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Review

Gastrointestinal Dysfunction after Traumatic Brain Injury: Mechanisms Linking The Gut, Inflammation, and The HPA Axis

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Abstract. Traumatic brain injury (TBI) is a major global health problem that often leads to systemic complications beyond neurological damage, notably gastrointestinal (GI) dysfunction. The mechanisms linking TBI to GI complications remain inconclusive. We conducted a systematic review using current clinical evidence on the pathophysiological processes underlying post-TBI GI dysfunction, focusing on two principal mechanisms: inflammatory-oxidative processes and hypothalamic–pituitary–adrenal (HPA) axis alterations. A comprehensive search was conducted through PubMed, Cochrane Library, and Scopus to identify eligible studies. Evidence indicates that surges of proinflammatory mediators and chemokines, along with reduced anti-inflammatory mediators, drive systemic immune imbalance. Moreover, iNOS upregulation and gut microbiota dysbiosis contribute to mucosal injury. Concurrently, HPA axis dysregulation exerts a bidirectional impact. Elevated ACTH and cortisol reflect an intact stress response that may stabilise metabolism if combined with early enteral nutrition, whereas critical illness-related corticosteroid insufficiency (CIRCI) and hypergastrinemia are strongly associated with gastrointestinal bleeding and mortality. Together, these findings underscore the synergistic role of inflammatory and endocrine disturbances in driving gastrointestinal vulnerability after TBI. Understanding these mechanisms is crucial for developing biomarker-based monitoring and targeted interventions to improve prognosis and reduce GI-related complications in TBI patients.

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1. Introduction

1.1. Traumatic Brain Injury

Traumatic Brain Injury is a major health problem that affects not only the health of individuals but also the health of society as a whole [1]. In 2021, there were 20.84 million new TBI cases reported worldwide and 37.93 million people living with TBI, resulting in 5.48 million years lived with disability (YLDs) [2]. Traumatic brain injury refers to damage to the brain that happens as a result of an external force and/or penetrating forces that lead to structural damage and/or impairment of brain function [3]. Neuronal tissue damage caused by TBI can be categorized into two types.

The first, known as primary injury, occurs immediately due to the mechanical forces exerted during the initial impact. The second, called secondary injury, involves further damage to tissues and cells that develops in the period following the initial trauma [4]. Primary brain injury leads to mechanical deformation of brain tissue, disruption of blood circulation, imbalances in osmotic pressure, activation of inflammatory cells, and ultimately, cell death [5]. Clinical manifestations of primary injury include intracranial hematomas, skull fractures, coup and contrecoup contusions, lacerations, penetrating wounds, or diffuse axonal injuries [6].

A primary injury triggers a series of pathological processes that impact distant areas of the brain that were initially unaffected. This leads to what is known as secondary injury, which describes the further damage occurring after the initial trauma in traumatic brain injury. Secondary injury encompasses a complex cascade of processes that intensify the initial damage, leading to further neurological dysfunction and tissue loss. Critical contributors following TBI include brain edema, inflammation, oxidative stress, and metabolic disturbances, all of which aggravate tissue damage and cognitive impairment [5].

TBI leads to the breakdown of the blood-brain barrier (BBB), resulting in the excessive release of neurotransmitters and disrupting the normal function of glutamate transporters responsible for glutamate reuptake. Glutamate and its metabolites then bind to and activate both ionotropic and metabotropic glutamate receptors [5]. Glutamate binding to its receptors will cause sodium (Na^+) and calcium (Ca^{2+}) influx. Ca^{2+} influx occurs especially through NMDA receptors, while AMPA receptors likely contribute less to this Ca^{2+} influx into neurons after an injury compared to NMDA receptors, as AMPA channels are primarily permeable to sodium [7]. When the balance of ions is disturbed, especially if the Na^+/K^+ pump stops working properly, sodium and water start to build up inside cells. This leads to cytotoxic edema, characterized by cellular swelling and disruption of normal function." Energy production within the cells also suffers. If untreated, this condition may cause irreversible cellular damage and result in neurological problems [5].

Excessive influx of Ca^{2+} will accumulate in the mitochondria, which responds by generating ROS. Ca^{2+} stimulates nitric oxide synthase (NOS), which in turn enhances the production of nitric oxide (NO) that promotes oxygen-derived reactive species capable of impairing the cell membrane. The excess of intracellular Ca^{2+} also activates calpain enzymes, while increased ROS levels exert damage on DNA, lipids, and proteins. Additionally, elevated Ca^{2+} impairs ATP production and induces the release of cytochrome c into the cytoplasm. This event activates the Apoptotic Protease-Activating Factor 1 (APAF1)/caspase 9 complex, subsequently triggering caspase 3, which causes apoptosis through DNA fragmentation [5], [8]. Together, these processes form a self-perpetuating cycle that continuously raises intracranial pressure (ICP) and worsens brain damage [9]. An increase in ICP lowers cerebral perfusion pressure (CPP), which is the leading cause of cerebral ischemia. This

ischemia then results in cerebral hypoxia and is also known to provoke secondary brain injury [10]. The pathophysiology of TBI is shown in Figure 1.

