiang et al. found restricted microbial diversity among patients with SLE when compared to health controls.[97]

Compared to SLE, less is known about the relationship between dysbiosis and PTSD. While human studies demonstrate a relationship between PTSD and dysbiosis, the results are limited.[98,99] For example, in a study of all male veterans with cirrhosis, participants with PTSD had a reduced microbial diversity (calculated with the Shannon-Wiener diversity index) even after controlling for alcohol intake and psychotropic medications.[98] Interestingly microbiota taxonomic patterns observed in this study are similar with those observed in SLE: decreased abundance of *Ruminococcaceae* and increased abundance of *Enterococcacea*.[97] However, in a study of South African residents, no differences in microbial diversity were observed between participants with PTSD and trauma-exposed controls.[99]

While these studies suggest that disruptions to the microbiome may be another mechanism facilitating heightened inflammation observed in PTSD, there are several limitations to these

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studies including inconsistent surrogate markers for microbial diversity (fecal microbial sequencing, fecal metabolite identification, serum metabolite identification), small sample sizes, and inconsistent controlling for biobehavioral factors. Nevertheless, these preliminary studies illuminate novel biological mechanisms which may underlie the epidemiological connection of PTSD with SLE.

5. Conclusion:

SLE is a complex and enigmatic autoimmune disease. Identifying the factors associated with its development, the populations most at risk, and risk factors for poor outcomes are crucial to prevention and improving outcomes. Epidemiologic studies have identified traumatic experiences, including adverse childhood experiences, and PTSD as strongly related to autoimmune disease risk. Although the biological mechanisms connecting PTSD with autoimmune diseases remain to be fully elucidated, these pathways are likely magnified in SLE due to the population at risk and the confluence of multiple potential psychological and biological mechanisms. PTSD may be responsible for some of the striking disparities seen in SLE incidence and outcomes given its prevalence among women and disadvantaged and minority individuals who are exposed to higher levels of trauma, abuse, and environmental stress. Moreover, it is highly likely that an increased prevalence of PTSD among patients living with SLE has a significant deleterious effect on both clinical outcomes and patient-reported quality of life. PTSD is a potentially modifiable factor that may explain some of the extreme and unexplained disparities in SLE incidence and poor outcomes.

We suggest future studies shift from peripheral blood markers of inflammation to neuroscience-based methodologies as blood samples may not be reliable proxies for neuroinflammation. Examples include further neuroimaging or utilization of brain tissue studies as demonstrated by Bhatt et al.[68] Additional longitudinal studies are needed to explore the potential role of treatment of PTSD on SLE-risk. Future prospective epidemiologic studies should have longer follow-up times and include large populations of women and men from diverse racial/ethnic backgrounds, as the relative rarity of both SLE and PTSD in male populations has posed challenges for past studies. As suggested by Koenen et al., mendelian randomization studies would be helpful to better characterize shared genetic risk between PTSD and SLE.[100] Because PTSD is a heterogeneous disorder, Koenen et al. also call for understanding and classifying PTSD by symptom clusters. Further studies characterizing the phenomenological presentations of PTSD unique to individuals with SLE would help our ability to be more precise in studying the link between these two diseases. Many important gaps in our understanding of this relationship exist and impede the best care we can offer our patients to improve their quality of life.

