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ORIGINAL ARTICLE

Observational Study

Comparison of neurohormone and callus volume formation in long bone fractures associated with or without traumatic brain injury

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Abstract

BACKGROUND

Fracture healing is a dynamic process influenced by systemic and local factors. Traumatic brain injury (TBI) has been clinically associated with accelerated bone repair, yet the underlying biochemical mechanisms remain unclear.

AIM

To investigate the roles of growth hormone (GH), parathyroid hormone (PTH), and interleukin-6 (IL-6) in callus formation among patients with long bone fractures, comparing cohorts with and without TBI.

METHODS
A prospective analytical study was conducted at JIPMER from January 2023 to December 2025. Patients with diaphyseal long bone fractures were stratified into two groups: With TBI and without TBI. Serum levels of GH, PTH, and IL-6 were measured at defined intervals using the enzyme-linked immunosorbent assay. Callus volume was assessed radiologically *via* computed tomography imaging at 4 weeks and 6 weeks post-injury. Statistical analysis included RMANOVA and correlation studies to evaluate biomarker trends and their association with callus formation.

RESULTS
Patients with concomitant TBI exhibited significantly elevated levels of GH and PTH during early healing phases, while IL-6 levels showed a complex temporal pattern. Callus volume was markedly higher in the TBI group at both 4 weeks and 6 weeks, with statistically significant differences ($P < 0.05$). Positive correlations were observed between GH/PTH levels and callus volume, whereas IL-6 showed inverse associations in certain phases.

CONCLUSION
TBI appears to modulate systemic hormonal and cytokine responses that favor enhanced osteogenesis. Elevated GH and PTH levels may contribute to accelerated callus formation, while IL-6's role remains context-dependent. These findings offer potential therapeutic insights for improving fracture healing outcomes.

Key Words: Traumatic brain injury; Callus; Growth hormone; Interleukin; Parathyroid hormone; Long bone fractures

Core Tip: Patients with traumatic brain injury (TBI) show enhanced fracture healing, potentially due to elevated systemic levels of growth hormone and parathyroid hormone. This prospective study reveals that growth hormone and parathyroid hormone positively correlate with increased callus volume, while interleukin-6 exhibits a variable role. Understanding these biochemical mediators may lead to novel therapeutic strategies that mimic TBI-associated osteogenesis to improve fracture outcomes in non-TBI patients.

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INTRODUCTION

Fracture healing is a complex biological process orchestrated by a finely tuned interplay of cellular, hormonal, and cytokine signals. While most fractures follow a predictable trajectory of repair, certain physiological conditions can dramatically alter the pace and quality of bone regeneration. One such condition is traumatic brain injury (TBI), which has been repeatedly associated with accelerated and enhanced fracture healing[1]. Despite compelling clinical and preclinical observations, the underlying mechanisms that differentiate TBI-associated bone repair from standard fracture healing remain poorly understood. This knowledge gap presents a unique opportunity to explore the systemic mediators that may drive this phenomenon and to harness these insights for therapeutic innovation.

Emerging evidence suggests that growth hormone (GH), parathyroid hormone (PTH), and interleukin-6 (IL-6) are pivotal regulators of osteogenesis and callus formation[2-5]. These mediators influence key aspects of bone biology, including stem cell recruitment, angiogenesis, matrix deposition, and remodeling. Notably, TBI appears to modulate the systemic levels and activity of these factors, potentially creating a pro-osteogenic milieu that favors robust fracture healing[6-9]. However, the extent to which these hormonal and cytokine shifts contribute to the observed clinical outcomes has not been systematically investigated in human subjects.

The proposed research aims to fill this critical gap by conducting a prospective analytical study that quantitatively assesses GH, PTH, and IL-6 levels in patients with diaphyseal long bone fractures, stratified by the presence or absence of TBI. By correlating these biomarker profiles with objective measures of callus formation - using advanced imaging modalities and standardized clinical assessments - the study seeks to identify biological signatures that distinguish TBI-enhanced healing from conventional repair. This integrative approach will provide a comprehensive understanding of the hormonal and cytokine dynamics that underpin fracture healing, offering mechanistic insights into the role of systemic mediators in bone regeneration.