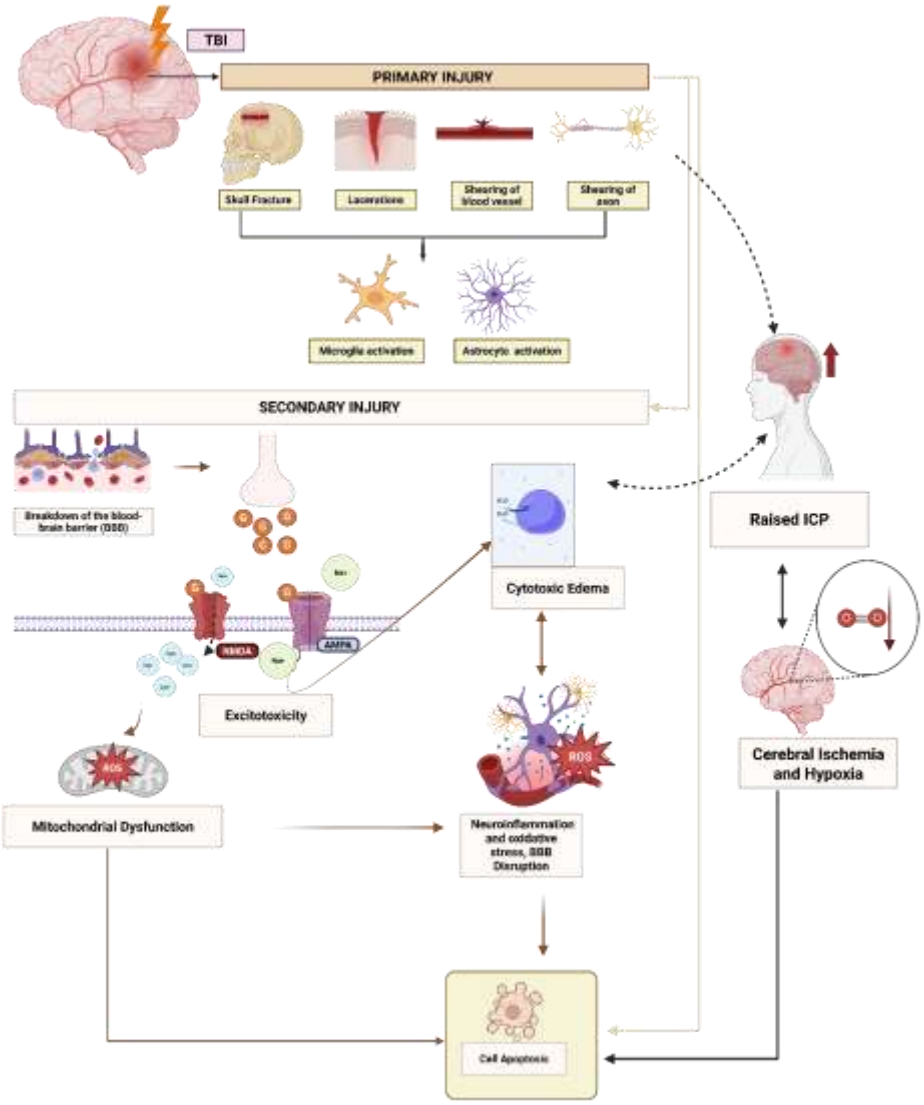

Figure 1. Traumatic Brain Injury pathophysiology
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1.2. Gastrointestinal Dysfunction in TBI

The complications that arise from TBI are not exclusively confined to the brain. The systemic inflammation that occurs has an impact on other body systems, such as GI tract, cardiovascular, and respiratory system [11]. Clinical evidence indicates that gastrointestinal dysfunction is a frequent complication in TBI patients. Approximately half of patients with severe TBI experience enteral feeding intolerance and impaired gastrointestinal motility within the first week after injury, with constipation or delayed defecation reported in up to 52% of cases, which is correlated with prolonged ICU stay. During the rehabilitation phase, as many as 70% of patients with acquired brain injury exhibit fecal incontinence [12].

In pediatric patients, Zhou et al. reported that 78.8% presented with GI dysfunction on the first day of admission, and 48.5% developed stress ulcers. Higher gastrointestinal failure (GIF) scores were inversely correlated with Glasgow Coma Scale (GCS) scores, with elevated scores predicting increased ICU mortality [13].

In addition, gastrointestinal bleeding (GIB) is also a notable complication in TBI. Traumatic brain injury increases the susceptibility of patients to gastrointestinal bleeding, which often arises as a complication of gastroduodenal ulcers. Gastrointestinal bleeding following brain injury is associated with severe TBI, intra-axial lesions, hypotension, and coagulopathies. These patients demonstrate lower GCS scores and serum hemoglobin levels, particularly in those with a GCS score below 9 [14], [15]. Traumatic brain injury can impair gastrointestinal function through multiple mechanisms, including neural, hormonal, and immune pathways that together form the brain–gut axis [12], [16-17].

1.3. Literature Gap

Gastrointestinal dysfunction after TBI is linked to three mechanisms. Those are inflammatory-oxidative processes, HPA-axis alterations, and autonomic disruption. However, clinical research has focused on inflammatory-oxidative processes and alterations in the HPA axis. The two mechanisms have been most frequently studied through biomarkers such as cytokines and hormones like cortisol, providing insight into the cellular processes underlying gastrointestinal dysfunction. While previous studies report hormonal and cytokine changes, results are inconsistent and the contribution of each pathway remains unclear. This systematic review integrates clinical evidence on inflammatory-oxidative pathways, and HPA-axis alterations in TBI-related gastrointestinal dysfunction. By synthesizing these findings, this review highlights important mechanisms and potential biomarkers relevant for risk assessment and therapeutic strategies.

