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Review

Biochemical and cytokine environment in skeletally immature patients after traumatic knee injuries

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Traumatic knee injuries in skeletally immature patients occur in a unique biological context shaped by growth, high tissue turnover, and distinct immune-repair dynamics. Beyond structural damage, acute post-traumatic changes in synovial fluid and cartilage metabolism can set the trajectory toward persistent symptoms and post-traumatic osteoarthritis. In this review, we synthesize recent evidence on the biochemical and cytokine milieu following common pediatric and adolescent knee injuries, including Anterior Cruciate Ligament tears, meniscal lesions, and osteochondral trauma. We highlight patterns of early inflammatory signaling, matrix-degradation biomarkers, and emerging pro-resolving mediators, and discuss how age, timing of sampling, and injury phenotype influence reported profiles. We then outline the translational relevance of these biomarkers for patient stratification, prognosis, and therapeutic targeting, including opportunities to define windows for disease-modifying interventions. Finally, we propose priorities for the field: standardized sampling and reporting, and longitudinal pediatric cohorts linked to imaging and outcomes.

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Introduction

Knee injuries in skeletally immature patients are common and clinically significant, presenting with distinct patterns, mechanisms, and risks compared with those observed in adults. Over recent decades, the incidence of acute knee trauma in children and adolescents has increased substantially, largely reflecting greater participation in competitive sports and early specialization [1]. Within this population, the most frequently reported traumatic knee injuries include chondral lesions, followed by anterior cruciate ligament (ACL) tears and meniscal injuries [2].

In children and adolescents, however, knee trauma occurs in the context of active skeletal maturation, high cellular turnover, and a long post-injury life expectancy, raising important questions regarding how early inflammatory events may influence long-term joint health [3]. The skeletally immature knee is characterized by unique anatomical and physiological features, including open physes, secondary ossification centers, and metabolically active cartilage and synovium. These features not only shape injury patterns but also fundamentally modulate how articular tissues perceive and respond to mechanical stress.

Mechanical disruption of cartilage, ligaments, menisci, and subchondral bone acts as a potent trigger for immune activation, linking biomechanical injury to cytokine release, synovial inflammation, and extracellular matrix remodeling [4]. This biologically driven response occurs within a joint environment that is highly dynamic and developmentally sensitive.

Beyond ligamentous and chondral injuries, the presence of open growth plates confers susceptibility to physeal fractures with potentially profound long-term consequences. Distal femoral physeal fractures, although accounting for approximately 1% of all pediatric fractures, are associated with a high risk of growth disturbance, with reported rates of growth arrest ranging from 40% to 52% and clinically relevant leg length discrepancy (> 1.5 cm) occurring in up to 22% of cases. In addition, injuries of the extensor mechanism, including tibial tubercle avulsion fractures and patellar sleeve fractures, represent characteristic patterns of pediatric knee trauma and may result in substantial morbidity,

such as extensor dysfunction, delayed rehabilitation, and, in severe cases, acute compartment syndrome [5].

Collectively, these injuries expose developing cartilage, physes, and synovium to acute mechanical and biochemical stress at a critical stage of musculoskeletal development. The ensuing inflammatory response unfolds within a biologically active joint environment, where the balance between catabolic and reparative signaling may have lasting implications for tissue remodeling, growth modulation, and long-term joint health.

Pathophysiology of knee injury in the immature skeleton

Emerging evidence indicates that the acute intra-articular immune response to knee trauma is strongly age dependent. In skeletally immature joints, post-traumatic synovial fluid is characterized by a distinct cytokine milieu in which pro-inflammatory mediators coexist with relatively elevated levels of anti-inflammatory and pro-resolving factors, including interleukin (IL)-10 and Resolvin E1 [6]. This more balanced inflammatory profile may promote timely resolution of inflammation and support tissue repair, potentially contributing to the greater regenerative capacity observed in pediatric patients.

In contrast, adult knees typically exhibit a sustained predominance of pro-inflammatory and catabolic cytokines, such as IL-6 and tumor necrosis factor-α (TNF-α), which have been implicated in chondrocyte apoptosis, extracellular matrix degradation, and progression toward post-traumatic osteoarthritis (PTOA) [7,8]. These divergent inflammatory trajectories underscore fundamental age-related differences in the biological response to joint injury.