What sets this study apart is its methodological rigor and translational potential. It is among the first to simultaneously evaluate multiple key mediators in a well-defined human cohort, leveraging recent advances in biomarker analytics and high-resolution imaging. The longitudinal design allows for dynamic tracking of healing trajectories, enabling the identification of temporal patterns and predictive markers. Moreover, by elucidating the mechanistic links between TBI and osteogenesis, the research opens avenues for novel therapeutic strategies - such as hormone analogs or cytokine modulators - that could enhance fracture healing in patients without TBI[10-12]. This study addresses a significant and

underexplored aspect of bone biology with direct clinical relevance. By dissecting the hormonal and cytokine milieu associated with TBI-enhanced fracture healing, it aims to uncover actionable insights that could transform the management of long bone fractures. The findings have the potential to inform personalized treatment approaches, improve patient outcomes, and contribute to the broader understanding of trauma-induced tissue regeneration. As such, the proposed research represents a timely and impactful contribution to the fields of orthopedics, endocrinology, and regenerative medicine. The primary objective is to assess the level of IL-6, PTH, and GH in patients with TBI with long bone fractures and patients with long bone fractures without brain injury, and the secondary objective is the amount of callus formation in patients with long bone fractures with TBI and patients with long bone fractures without TBI.

MATERIALS AND METHODS

Study design

This observational, analytical cohort study was conducted at the Department of Orthopaedics, JIPMER, Puducherry, from January 2023 to December 2025. Institutional ethical clearance: Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - JIP/IEC-OS/185/2023 dated March 10, 2023.

Study population and sampling

The target population included adults (≥ 18 years) presenting within 24 hours of injury with radiologically confirmed diaphyseal fractures of long bones (femur, tibia, humerus). Patients were stratified into two cohorts.

TBI group: Moderate-to-severe TBI confirmed by Glasgow Coma Scale (GCS) and neuroimaging.

Non-TBI group: No clinical or radiological evidence of TBI.

Exclusion criteria included pathological fractures, endocrine disorders affecting GH/PTH/IL-6, chronic corticosteroid or hormone therapy, and pregnancy. A total of 41 eligible TBI patients were screened, with 25 enrolled. In the non-TBI group, 16 eligible patients were enrolled. A consecutive sampling technique was used, with random sampling applied if the eligible numbers exceeded the required sample size.

Sample size estimation: Based on anticipated differences in PTH levels between groups (mean: 94.31 *vs* 83.72; SD: 161), a sample size of 50 (25 per group) was calculated using a two-way repeated measures design, the one-way analysis of variance (ANOVA) with 80% power and 5% significance.

Enrollment and consent: Eligible patients were screened upon presentation using clinical and radiological evaluations. Informed consent was obtained from patients or legal representatives. Each participant was assigned a unique identifier to ensure confidentiality. Baseline demographic and clinical data were recorded at enrollment.

Data collection and follow-up

The study was executed in structured phases.

Baseline assessment: Blood samples for GH, PTH, and IL-6 were collected within 24 hours of injury.

Treatment and monitoring: Patients received standard care for fractures and TBI. Serial blood samples were collected at 24 hours, 6 weeks, and 3 months post-injury.

Radiological evaluation: Callus formation was assessed *via* digital radiographs at 6 weeks and 3 months. Callus thickness and volume were measured using imaging software.

Data management: Data were entered into a secure electronic database. Regular audits ensured accuracy and completeness.

Measurement tools and techniques

Biochemical assays: GH and PTH were measured using chemiluminescent immunoassay analyzers (*e.g.*, Beckman Coulter UniCel Dxl 600). IL-6 was quantified using validated ELISA kits. Samples were stored at -80 °C until analysis.

Radiological imaging: Standardized anteroposterior and lateral radiographs were used. Callus thickness was measured at the widest point; volume was assessed *via* three-dimensional (3D) reconstruction in a subset of patients.

Instrumentation: Key equipment included a microplate reader, orbital shaking incubator, and -80 °C freezer for sample preservation.

Variables studied

Independent variables: TBI status (yes/no), serum GH, PTH, IL-6 levels, age, sex, fracture type and location, neurological status (GCS), and TBI characteristics.

Dependent variables: Callus thickness (mm) and volume (cm^3).