2. Method

This systematic review was conducted in accordance with the Population, Intervention/Exposure, Comparison, and Outcome (PICO) framework. The population included adult and pediatric patients with TBI, regardless of severity (mild, moderate, or severe) and phase (acute or chronic). The intervention or exposure of interest was gastrointestinal complications after TBI, such as stress ulcer, gastrointestinal bleeding, motility disorders, dysbiosis, or nutritional intolerance. Comparisons included patients without TBI, TBI patients without gastrointestinal complications, or subgroups stratified by severity or clinical presentation.

The primary outcomes were inflammatory or immune markers and/or HPA axis hormones. Eligible study designs comprised observational studies (cohort, case–control, cross-sectional), randomized controlled trials (RCTs), and mixed-method studies reporting relevant laboratory outcomes. Studies were excluded if they involved non-traumatic neurological conditions, reported only clinical symptoms or functional outcomes without laboratory or hormonal data, or were animal studies, preclinical studies, case reports, or review articles. We include studies published between January 2000 and January 2025 in English or Indonesian. To ensure validity, only studies meeting the eligibility criteria outlined in Table 1 were included.

A systematic literature search was performed through PubMed, Cochrane Library, and Scopus. The search combined Medical Subject Headings (MeSH) and free-text keywords related to traumatic brain injury, gastrointestinal complications, and inflammatory or hormonal outcomes, using Boolean operators to refine the strategy. The study selection process is summarized in the PRISMA flow diagram (Figure 2)

Table 1. PICO table to conduct research question

PICO	Criteria
Populations	Patients with TBI (all severities, adults & children)
Intervention/ Exposure	Gastrointestinal complications or gastrointestinal-related interventions
Comparisons	Patients without TBI, or TBI patients without gastrointestinal complications/interventions
Outcome	Inflammatory markers level and HPA axis hormones level, clinical outcomes associated with gastrointestinal dysfunction