Importantly, inflammation in skeletally immature patients occurs in the context of active growth and ongoing tissue differentiation. Cytokine signaling may interfere with physeal biology, chondrocyte proliferation, and mechanotransduction pathways, rendering the developing joint particularly vulnerable to persistent or dysregulated inflammatory stimuli. If inadequately resolved, early post-traumatic immune activation may leave lasting 'biochemical scars' that alter joint homeostasis, promote maladaptive remodeling, and increase susceptibility to early-onset osteoarthritis later in adulthood [8,9].

Understanding how trauma-induced immune responses interact with skeletal maturation is therefore essential. Elucidating age-specific cytokine dynamics may enable the identification of prognostic biomarkers, improve risk stratification, and define therapeutic windows for targeted immunomodulatory interventions tailored to the growing joint. Such insights are increasingly relevant as pediatric knee injuries continue to rise and their long-term biological consequences emerge as a central concern at the intersection of immunology, mechanobiology, and musculoskeletal disease.

Acute biochemical response after injury

In skeletally immature patients, acute traumatic knee injuries induce a rapid biochemical response reflecting both structural tissue damage and the distinctive biological features of the developing joint. Mechanical injury to cartilage, ligaments, and subchondral bone leads to the immediate release of extracellular matrix degradation products into the synovial fluid, including aggrecan neoepitopes, cartilage oligomeric matrix protein (COMP), and type II collagen fragments. These markers have been consistently detected shortly after ACL injury and are widely used as indicators of acute cartilage matrix disruption [10,11]. Although most longitudinal biomarker studies have been conducted in adult cohorts, similar matrix-derived molecules have also been identified in the synovial fluid of adolescent patients following traumatic knee injuries, supporting the presence of an early catabolic response in the immature joint [4].

Post-traumatic synovial fluid in skeletally immature individuals is characterized by a marked increase in inflammatory mediators, including IL-1β, TNF-α, IL-6, and IL-8, together with elevated levels of matrix-degrading enzymes, such as matrix metalloproteinases (MMPs), which collectively create a highly catabolic intra-articular environment [4]. Importantly, several of these molecules not only serve as biomarkers of injury but may also function as damage-associated molecular patterns, further amplifying synovial inflammation. The synovium plays a central role in this acute response, acting as an active source of inflammatory and catabolic mediators rather than a passive bystander. Synovial lining cells and infiltrating immune cells rapidly respond to mechanical stress and matrix fragments by producing cytokines that promote cartilage degradation and inhibit anabolic repair processes. Emerging evidence suggests that synovial activation in skeletally immature patients may be biologically distinct, potentially influenced by open physes and the immature cartilage phenotype, which can modulate both inflammatory intensity and resolution pathways [4,6]. If inadequately resolved, this early inflammatory milieu is increasingly recognized as a critical contributor to long-term joint degeneration following pediatric knee trauma.

Cytokine and chemokine profile

Traumatic knee injury in skeletally immature patients is associated with a rapid and profound alteration of the intra-articular cytokine and chemokine milieu, characterized by the early predominance of pro-inflammatory mediators that directly influence cartilage and synovial

tissue turnover. Synovial fluid analyses performed shortly after injury have consistently demonstrated increased levels of IL-1β, TNF-α, IL-6, and IL-8, together with chemokines such as Monocyte Chemoattractant Protein-1 (MCP-1), reflecting an active inflammatory response within the joint [12,13]. These mediators promote cartilage matrix degradation by inducing matrix MMPs and aggrecanases, while simultaneously sustaining synovial activation and inflammatory cell recruitment. Although much of the mechanistic evidence derives from adult or mixed-age cohorts, similar inflammatory patterns have been reported in adolescent patients following traumatic knee injuries, supporting the relevance of these pathways in the skeletally immature joint.

Alongside this pro-inflammatory cascade, anti-inflammatory and reparative mediators are also detectable in post-traumatic synovial fluid, indicating the early activation of counter-regulatory mechanisms. Cytokines such as IL-10 and the IL-1 receptor antagonist (IL-1ra), as well as growth-related factors (e.g. insulin-like growth factor-1 (IGF-1)), coexist with catabolic mediators, highlighting the dynamic balance between tissue damage and repair signals within the injured joint [14]. In skeletally immature patients, this balance may be biologically distinct, as the developing cartilage and synovium may retain a greater capacity for inflammation resolution and regeneration. Supporting this concept, recent studies have identified higher levels of pro-resolving mediators, including Resolvin E1, in immature compared with adult joints, suggesting that resolution pathways may be more active during skeletal growth (Figure 1) [6].