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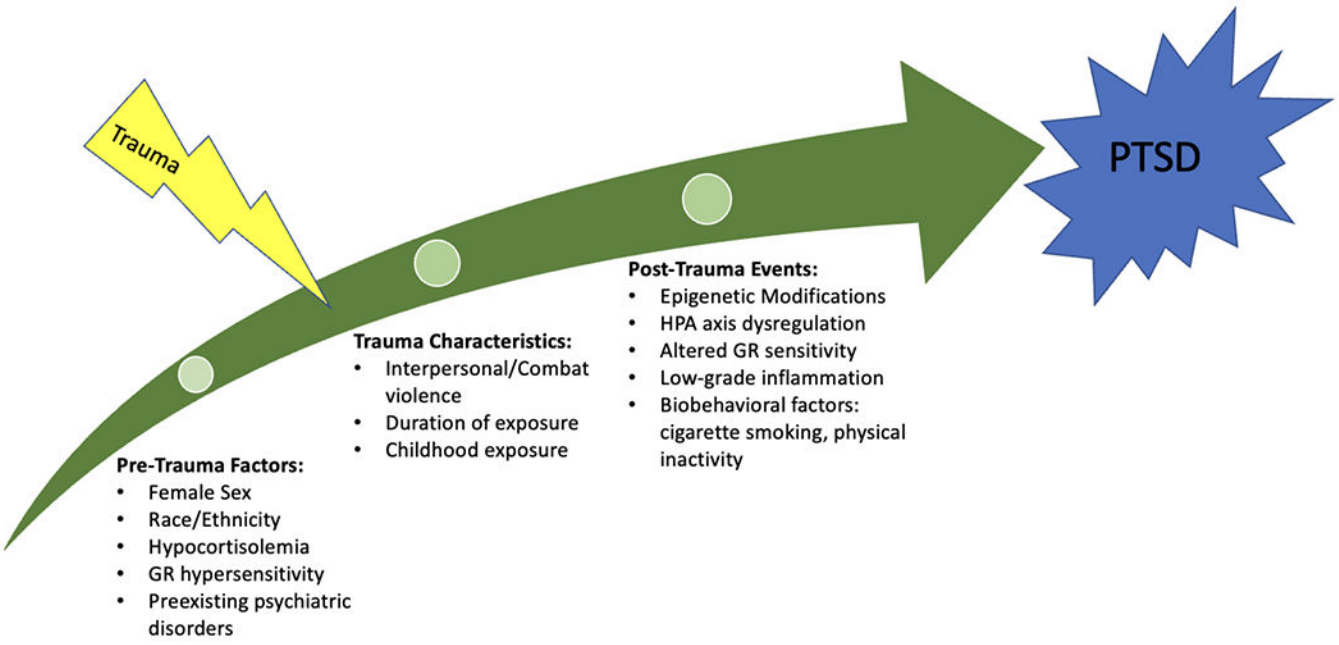

Figure 1.

Only some people exposed to trauma develop PTSD. Below are factors pre- and post-trauma exposure which contribute to risk of PTSD pathology. An individual's subset of vulnerability factors may contribute to a unique PTSD trajectory and may help explain the heterogeneous presentations of PTSD.

Abbreviations: GR (glucocorticoid receptor); hypothalamic-pituitary-adrenal (HPA) axis

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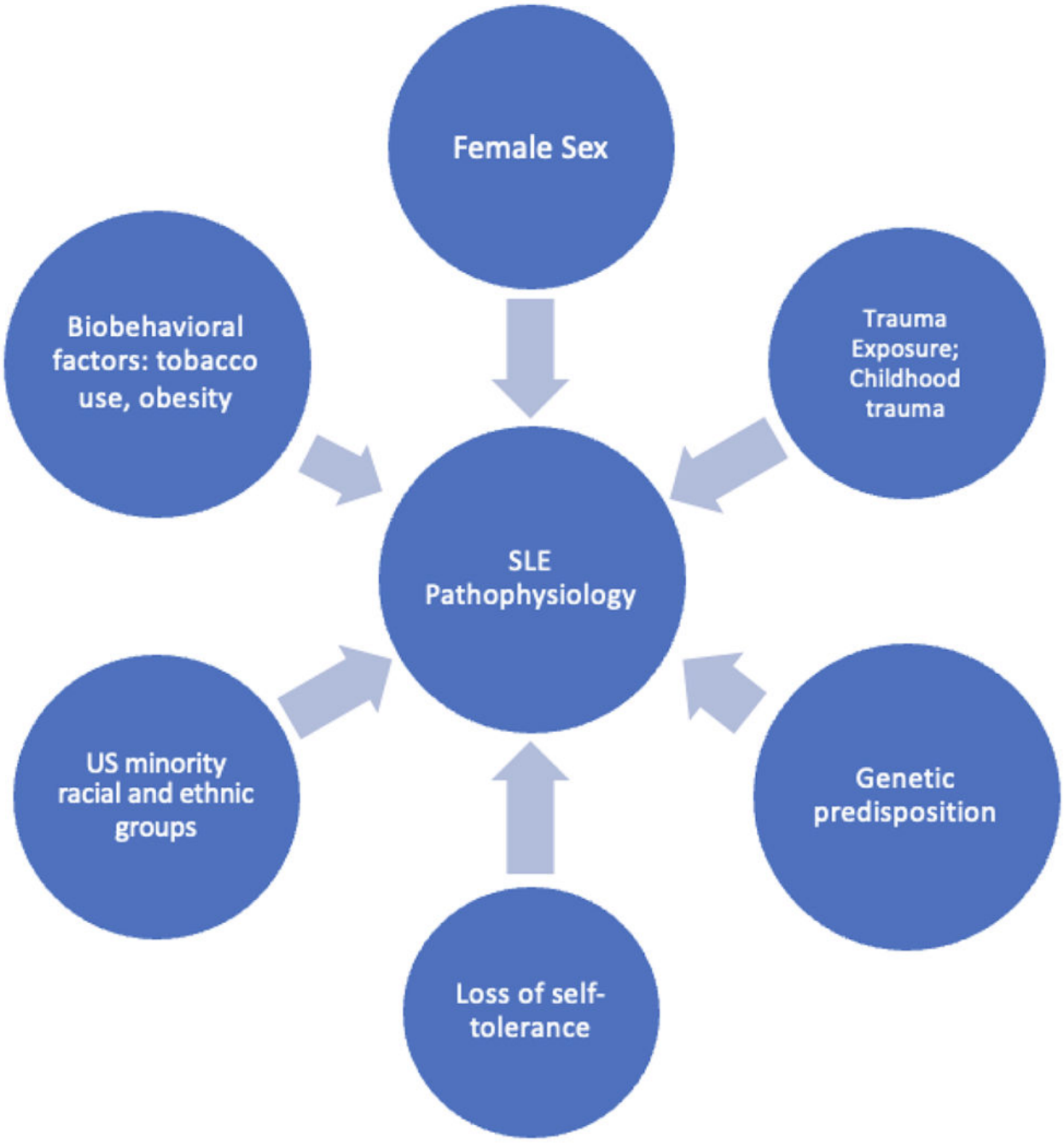