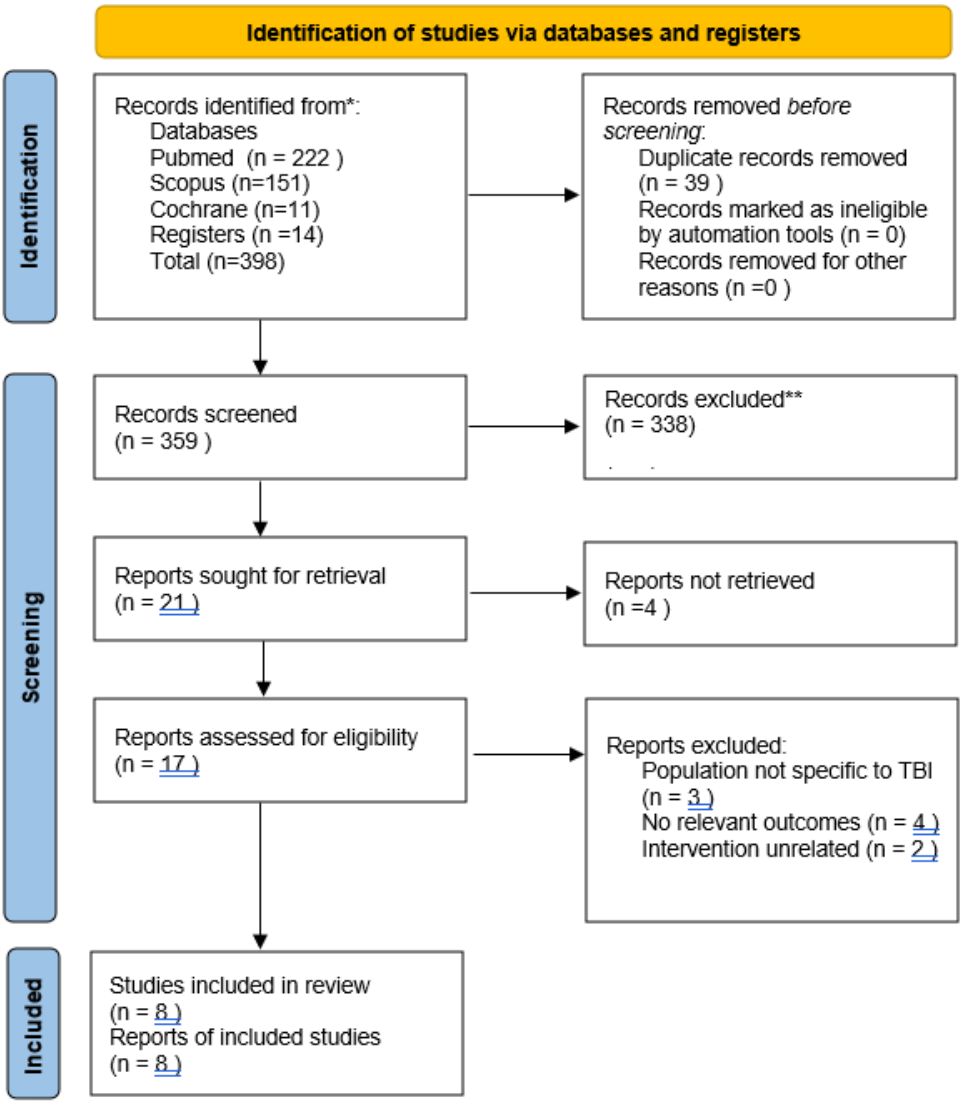

Figure 2. Study selection diagram flow

3. Results and Discussion

3.1 Risk of BIAS of Included Studies

Risk of bias was assessed separately according to study design. For Randomized Controlled Trials (RCTs), the Cochrane Risk of Bias 2.0 tool (RoB-2) was applied, while for observational studies, the Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E) tool was used. Figure 3 presents the RoB-2 assessment for the three RCTs and Figure 4 summarizes the ROBINS-E assessment for the five observational studies. In RoB-2 assessment for RCTs, the overall judgment was "some concerns," primarily due to incomplete reporting of the randomization process, lack of allocation concealment, and absence of blinding of participants and outcome assessors. Nevertheless, attrition was low, and most outcomes were objective laboratory or clinical measures, lowering the likelihood of outcome measurement bias. Results for RoB-2 assessment are summarised in Figure 3.

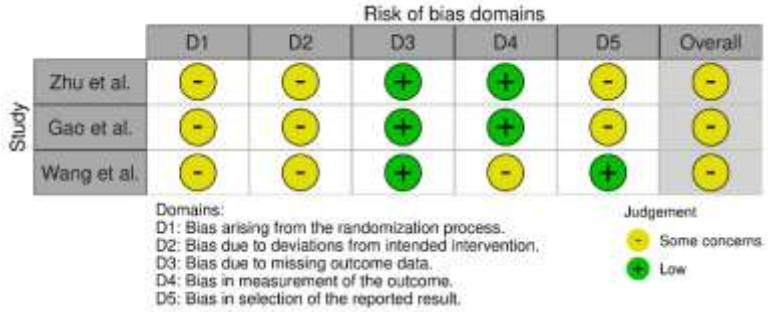

Figure 3. RoB-2 assessment for the three RCTs

In ROBINS-E assessment for observational studies, three studies were assessed to have a high risk of bias, primarily due to confounding (D1) and measurement of exposure (D2). These domains consistently demonstrated serious limitations across these studies, which significantly compromised the reliability of their findings. The fourth study was rated as having some concerns, with potential issues noted in confounding (D1), participant selection (D3), and reported results (D7), though other domains were rated as low risk. The fifth study was assessed as having the lowest overall risk, judged as "some concerns" mainly due to confounding (D1) and reporting bias (D7), but with low risk across most other domains. In summary, while most studies demonstrated acceptable quality in terms of missing data (D5), outcome measurement (D6), and post-exposure interventions (D4), the persistent high risk in confounding and exposure measurement indicates that results from these studies should be interpreted with caution. Results for ROBINS-E assessment is summarised in Figure 4.

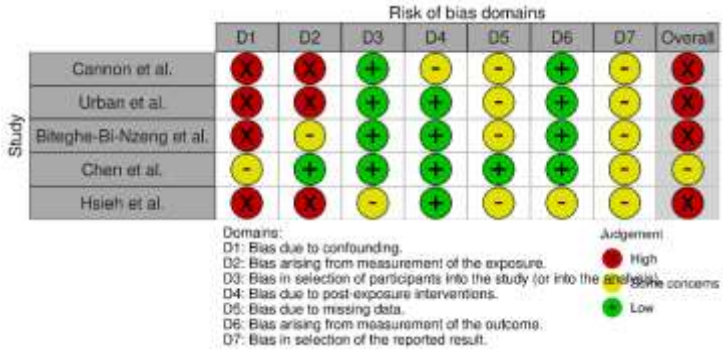

Figure 4. ROBINS-E assessment for the five observational studies

3.2 Mechanism of Gastrointestinal Dysfunction in Traumatic Brain Injury

3.2.1 Inflammatory Immune Responses and Oxidative Stress

Mechanical shear stress during TBI damages cell membranes and vessels, releasing intracellular components that act as damage-associated molecular patterns (DAMPs). These are recognized by pattern recognition receptors (PRRs), activating immune responses.[18] Those processes promote a surge in pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), IL-6, IL-17, tumor necrosis factor-alpha (TNF-α), and IFN-γ and chemokines such as MCP-1, MIP-2, and CCL5, alongside reduced anti-inflammatory mediators, including IL-4, IL-10, IL-13, and TGF-β1. This imbalance shapes microglial activation, shifting between pro-inflammatory (M1) and reparative (M2) states, with mixed phenotypes possible over time. Injury severity, age, sex and comorbidities are factors that further influence patient outcomes. Moreover, blood-brain barrier (BBB) disruption allows peripheral immune infiltration and fibrinogen deposition, activating TGF-β pathways that sustain chronic neuroinflammation [19-20].

The inflammatory response triggered by trauma plays a significant role in traumatic brain injury. The secondary injury results in biochemical alterations in both nearby and remote tissues. The injury induces neuroinflammation not only within the brain but also triggers a systemic inflammatory response throughout the body [21]. Signalling molecules released from damaged brain tissue enter the circulatory system, triggering widespread inflammation in organs outside the central nervous system. This encompasses effects on the gastrointestinal, cardiovascular, pulmonary, renal, and endocrine systems [11]. Digestive disorders following TBI can result in associated symptoms, including gastrointestinal bleeding, gastroesophageal reflux, and reduced intestinal motility [16].