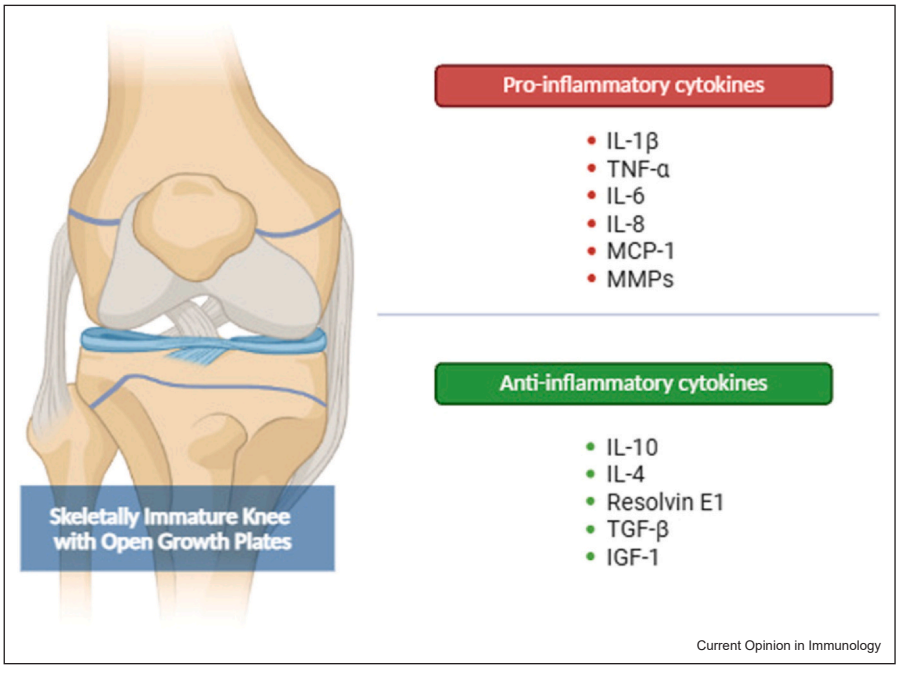
Cellular contributions to the traumatic knee injuries cytokine milieu

Cytokines and growth factors detected after traumatic knee injury arise from a network of joint tissues, including synovium, cartilage, and subchondral bone, each with distinct yet overlapping contributions to the inflammatory and remodeling milieu.

Synoviocytes represent a primary source of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, actively sustaining joint inflammation and leukocyte recruitment. Chondrocytes, although traditionally viewed as passive targets, contribute to the inflammatory cascade by producing matrix-degrading enzymes and cytokines in response to injury-related stimuli [15–19].

Importantly, osteoblasts and osteoclasts play an increasingly recognized role in shaping the joint microenvironment after trauma. Osteoblasts regulate bone

Figure 1



Overview of cytokines involved in patients with immature skeletons after traumatic knee injuries. Pro-inflammatory biomarkers: IL-1β = interleukin 1β, TNF-α = tumor necrosis factor α, IL-6 = interleukin 6, IL-8 = interleukin 8, MCP-1 = monocyte chemoattractant protein-1, MMPs = metalloproteinases. Anti-inflammatory biomarkers: IL-10 = interleukin 10, IL-4 = interleukin 4, Resolvin E1 = resolvin, TGF-β = transforming growth factor β, IGF-1 = insulin growth factor 1.

turnover and inflammatory signaling through the production of mediators such as osteoprotegerin (OPG) and TGF-β, thereby influencing osteoclast differentiation and activity. Osteoclasts are key effectors of subchondral bone resorption and are activated by inflammatory cytokines such as TNF-α and IL-1β, linking inflammation to structural joint damage [12,16,20].

This tight interaction between immune cells, bone cells, and cytokine networks contributes to a pro-inflammatory microenvironment that promotes cartilage degradation, synovial inflammation, and subchondral bone remodeling [21].

Overall, synovial cells, chondrocytes, osteoblasts, and osteoclasts jointly shape the cytokine and growth factor profile after knee trauma. Subchondral bone cells are not passive bystanders but active participants in both inflammation and structural progression, supporting the rationale for therapies that target bone remodeling pathways alongside classical anti-inflammatory approaches.