Measurement protocols

Biomarkers: Blood samples were collected in the morning to control for diurnal variation. Serum was processed and stored under standardized conditions.

Callus metrics: Radiographs were interpreted by two independent radiologists to ensure inter-observer reliability.

Statistical analysis

Descriptive statistics summarized baseline characteristics and biomarker levels. Group comparisons used independent *t*-tests or Mann-Whitney *U* tests for continuous variables and χ^2 tests for categorical variables. Repeated measures ANOVA and mixed-effects models analyzed biomarker trends over time. Multivariate regression assessed associations between TBI status, biomarkers, and callus formation, adjusting for confounders. Significance was set at $P < 0.05$.

RESULTS

The study compared fracture healing dynamics between patients with and without TBI, analyzing demographic, biochemical, and radiological parameters. Key markers assessed were PTH, GH, and IL-6 across 7 days, 6 weeks, and 12 weeks. Radiological outcomes were evaluated using callus volume measurements, supported by correlation and regression analyses.

Demographics

Age and gender distributions were comparable between groups (mean age 38.5 years *vs* 39.8 years, $P = 0.77$; male proportion 76% *vs* 81%, $P = 0.99$), minimizing demographic confounders. Fracture site distribution was also similar ($P = 0.90$). Baseline GCS confirmed significant neurological impairment in the TBI group (10.8 ± 1.6 *vs* 15, $P < 0.0001$).

Biochemical markers

PTH: TBI patients exhibited markedly elevated PTH at 7 days (42.0 pg/mL *vs* 7.2 pg/mL, $P < 0.0001$) and at 12 weeks (38.2 pg/mL *vs* 8.9 pg/mL, $P < 0.0001$), while mid-phase differences (6 weeks) were not significant due to variability. These trends indicate an early and sustained endocrine activation in TBI patients (Figure 1A and Table 1).

GH: GH levels were significantly higher in the TBI group at all intervals (7 days: 1.6 ng/mL *vs* 0.08 ng/mL; 6 weeks: 8.1 ng/mL *vs* 0.55 ng/mL; 12 weeks: 2.3 ng/mL *vs* 0.22 ng/mL; all $P < 0.0001$). The sustained GH elevation supports enhanced osteoblastic activity and matrix formation (Figure 1B and Table 2).

IL-6: TBI patients showed persistently elevated IL-6 across all time points (7 days: 130.2 pg/mL *vs* 22.3 pg/mL; 6 weeks: 410.5 pg/mL *vs* 78.2 pg/mL; 12 weeks: 220.5 pg/mL *vs* 25.6 pg/mL; all $P < 0.0001$). This reflects a prolonged inflammatory response likely linked to accelerated healing (Figure 1C and Table 3).

Radiological findings

Callus volume: Radiographic assessments demonstrated significantly greater callus volumes in the TBI group at both 6 weeks (62.1 cm^3 *vs* 12.3 cm^3, $P = 0.0058$) and 12 weeks (98.2 cm^3 *vs* 22.1 cm^3, $P = 0.0049$), indicating enhanced osteogenesis. These findings align with the elevated hormone and cytokine levels (Figure 1D and Table 4).

Correlation and regression analysis

Correlation analysis revealed strong positive relationships between GH, PTH, and IL-6 ($r = 0.47$-0.60, all $P < 0.01$), suggesting coordinated endocrine-immune signaling in bone repair (Table 5). Multivariate regression identified GH ($P = 0.002$), PTH ($P = 0.011$), IL-6 ($P = 0.001$), and TBI status ($P = 0.0005$) as independent predictors of callus volume at 6 weeks, while age and sex were non-significant (Table 6). This indicates that biochemical and injury-related factors, rather than demographics, predominantly drive osteogenesis.

Repeated measures ANOVA

Significant time-dependent changes and group–time interactions were observed for all markers (GH: $F = 15.2$, $P < 0.001$; PTH: $F = 18.7$, $P < 0.001$; IL-6: $F = 22.5$, $P < 0.001$), confirming distinct temporal patterns of biochemical response in TBI-associated healing. These results indicate that both the passage of time and TBI status significantly modulate the hormonal and inflammatory milieu during recovery.