Clinical evidence observed in our study by Cannon et al. demonstrated that patients with acute TBI exhibit both immune dysregulation and gut microbiota alterations. The elevation of IFN-γ and MCP-1, along with trends toward increased IL-6 and IL-8, reflect activation of systemic pro-inflammatory pathways. Reduced IL-4 in contrast suggests impaired anti-inflammatory regulation, further highlighting a cytokine imbalance following TBI.[20] These findings are consistent with evidence demonstrating that TBI inducing widespread release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [22-23].

In parallel, gut microbiota analysis revealed dysbiosis, characterized by increased *Bilophila wadsworthia*. *B. wadsworthia* has been linked to impaired gut integrity, characterized by increased intestinal permeability and infiltration of hepatic macrophages [24]. The study also found reduced *Lactobacillus* in TBI patients, which normally contributes to intestinal barrier protection. *Lactobacillus species* help regulate immune activity in the gut, lowering pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α while enhancing anti-inflammatory mediators such as IL-10. Through this mechanism, they protect the intestinal barrier from inflammation-related injury [25–27].

The finding aligned with the preclinical data that TBI leads to gut microbiota dysbiosis, marked by alterations in both the composition and diversity of intestinal bacteria. The imbalance is linked to gastrointestinal disturbances and inflammatory responses [20], [28-29]. Another study by Zhu et al. provides compelling evidence that individualized enteral nutrition (EN) improves systemic and intestinal manifestations in patients with severe TBI. Compared with conventional EN, individualized EN was associated with a significant reduction in pro-inflammatory mediators such as TNF-α, CRP, and IL-6, alongside enhanced immunoglobulin levels including IgG, IgA, and IgM. This indicates that personalised nutritional support may both suppress hyperinflammation and restore immune competence in TBI patients. In addition, lowered level of Intestinal fatty acid-binding protein (I-FABP) and D-lactic acid, markers of enterocyte injury and bacterial translocation, show that individualized EN preserved intestinal barrier integrity. Elevated I-FABP is a sensitive indicator of intestinal damage and permeability [30-31].

Gao et al. demonstrated that the combination of early EN and anti-infection treatment reduced systemic inflammation and improved immune–nutritional profiles in patients with severe TBI. Traumatic brain injury group with early EN exhibited lower levels of TNF-α and IL-6 compared with TBI group with only routine care, this is consistent with the suppression of the systemic inflammatory response. Furthermore, improvements in CD4+ T-cell counts and CD4+/CD8+ ratios highlight restoration of cellular immunity [32-33].

In addition, enhanced nutritional markers such as albumin, transferrin, and total protein suggest better metabolic support. Albumin is a negative acute-phase protein, whose concentration decreases during inflammation and tissue injury. Clinically, this decline is often used as an indicator of nutritional status and systemic inflammation in patients with gastrointestinal diseases [34-35]. Transferrin, beyond its role in iron transport, is also involved in immune regulation and gastrointestinal inflammation. For instance, in inflammatory bowel disease (IBD), altered transferrin levels and saturation reflect the effects of chronic inflammation and iron deficiency [36].

Urban et al. extended the evidence for the effects of TBI that may contribute to GI dysfunction after TBI. The study demonstrated long-term alterations in microbiota composition and associated metabolic changes. Chronic TBI patients exhibited reduced *Prevotella* and *Bacteroides*. *Prevotella* represents a prominent genus within the gastrointestinal microbiota, playing a crucial role in nutrient metabolism. *Prevotella* demonstrates enhanced growth in response to dietary carbohydrates, particularly isomalto-oligosaccharides (IMO) and inulin [37]. *Bacteroides* are highly prevalent in the gut and contribute to intestinal homeostasis through short-chain fatty acid production and participation in bile acid metabolism [38]. The study also found an increase in Ruminococcaceae and Firmicutes, taxa that often associated with dysbiosis and impaired metabolic homeostasis. Ruminococcaceae are key contributors to Short-Chain Fatty Acids (SCFA) metabolism, and their depletion has been linked to gastrointestinal disorders. In IBD, reduced levels of Ruminococcaceae and other SCFA-producing bacteria are associated with heightened inflammation and greater disease severity [39–41].

Firmicutes, particularly genera such as *Lactobacillus* and *Clostridium*, are key in fermenting dietary fibers into SCFAs including acetate, propionate, and butyrate that promote gut health by maintaining barrier integrity and regulating immune responses [42-43]. The metabolic consequences of this dysbiosis were reflected in reduced postprandial amino acid levels, particularly tryptophan, a precursor of serotonin and kynurenine pathway metabolites. Another study showed that dysbiosis has been shown to disrupt amino acid metabolism in ulcerative colitis, with notable alterations in valine, leucine, lysine, tyrosine, and tryptophan. These changes are closely correlated with inflammatory markers, including C-reactive protein (CRP) and fecal calprotectin, which are commonly used to evaluate disease severity [44–46].