In skeletally immature patients, where bone turnover and growth plate activity are heightened, these mechanisms may be particularly relevant, suggesting that therapeutic strategies targeting bone remodeling pathways, alongside modulation of synovial inflammation, could offer additional benefits in preserving joint integrity and preventing long-term degeneration.

Potential predictive biomarkers of outcome

Beyond their mechanistic role, cytokines and chemokines have emerged as potential biomarkers for predicting clinical outcome after traumatic knee injury [10,22]. Although longitudinal data in skeletally immature cohorts remain limited, these findings support the hypothesis that the early balance between pro-inflammatory and reparative cytokines may critically influence long-term joint remodeling and represent a promising tool for risk stratification and personalized management in young patients.

In fact, a large percentage of patients included in clinical trials undergo surgery, offering a valuable and often underutilized opportunity for the collection of synovial fluid and tissue biopsies. Integrating these samples into transcriptomic analyses could significantly improve our understanding of the molecular pathways driving post-injury joint remodeling, as demonstrated by some studies conducted to date [9,23–28]. However, to fully exploit this potential, it is essential to establish and implement standardized protocols for sample collection, storage, and processing, thus ensuring reliability, reproducibility, and comparability across studies. Such an approach would not only bridge the gap between clinical observations and underlying biological mechanisms but would also strengthen the translational relevance of current research by enabling the identification of robust molecular signatures and actionable therapeutic targets.

Long-term consequences of altered cytokine balance

Traumatic knee injuries in skeletally immature patients generate a unique, sustained intra-articular inflammatory response.

Persistent elevation of key proinflammatory mediators (IL-1β, IL-6, IL-8, and TNF-α) has been consistently associated with early cartilage matrix degradation, chondrocyte apoptosis, and the initiation of pathways leading to PTOA in adults [15], consequently there is increasing interest in surgical strategies aimed at mitigating joint degradation in skeletally immature patients.

These include procedures to prevent loose bodies or detached Osteochondritis Dissecans (OCD) lesions through OCD fixation, meniscal allograft transplantation, meniscal repair, and surgical intervention to enhance knee stability.

However, the direct impact of these procedures on intra-articular pathways remains to be fully elucidated.

Interference with growth, remodeling, and mechanotransduction

This catabolic response appears notably more pronounced in patients with open physes, especially when the injury is accompanied by meniscal tears, indicating that the immature joint possesses a unique biological vulnerability to cytokine-mediated damage [4].

A critical distinction in pediatric patients is that inflammation unfolds in the context of active growth and high metabolic turnover. While resolving mediators like Resolvin E1 are initially higher in adolescents compared to adults, their concentrations decrease over time, potentially leaving the joint vulnerable if the inflammatory stimulus persists [6].

Cytokine-driven perturbation of the physis may impair chondrocyte proliferation and hypertrophy. Experimental study suggested that proinflammatory mediators can disrupt physeal biology, potentially leading to growth arrest, angular deformity, or altered limb alignment [29].

Furthermore, persistent IL-6 and TNF-α signaling interferes with subchondral bone metabolism, shifting turnover toward sclerosis rather than orderly remodeling [30].

Cytokines and growth factors such as Transforming Growth Factor-β (TGF-β) and Bone Morphogenetic

Protein-2 (BMP-2), when dysregulated by the inflammatory milieu, can stimulate aberrant osteophyte formation and subchondral thickening, features typical of early PTOA rather than normal joint maturation [31].

Furthermore, cytokine signaling and mechanical factors can reinforce each other after trauma: excessive or unbalanced joint loading increases chondrocyte mechanovulnerability, cell death, and inflammatory activity, whereas appropriately dosed dynamic loading may dampen post-injury inflammation (e.g. reduced synovial IL-1β and TNF-α) and downregulate catabolic pathways [32]. In skeletally immature patients, this mechanobiologic framework further supports the timely restoration of joint stability and alignment, rather than prolonged periods of instability while waiting for skeletal maturity.

Links to post-traumatic osteoarthritis in adulthood

A strong mechanistic and epidemiologic continuum connects adolescent trauma to adult PTOA, driven by "biochemical scars" left by the initial injury.

Longitudinal studies demonstrate that patients with sustained elevations of COMP, leptin, TNF-α, IL-1β, and MMP-3 after joint injury later exhibit joint space narrowing, osteophyte formation, and subchondral sclerosis [33]. This structural failure is often exacerbated by compromised IL-10 signaling, a key anti-inflammatory mediator associated with greater OA severity [34].