Figure 2.
Genetic, environmental, and biological factors contribute to SLE risk and pathophysiology. Many of these characteristics are also found among individuals with PTSD.

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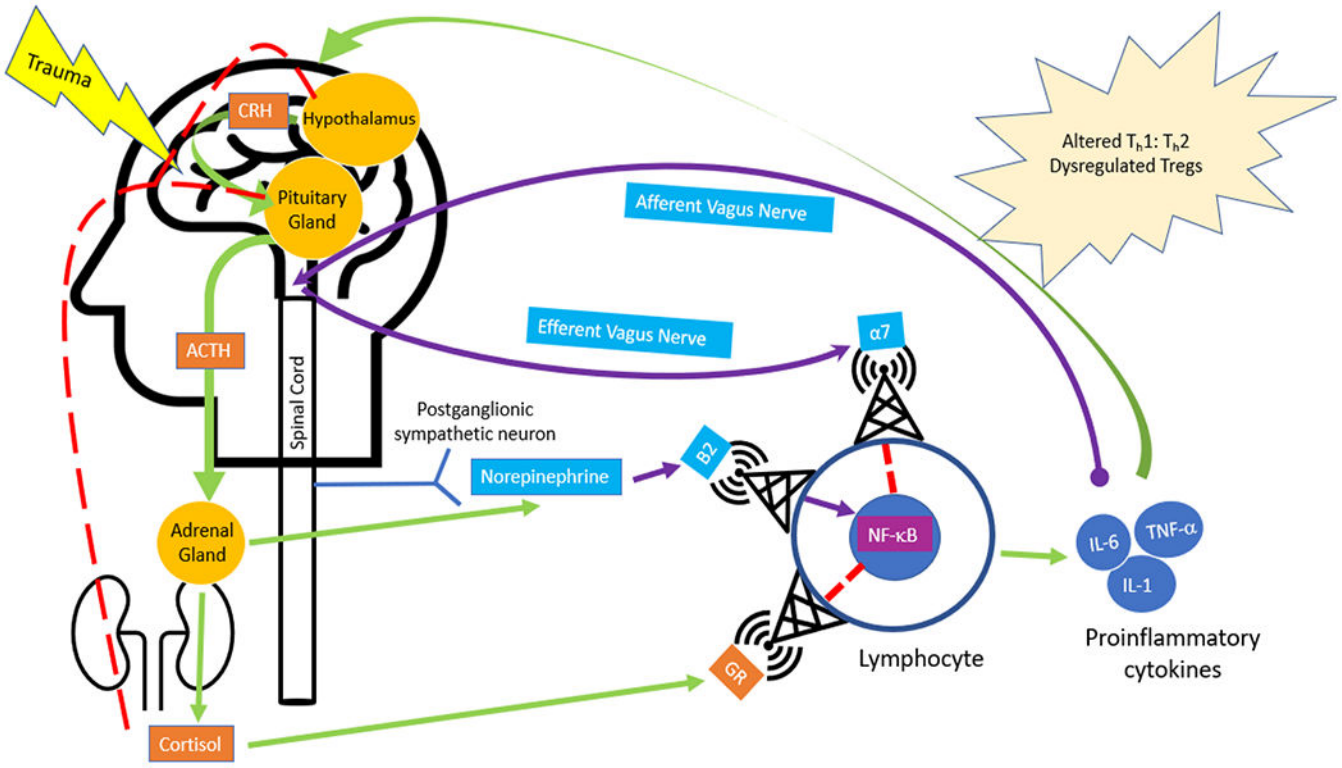