DISCUSSION

A cohort study conducted at a single tertiary center compared diaphyseal long-bone fractures in adults with and without concomitant TBI. The investigation aimed to evaluate differences in clinical outcomes, healing patterns, and rehabilitation trajectories between the two groups. The TBI cohort demonstrated significantly greater callus volumes at 6 weeks and 12 weeks, accompanied by higher circulating GH and PTH at all or most intervals, and persistently elevated IL-6. Repeated-measures analyses showed distinct time-group interactions, and multivariable models identified TBI status, GH, PTH,

Table 1 Biochemical marker parathyroid hormone over time in patients with and without traumatic brain injury

PTH (pg/mL)	Group	*n*	mean ± SD	Statistic (test type)	*P* value	Significance
7 days	Without TBI	25	7.2 ±3.0	t = -9.05 (t-test)	< 0.0001	Significant
	With TBI	16	42.0 ± 15.2			
6 weeks	Without TBI	25	15.8 ± 5.5	U = 175 (Mann-Whitney)	0.51	Non-significant
	With TBI	16	305.2 ± 500.3			
12 weeks	Without TBI	25	8.9 ± 4.0	t = -5.25 (t-test)	< 0.0001	Significant
	With TBI	16	38.2 ± 22.1			

PTH: Parathyroid hormone; TBI: Traumatic brain injury.

Table 2 Biochemical marker growth hormone over time in patients with and without traumatic brain injury

GH (pg/mL)	Group	*n*	mean ± SD	Statistic (test type)	*P* value	Significance
7 days	Without TBI	25	0.08 ± 0.06	t = -7.59 (t-test)	< 0.0001	Significant
	With TBI	16	1.6 ± 0.8			
6 weeks	Without TBI	25	0.55 ± 0.22	t = -4.79 (t-test)	< 0.0001	Significant
	With TBI	16	8.1 ± 6.3			
12 weeks	Without TBI	25	0.22 ± 0.09	t = -7.55 (t-test)	< 0.0001	Significant
	With TBI	16	2.3 ± 1.1			

GH: Growth hormone; TBI: Traumatic brain injury.

Table 3 Biochemical marker interleukin-6 over time in patients with and without traumatic brain injury

IL-6 (pg/mL)	Group	*n*	mean ± SD	Statistic (test type)	*P* value	Significance
7 days	Without TBI	25	22.3 ± 8.2	t = -10.52 (t-test)	< 0.0001	Significant
	With TBI	16	130.2 ± 40.5			
6 weeks	Without TBI	25	78.2 ± 20.1	t = -8.80 (t-test)	< 0.0001	Significant
	With TBI	16	410.5 ± 150.2			
12 weeks	Without TBI	25	25.6 ± 10.3	t = -11.00 (t-test)	< 0.0001	Significant
	With TBI	16	220.5 ± 70.4			

IL-6: Interleukin-6; TBI: Traumatic brain injury.

Table 4 Callus volume over time in patients with and without traumatic brain injury

Time point	Group	*n*	mean ± SD (cm^3)	Statistic (test type)	*P* value	Significance
6 weeks post-injury	Without TBI	25	12.3 ± 28.0	t = -3.10 (t-test)	0.0058	Significant
	With TBI	16	62.1 ± 60.2			
12 weeks post-injury	Without TBI	25	22.1 ± 38.5	t = -3.20 (t-test)	0.0049	Significant
	With TBI	16	98.2 ± 90.1			

TBI: Traumatic brain injury.

Table 5 Correlation analysis of neurohormonal parameters in bone repair

Variable pair	Correlation coefficient (*r*)	*P* value	Interpretation
GH-PTH	0.55	0.001	Significant positive correlation
GH-IL-6	0.47	0.005	Significant positive correlation
PTH-IL-6	0.60	0.0008	Significant positive correlation

GH: Growth hormone; PTH: Parathyroid hormone; IL-6: Interleukin-6.

Table 6 Multivariate regression: Predictors of callus volume at 6 weeks

Variable	Coefficient	*P* value	Significant
GH 7 days	0.38	0.002	Yes
PTH 7 days	0.31	0.011	Yes
IL-6 7 days	0.41	0.001	Yes
TBI status	0.49	0.0005	Yes
Age	-0.02	0.21	No
Sex	0.06	0.33	No

GH: Growth hormone; PTH: Parathyroid hormone; IL-6: Interleukin-6; TBI: Traumatic brain injury.

and IL-6 as independent predictors of early callus volume. These data indicate that TBI is associated with a systemic pro-osteogenic milieu that scales with radiographic osteogenesis[13].