Beyond these inflammatory responses, TBI also promotes excessive production of reactive oxygen species, thereby linking neuroinflammation to the onset of oxidative stress [47]. Hsieh et al. highlighted the significant burden of gastrointestinal mucosal injury in acute severe TBI. Despite routine prophylaxis with omeprazole, more than two-thirds of patients exhibited persistent gastric lesions by day 7, underscoring the resilience of stress-related mucosal damage (SRMD) in this population. At the molecular level, persistent upregulation of ET-1, iNOS, and MIP-1α in the gastric mucosa suggests that TBI triggers robust local inflammatory and vasoactive pathways, which contribute to sustained mucosal injury [48].

As a response to pro-inflammatory cytokines and endotoxins, macrophages and glial cells will express iNOS, enzyme that synthesizes NO [47]. NO is produced from the amino acid L-arginine by the enzyme NOS. The oxidation of L-arginine by NOS occurs in two phases: initially, L-arginine undergoes hydroxylation to produce N-hydroxy-L-arginine, which is then oxidized to generate L-citrulline and NO [49]. NOS has three isoforms, each encoded by a specific gene. These isoforms are neuronal (nNOS) and endothelial (eNOS), both of which rely on calcium and calmodulin, and the third isoform, inducible NOS (iNOS), functions independently of calcium and calmodulin [50].

The constitutive forms of NOS include eNOS and nNOS isoforms, which are found in vascular endothelial cells and nervous system cells, respectively quickly produce small quantities of NO to facilitate homeostatic functions like vasodilation and maintaining platelet fluidity. In contrast, the inducible isoform, iNOS, generates significantly higher levels of NO in response to pathogen infections, leading to defense mechanisms that can result in localized cell death due to NO release [51-52].

Research showed that NO synthesized by iNOS plays a role in neurotoxicity following traumatic brain injury. The expression of iNOS significantly increases after brain injury, peaking around 1 to 2 days later. Patients exhibiting higher levels of iNOS are associated with poorer clinical outcomes. A clinical trial evaluated the NOS inhibitor in TBI patients showed a significant improvement in extended GCS Scores for those receiving the treatment compared to the placebo group [47]. Increased levels of iNOS lead to an excess of NO, which compromises the integrity of the gastric mucosa. This occurs through its interaction with superoxide anions, resulting in the formation of peroxynitrite, a powerful free radical.

Peroxynitrite disrupts cellular macromolecules by causing lipid peroxidation, directly impairing mitochondria, inhibiting the activity of membrane Na+/K+-ATPase, and modifying proteins through oxidative processes [53]. In a study about stress-induced gastric ulcer, NO can have either protective or harmful effects based on the level of its production. NO produced by eNOS is crucial for both the formation and healing of gastric ulcers, whereas NO produced by iNOS is solely involved in ulcer formation [54].

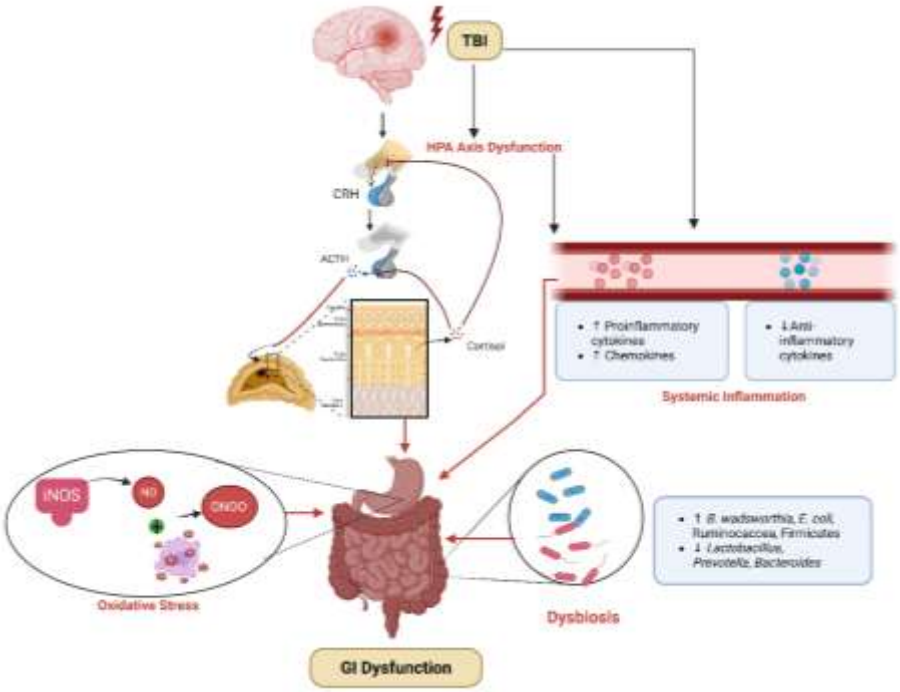

Figure 5. Proposed mechanisms of GI dysfunction following TBI.
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3.2.2 Alterations in Hormonal Levels (HPA Axis Dysfunction)

The hypothalamic–pituitary–adrenal axis, consisting of the hypothalamus, pituitary gland, and adrenal glands, plays a central role in maintaining homeostasis under stress conditions, such as TBI. Activation of this axis initiates with the hypothalamic release of corticotropin-releasing hormone

(CRH), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH then acts on the adrenal cortex, particularly the zona fasciculata, to promote the synthesis of glucocorticoids, primarily cortisol [55].