Studies in mice demonstrate that knee injury activates transcriptomic programs typical of joint aging, with enhanced expression of pro-inflammatory cytokine and chemokine genes and reduced expression of cartilage anabolic and extracellular matrix genes [35]. This 'inflamm-aging' phenomenon suggests that the joint's biological age advances significantly faster than the patient's chronological age.

Furthermore, in patients with isolated meniscal injury, older age at surgery was independently associated with higher preoperative synovial IL-6. In more chronic cases, statistical models suggested that age was also linked to higher Vascular Endothelial Growth Factor (VEGF) and IL-1ra, and that some age-related differences (indirect positive with Macrophage Inflammatory Protein (MIP)-1β, VEGF, and MMP-3 alongside indirect negative with Tissue Inhibitor of Metalloproteinases (TIMP)-1 and -2) may be mediated by baseline cartilage damage (Outerbridge grade) [8].

Regarding long-term outcomes, higher preoperative TIMP-1 was associated with better Knee injury and Osteoarthritis Outcome Score–Physical Function Short Form (KOOS-PS) at 10-year follow-up, supporting a potentially protective (associative) role of TIMP-1 in long-term function after meniscal surgery [8].

Collectively, the evidence suggests that the inflammatory cascade initiated by traumatic injury during skeletal immaturity does not merely cause transient inflammation but reprograms the joint biology, setting the stage for early-onset, progressive PTOA (Table 1).

Therapeutic and preventive perspectives

Growing evidence indicates that early modulation of the post-traumatic inflammatory microenvironment may represent a key therapeutic and preventive strategy in skeletally immature patients with knee injuries. Pharmacological approaches targeting inflammatory mediators such as IL-1β and TNF-α have demonstrated the ability to reduce cartilage catabolism and synovial activation in preclinical models and adult PTOA cohorts, highlighting the biological plausibility of early intervention after joint injury [36,37]. However, translation of these strategies to pediatric and adolescent populations remains limited, as concerns regarding safety, effects on skeletal growth, and the lack of age-specific clinical trials currently restrict their routine use in skeletally immature patients.

In parallel, biologic and regenerative approaches have gained increasing attention as potential tools to both modulate inflammation and support tissue repair. In skeletally immature patients, a wide range of surgical procedures aimed at repairing intra-articular structures, such as proximal ACL tear repair, tibial spine fixation, meniscal repair, and osteochondral defect fixation, are routinely performed, often in conjunction with biologic augmentation strategies. Platelet-rich plasma, fibrin clots, bone marrow stimulation, meniscal wrapping, and emerging bioscaffolds are increasingly used to enhance healing; however, the biological rationale underlying their application in the immature joint remains incompletely defined. Experimental evidence suggests that age-related differences in cellular responsiveness may be highly relevant, as ligament-derived fibroblasts from immature patients display a stronger *in vitro* response to platelet concentrates compared to cells from skeletally mature individuals [38]. Despite these observations, the complex intra-articular microenvironment receiving these biological stimuli and its role in driving effective tissue repair during growth remain poorly characterized.

Looking ahead, personalized therapeutic strategies based on biological age, skeletal maturity, and early cytokine or biomarker profiles represent a promising direction for improving outcomes after traumatic knee injuries in young patients. A more accurate definition of the intra-articular microenvironment in skeletally immature joints will be essential to understand the mechanisms underlying successful tissue repair and to rationalize the use of biologic augmentation during

Table 1

Studies on inflammatory profiles using different biological samples after traumatic knee injuries.