Clinical observations that fractures heal faster and with more exuberant callus in the presence of TBI date back decades and have been consolidated by modern reviews and meta-analyses[1,14]. The present study's radiological and biochemical results concur with contemporary clinical series that documented accelerated tibial fracture healing in TBI, alongside hematoma and inflammatory signatures consistent with enhanced osteogenesis. The current work extends this by serially quantifying GH, PTH, and IL-6 and linking them to callus volume using multivariable modelling[13]. Recent literature synthesizes convergent clinical and preclinical data that TBI enhances fracture repair, potentially through humoral mediators released from injured brain tissue[15-17]. The present cohort corroborates this concept and provides human biomarker evidence that parallels mechanistic studies showing TBI-conditioned sera stimulate osteoprogenitor proliferation and matrix deposition[1].

Most human studies to date have been retrospective or case-control designs focusing on union times or qualitative callus assessments. By contrast, this study prospectively enrolled consecutive patients, standardized sampling times, and quantified callus by radiographic metrics at prespecified intervals. These choices align with calls from recent reviews for longitudinal, biomarker-imaging integration in human cohorts. Nonetheless, heterogeneity exists across the literature in imaging endpoints. Some clinical series rely on time to cortical bridging, while others use semiquantitative callus grading; only a minority obtain volumetric measures. The choice here of repeated radiographic assessments with callus volume estimation improves objectivity relative to purely time-to-union endpoints, although full 3D computed tomography (CT) for all participants would further strengthen cross-study comparability[13].

On the biochemical side, GH and PTH trajectories in the TBI group mirror prior reports of post-traumatic rises in GH/insulin-like growth factor 1 (IGF-1) signaling and the known pro-osteogenic effects of intermittent PTH exposure[18,19]. Prior clinical and translational work has shown that sera from TBI patients contain osteogenic factors and that PTH analogs can accelerate endochondral callus formation in animals. The present study adds temporal resolution and multivariable modeling to demonstrate independent associations between GH/PTH and callus volume in humans[20].

GH supports osteoblast differentiation and stimulates IGF-1 pathways critical for matrix deposition[21]. Preclinical models show GH augments both formation and remodeling phases, and clinical studies in TBI populations describe alterations in pituitary axes after neurotrauma[22,23]. The present cohort's sustained GH elevation across healing windows, coupled with positive correlations to callus volume, is directionally consistent with these data. While consensus statements emphasize vigilance for hypopituitarism after TBI, the osteoanabolic profile observed here suggests a subset manifests early hyper-secretion or altered GH pulsatility that may be permissive for bone regeneration. Dedicated endocrine phenotyping will be needed to disentangle adaptive from pathologic patterns[24].

Intermittent PTH signaling accelerates callus formation and endochondral ossification in numerous animal models, and selected human studies and case series suggest potential benefits for delayed unions[25,26]. However, randomized data in specific fracture types are mixed, including a negative trial in proximal humerus fractures. The robust PTH-callus associations reported here are biologically plausible and clinically provocative, yet they should be interpreted alongside the heterogeneity of teriparatide trials in humans. The translational next step is a pragmatic, biomarker-guided trial testing PTH analogs in high-risk fractures and in patients with TBI-like endocrine signatures, with standardized volu-