Glucocorticoid hormones secreted by the adrenal glands are vital for regulating numerous physiological functions, such as vascular tone, protection of the gut mucosa, and maintenance of immune balance [56]. Glucocorticoid hormones regulate this balance by displaying either pro-inflammatory or anti-inflammatory actions, which vary according to its levels and the circumstances of its secretion [55]. Glucocorticoids modulate their own production by regulation of the HPA axis. It is maintained through a negative feedback loop, whereby glucocorticoids suppress further secretion of CRH from the hypothalamus and ACTH from the pituitary [57-58].

Endocrine dysfunctions following TBI have been clinically observed across all HPA axis [21]. After TBI, elevated glucocorticoid levels negatively impact the function of almost all types of immune cells, while the surge of catecholamines caused by acute neuroinflammation leads to increased pro-inflammatory cytokines that weaken mucosal and cellular immunity in the gastrointestinal tract [59]. Brain injury triggers a systemic stress response that increases sympathetic nervous system activity and releases stress hormones [60].

Experimental evidence shows that glucocorticoids released from HPA axis activation play a central role in protecting the gastrointestinal tract under stress conditions. In ischemia–reperfusion models, remote ischemic preconditioning preserved gastric mucosal integrity through glucocorticoid signaling, whereas inhibition of glucocorticoid synthesis or receptor blockade abolished this protective effect. These findings emphasize the importance of hormonal regulation in gastrointestinal resilience, providing a mechanistic link that is also relevant to stress responses following traumatic brain injury [61]. Glucocorticoids are therefore essential for gastrointestinal resilience under stress, underscoring the role of hormonal regulation in TBI-related gastrointestinal dysfunction.

In patients with traumatic intracerebral hemorrhage (TICH), Wang et al. observed that ACTH and cortisol levels were markedly elevated at two weeks after early enteral nutrition, reflecting an adequate HPA axis response. Interestingly, this hormonal increase coincided with reductions in blood glucose and glucagon, indicating that although the acute stress response persisted, metabolic stress was better regulated in the early EN group.These results suggest that early EN may help restore metabolic stability in critically ill TBI patients. Beyond endocrine modulation, early EN improved nutritional markers such as hemoglobin, albumin, and prealbumin, and enhanced neurological outcomes as shown by increased GCS and Glasgow Outcome Scale (GOS) scores and lower modified Rankin Scale (mRS) scores [62]. Wang et al also found that early EN promoted an increase in Bifidobacterium, a genus associated with mucosal protection and anti-inflammatory effects. Bifidobacterium strains strengthen the intestinal barrier by increasing the expression of tight junction proteins, including Zonula Occludens-1 (ZO-1), occludin, and claudin-1, which are essential for preserving mucosal integrity [62-63]. However, both groups in this study exhibited a persistent elevation in Enterococcus and Escherichia coli levels.

Another study by Chen et al. underscored the clinical evidence of adrenal insufficiency in the context of acute TBI. The incidence of CIRCI rose substantially with injury severity, reaching over 50% in severe TBI cases. This impaired adrenal response was strongly associated with adverse outcomes, including a threefold higher incidence of GI bleeding and a fourfold increase in 28-day mortality [64]. Importantly, the link between CIRCI and poor outcomes in TBI complements previous evidence of heightened systemic inflammation by Cannon et al. and stress-induced gut vulnerability by Hsieh et al. Together, these studies point to an intertwined axis of endocrine dysfunction, gastrointestinal injury, and systemic inflammation as key mediators of secondary complications in TBI [20], [48], [64].

Biteghe-Bi-Nzeng et al. provided evidence linking neuroendocrine stress responses to gastrointestinal complications in TBI. Elevated ACTH, cortisol, and gastrin levels were correlated with injury severity, reflecting activation of the HPA axis and gastric secretory pathways. Importantly,

hypergastrinemia emerged as an independent risk factor for post-traumatic GI bleeding [66]. The incidence of GI bleeding in this cohort (24.4%) is consistent with prior reports highlighting the high burden of stress-related mucosal damage in TBI by Hsieh et al. [49], [66]. These findings align with Chen et al., who showed that endocrine dysfunction (CIRCI) is linked to GI bleeding and mortality. Together, these studies point toward a bidirectional relationship between endocrine dysregulation and gastrointestinal vulnerability in TBI. The summary of the mechanisms of GI dysfunction following TBI is shown in Figure 5 and the overview of the methodological features and major outcomes of the eligible studies is presented in Table 2.