Figure 3.

Following exposure to stress, the HPA axis and sympathetic nervous system are activated to mobilize fight-or-flight behavior which results in increased production of pro-inflammatory cytokines via NF-κb pathways. At the same time, cortisol is produced to terminate the threat-response via negative feedback mechanisms at various sites including the pituitary gland, hypothalamus, and lymphocytes. Inflammation is thought to be sustained in PTSD due to disruptions in these pathways. Specifically, altered GR signaling, hypocortisolemia, heightened sympathetic nervous system activity, and insufficient parasympathetic activity are thought to contribute to excessive inflammation and skewed immune system balance. Abbreviations: CRH (Corticotropin-releasing hormone); ACTH (Adrenocorticotropic hormone); GR (glucocorticoid receptor); β2 (beta-2 adrenergic receptor); α7 (alpha-7 nicotinic receptor); IL (Interleukin); NF-κB (nuclear factor kappa B); Treg (regulatory T cells); T_h (T helper cells)

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Table 1.

Epidemiologic studies exploring the relationship between PTSD to SLE Risk

Author, year	Ref.	Study population	Sample (n); Male (%)	Design	Significant clinical findings
Boscarino, 2004	[18]	Vietnam Experience Study Participants	2,490 (100%)	Case control	Among Vietnam veterans with PTSD, the adjusted odds ratio for an autoimmune disease was 3.3 (95% CI 2.0-5.7).
Dube, 2009	[19]	Adverse Childhood Experiences Study	15,357 (46%)	Retrospective cohort	Women with an ACE score ≥2 were at an elevated risk of being hospitalized with an autoimmune disease (HR = 2.1, 95% CI: 1.4-3.2). An ACE score ≥2 among men and women was associated with an increased risk of being hospitalized for a T_h2 rheumatic disease, including SLE (HR = 2.0, 95% CI: 1.3-3.2).
O'Donovan, 2015	[25]	US veterans previously deployed to Iraq or Afghanistan	666,269 (89%)	Retrospective Cohort	Veterans with PTSD had a significantly higher relative risk of an autoimmune disease (ARR = 2, 95% CI: 1.91-2.09). Risk of SLE was not statistically significant (HR 1.18, 95% CI 0.85-1.51).
Roberts, 2017	[7]	Female nurses enrolled in the Nurses' Health Study II	50,242 (0%)	Prospective cohort	Trauma exposure and PTSD were associated with an almost tripled SLE risk (HR = 2.94, 95% CI: 1.19-7.26).
Feldman, 2019	[20]	Female nurses enrolled in the Nurses' Health Study II	67,516 (0%)	Prospective cohort	Childhood physical and emotional abuse was associated with a 2.57 greater risk of SLE (95% CI: 1.30-5.12). The largest percentage of the association (23% p<0.0001) was explained by PTSD.
Bookwalter, 2020	[26]	Active-duty U.S. military personnel	120,572 (71%)	Prospective cohort	Among those with PTSD, there was a 58% higher risk of an autoimmune disease. (HR = 1.58, 95% CI: 1.25-2.01). Risk of SLE was not statistically significant (HR = 1.4, 95% CI 0.7-2.8).
Cozier, 2020	[21]	Black Women's Health Study	36,152 (0%)	Prospective cohort	Exposure to severe sexual abuse and severe physical abuse was associated with an increased SLE risk (HR = 2.51, 95% CI: 1.29-4.85), and (HR = 2.37 95% CI: 1.13-4.99).
Case, 2021	[22]	Adults enrolled in Medicaid	120,362 (6%)	Case-control	Among participants with PTSD, the adjusted odds ratio for SLE was 2 (95% CI 1.64-2.46).