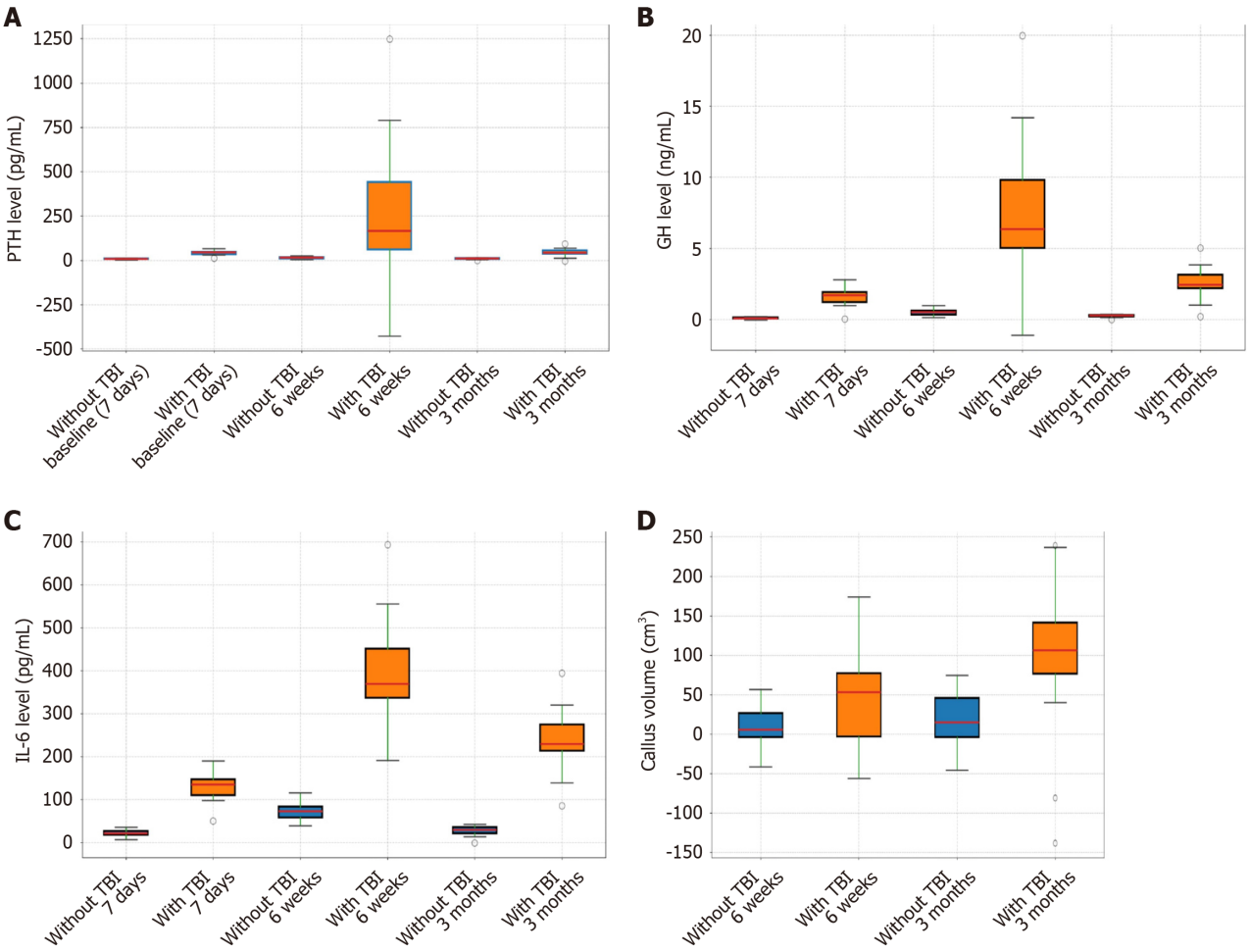


Figure 1 The level of comparison over time by groups. A: Parathyroid hormone level comparison over time by groups; B: Growth hormone level comparison over time by group; C: Interleukin-6 level comparison over time by group; D: Callus volume comparison over time by group. GH: Growth hormone; PTH: Parathyroid hormone; IL-6: Interleukin-6; TBI: Traumatic brain injury.

metric endpoints[25].