Table 2. Summary of evidence from the included studies

Mechanism	Author	Study Design	Population	Outcomes
Inflammation & Microbiota Alterations	Cannon et al. (2023) [20]	Observational	• 12 adult trauma patients with acute TBI. • Controls: healthy subjects	TBI patient Plasma • ↑IFN-γ, ↑MCP-1 • Trend ↑IL-6 and IL-8 • ↓IL-4 Fecal microbiota • ↑*Bilophila wadsworthia* • Trend ↑Enterobacteriaceae, ↓Lactobacillus
	Zhu et al. (2021) [65]	Prospective RCT	80 Severe TBI patients • Experimental group (n=40) → individualized enteral nutrition (EN) formula. • Control group (n=40) → conventional EN formula.	TBI patient (without EN therapy) • ↑TNF-α, ↑CRP, ↑IL-6 Individualized EN in TBI patients • ↓TNF-α, ↓CRP, ↓IL-6 • ↑IgG, ↑IgA, ↑IgM • Improved intestinal barrier (↓I-FABP, ↓D-lactic acid) • Better GI tolerance (10% vs 27.5% adverse events)
	Gao et al. (2020) [33]	RCT	102 Severe TBI patients • Observation group (n=51): early enteral nutrition (EN) + anti-infection strategies (from day 1 post-op). • Control group (n=51): routine care.	TBI patient (Control group) • ↑TNF-α, ↑IL-6 • ↑Infection incidence • ↑Complications • 2 cases of Upper Gastrointestinal (UGI) bleeding TBI with EN and antibiotic therapy • ↓TNF-α, ↓IL-6 • ↓Infection incidence • ↓Complications • No difference in mortality • ↑CD4+, ↑CD4+/CD8+. • ↑Total protein, ↑Albumin, ↑Transferrin. • 2 cases of UGI bleeding
	Urban et al. (2020) [66]	Cross-sectional	22 Chronic TBI patients vs 18 healthy controls	• Significant alterations in gut microbiota in TBI patients: ↓Prevotella spp. and Bacteroides spp., ↑Ruminococcaceae and Firmicutes.

				• Postprandial plasma amino acids reduced in TBI vs. controls (notably tryptophan, threonine, sarcosine). • Positive correlation between Prevotella abundance and amino acid levels; negative correlation with Ruminococcaceae.
	Hsieh J-S et al. (2006) [48]	Observational	25 patients with acute severe TBI	• High expression of ET-1, iNOS, and MIP-1α in gastric mucosa persisted even after Omeprazole prophylaxis. • High baseline incidence of GI lesions: 72% had mucosal lesions at first endoscopy; 70% still had lesions at day 7. • Omeprazole → reduced *severity* of lesions but did not eliminate them.
HPA Axis & Hormonal Response	J. Wang et al. (2023) [62]	Prospective RCT	152 patients with traumatic intracerebral hemorrhage (TICH) • Early Enteral Nutrition (EN) group (n=77) • Control: Delayed EN group (n=75)	TBI patients (Control, delayed EN) • ACTH: increase (but not significant) / lower than treatment • Cortisol: ↑ (stress response, but lower than treatment) • Glucagon (GC) ↑ • Blood glucose (Glu) ↑ • Bifidobacterium ↓ • Enterococcus ↑ • Escherichia coli ↑ • Hemoglobin ↓ • Albumin ↓ • Prealbumin ↓ • Neurological scores: GCS ↓, GOS ↓, mRS ↑ TBI with Early EN group • ACTH ↑ • Cortisol ↑ • Glucagon (GC) ↓ • Blood glucose (Glu) ↓ • Bifidobacterium ↑ • Enterococcus ↑ • Escherichia coli ↑ • Hemoglobin ↑ • Albumin ↑ • Prealbumin ↑ • Neurological scores: GCS ↑, GOS ↑, mRS ↓ • Complications: Intracranial rebleeding ↓, Hydrocephalus ↓, Mortality ↓
	Chen et al., 2020 [64]	Observational	140 patients with acute TBI with corticosteroid insufficiency (CIRCI) examination	• TBI severity ↑ → CIRCI incidence ↑ (mild 5.6% → severe 52.2%).

			• TBI with CIRCI → GI bleeding ↑ (47% vs. 13%). • CIRCI → 28-day mortality ↑ (25% vs. 6%)
Biteghe-Bi-Nzeng et al. (2010) [67]	Observational	• 41 TBI patients • 13 Healthy control	TBI patient • ↑ACTH, ↑cortisol, ↑gastrin correlated with injury severity. • Higher ACTH (>100 pg/mL) and hypergastrinemia were associated with GI bleeding. • Gastrin was an independent risk factor for post-traumatic GIB (OR=26.6). • GI bleeding incidence 24.4% overall, with higher mortality (20%)

4. Conclusion

This systematic review highlights two principal mechanisms driving gastrointestinal dysfunction after TBI. Those are inflammatory-oxidative stress processes and HPA axis alterations. The inflammatory response is marked by the elevation of IL-1β, IL-6, TNF-α, IFN-γ, and chemokines such as MCP-1, accompanied by reduced anti-inflammatory mediators such as IL-4 and IL-10. Gut microbiota dysbiosis, such as reduced *Lactobacillus* and increased *Bilophila*, further impairs barrier integrity and fuels systemic inflammation. In addition, iNOS upregulation contribute to oxidative damage and persistent GI mucosal lesions. Inflammatory mediators, dysbiosis and oxidative stress, collectively contribute to mucosal injury.

In parallel, endocrine dysregulation of the HPA axis exerts a bidirectional influence on gastrointestinal outcomes. Elevated ACTH and cortisol levels in traumatic intracerebral hemorrhage reflect an intact stress response, which may help metabolic stabilization, especially when coupled with early enteral nutrition. Conversely, CIRCI and hypergastrinemia are strongly associated with higher rates of gastrointestinal bleeding and mortality. Collectively, these findings emphasize that both immune and endocrine disturbances act synergistically to heighten gastrointestinal vulnerability and worsen prognosis in TBI patients. Clarifying these pathways through larger trials and biomarker-based approaches may enable targeted prevention, improve nutritional management, and ultimately reduce gastrointestinal complications and mortality in TBI patients.

5. Acknowledgement

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