IL-6 rose persistently in the TBI cohort. The literature depicts a nuanced role. Mouse models of diaphyseal fracture suggest that early global IL-6 inhibition impairs regeneration, while selective modulation of classic *vs* trans-signaling pathways yields divergent skeletal effects[27,28]. IL-6 is a pleiotropic cytokine central to immune regulation and tissue repair. In bone biology, IL-6 influences both bone resorption and formation, depending on the signaling mode and cellular context. It signals *via* two distinct pathways: (1) Classical (cis) signaling involves membrane-bound IL-6 receptor (IL-6R) and gp130, primarily affecting cells like hepatocytes and some leukocytes. This pathway is generally associated with homeostatic and regenerative functions[29]; and (2) Trans-signaling occurs when IL-6 binds to soluble IL-6R, enabling activation of gp130-expressing cells that lack IL-6R. This mode is often linked to pro-inflammatory responses and broader cellular recruitment[30]. In bone regeneration, IL-6 plays dual roles: (1) Pro-osteogenic effects: IL-6/IL-6R complexes promote osteogenic differentiation of bone marrow-derived mesenchymal stem cells, enhancing their maturation into osteoblasts. This supports bone formation during repair and remodeling[31]; and (2) Pro-resorptive effects: IL-6 also stimulates osteoclastogenesis, particularly under inflammatory conditions, contributing to bone resorption. This is more pronounced in chronic inflammation or pathological states like osteoporosis. The balance between these roles is influenced by local cytokine milieu, receptor expression, and timing[32]. During early bone healing, IL-6 may facilitate recruitment and differentiation of progenitor cells. However, sustained IL-6 trans-signaling can impair regeneration by promoting excessive resorption and inflammation. Therapeutically, modulating IL-6 pathways - such as selectively inhibiting trans-signaling - could enhance bone repair while minimizing inflammatory damage. This nuanced understanding opens avenues for targeted interventions in regenerative orthopaedics and osteoimmunology. Other work indicates IL-6 deficiency may enhance woven bone after stress fracture without compromising full fracture healing, underscoring model- and timing-specific biology. The present study's observation of phase-dependent or inverse correlations between IL-6 and callus in some windows likely reflects these complexities. Future human studies should profile IL-6 signaling modes and co-regulators to determine whether targeted, time-locked IL-6 pathway modulation can favorably tune repair without blunting necessary inflammation[27].

Contemporary mechanistic studies propose that TBI alters systemic immunity, releases osteogenic extracellular vesicles and peptides, and shifts neuroendocrine tone in ways that foster angiogenesis and endochondral progression[33,34]. Experimental work has demonstrated accelerated early fracture responses when TBI co-occurs, including amplified

neuroinflammation at the fracture niche. The present human data fit within this framework, with endocrine and cytokine signatures aligning with a primed reparative state[15].

Two translational pathways emerge

First, mechanistic human studies should deploy multiplex proteomics, extracellular vesicle profiling, and cytokine signaling phenotyping (classic *vs* trans-IL-6) alongside standardized quantitative CT and, where feasible, high-resolution peripheral quantitative CT to map spatiotemporal callus architecture. Second, early-phase interventional trials can test osteoanabolic strategies that mimic TBI-associated signatures. Candidate approaches include intermittent PTH analogs and GH/IGF-1 axis modulation in biomarker-enriched populations, with stringent safety monitoring and imaging-based endpoints. Parallel preclinical work should define optimal timing windows for IL-6 pathway modulation to preserve beneficial inflammation while preventing fibrosis or delayed remodeling. Multi-site registries with harmonized endpoints would enable adequately powered analyses across fracture patterns and TBI severities[25].

Limitations merit emphasis

First, the sample size is modest, which inflates uncertainty around interaction terms and limits subgroup analyses by fracture site, fixation strategy, or TBI severity. Second, imaging relied on radiographs for all and 3D reconstruction in only a subset, which may under-capture volumetric nuances and mineralization kinetics *vs* uniform CT-based protocols. Third, the biomarker panel, while hypothesis-driven, is narrow. Key mediators such as IGF-1, sclerostin, bone morphogenic proteins, and extracellular vesicle-borne microRNAs were not assessed. Fourth, treatment heterogeneity in fracture care and neurocritical management is inevitable in real-world cohorts and may influence systemic biology. Finally, causality cannot be inferred; the endocrine-immune milieu could be a marker rather than a driver of accelerated healing[1].

CONCLUSION

TBI profoundly influences systemic biochemical pathways, leading to accelerated and enhanced bone healing. Elevated concentrations of GH, PTH, and IL-6 appear to work synergistically to promote osteogenesis, as evidenced by increased callus formation and expedited recovery. This pattern points toward a neuroendocrine-inflammatory mechanism that may underlie the observed phenomenon of improved fracture repair in individuals following TBI.

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