Author (year)	Population	Lesion	Markers	Main findings	Limitations	Refs
Bigoni M et al. (2018) [4]	Adolescents (~15.8 ± 1.5 years)	- physis open/ closing/closed - ACL tear	IL-1β IL-1ra IL-6 IL-8 IL-10 TNF-α	- time-dependent intra-articular cytokine pattern - high IL-6/IL-8/IL-10	- association with physis status - small sample (n=17) - variable sampling times	[4]
Tourville TW et al. (2015) [39]	Mixed (adults with ACL trauma)	- severe knee trauma/ACL disruption	ARGS	- elevated ARGS in SF after severe trauma - association with inflammatory activity	- heterogeneous timing - not pediatric-specific	[39]
Struglics A et al. (2015) [11]	Adults after ACL injury	- ACL tear	IL-6 IL-8 IL-10 TNF-α ARGS-aggrecan CTX-II	- large acute increases in cytokines (IL-6 up to ~1000x) - ARGS and CTX-II elevated	- different half-lives for markers - mostly adult cohorts - observational study	[11]
Kaplan DJ et al. (2017) [40]	ACL injured patients (various ages)	- ACL tear	MMP-3 TIMP-1 TIMP-2 FGF-2 IL-6 MIP-1β	- retrospective comparative study	- mixed cohorts	[40]
Neuman P et al. (2017) [10]	ACL injured patients (long-term follow-up cohorts)	- ACL tear	ARGS-aggrecan COMP MMP-3 TIMP-1	- higher aggrecan/COMP early after ACL	- early levels did not consistently predict OA 16 years later - longitudinal but biomarker predictive value limited	[10]
King JD et al. (2020) [21]	Acute ACL rupture patients (adults)	- ACL rupture	Proteomic profiling of synovial fluid (multiple proteins)	- significant proteome changes after ACL rupture - candidate biomarkers identified - adult-focused	- discovery proteomics needs validation	[21]
Kingery MT et al. (2022) [13]	Adults (~30 years)	- Acute ACL injury with serial sampling (acute vs pre-op)	bFGF IL-6 MCP-1 MIP-1β TIMP-1 IL-1Ra VEGF	- microenvironment shifts within first month	- limited age range	[13]
Dwivedi G et al. (2022) [15]	Experimental CBS coculture	- human tissue models - mechanical injury models simulating joint trauma	IL-1β IL-6 IL-8 TNF-α sGAG ARGS-aggrecan	- mechanical injury - cytokines induce PTOA-like changes	- links inflammation to tissue degeneration - *in vitro* model - translational steps to human pediatric *in vivo* needed	[15]
Turati M et al. (2021) [42]	Skeletally immature (10–17 years) vs adults	- ACL tear	Resolvin E1 IL-1β IL-10 TNF-α	- immature patients show higher RvE1 and IL-10 (suggesting increased resolution activity) vs adults	- preliminary - small sample	[6]
Larsson S et al. (2022) [22]	Adults	- ACL injury/OA contexts	ARGS-aggrecan	- ARGS biological variation lower in serum than SF	- SF reflects joint-specific release - not pediatric-specific - methodological focus	[22]
Meehan RT et al. (2021) [14]	OA patients (adults)	- Knee OA with pain	cytokines chemokines MMPs in SF	- OA SF profile similar to RA in many cytokines/MMPs	- chronic OA focus, not acute trauma in youth	[14]
Zhao Y et al. (2025) [41]	Adults (18–50 years)	- ACL tear with cartilage lesions	Metabolomic profiles in synovial fluid	- severity of cartilage injury significantly affects synovial metabolome	- needs replication and pediatric-specific cohorts	[41]
Turati M et al. (2023) [42]	Various	- Degenerative or traumatic knee disease	Prokineticin 2, cytokines (PK2)	- PK2 is implicated in inflammation/pain in knee disease	- exploratory study	[42]

surgical reconstruction. Identifying adolescents with a persistent pro-inflammatory synovial profile could enable risk stratification and targeted intervention aimed at preventing maladaptive joint remodeling and PTOA. At present, major gaps remain, including the scarcity of longitudinal studies in skeletally immature cohorts, the absence of standardized biomarker panels, and limited integration of biological data into clinical decision-making. Addressing these limitations will be essential to translate mechanistic insights into effective, evidence-based therapeutic and preventive strategies tailored to the unique biology of the growing joint.

Conclusions and future directions

Traumatic knee injuries in skeletally immature patients occur within a developmentally distinct joint environment, where open physes, high tissue turnover, and age-specific immune-repair programs shape the early post-traumatic response. Available data indicate that acute injury triggers a rapid intra-articular surge of pro-inflammatory mediators alongside matrix-degradation biomarkers, supporting the concept that biochemical changes accompany structural damage from the earliest phases. Importantly, in adolescents, these catabolic signals may coexist with comparatively stronger counter-regulatory and pro-resolving pathways, suggesting a potentially greater capacity for inflammation resolution, although this advantage may be transient and can be offset by ongoing instability, concomitant meniscal injury, hemarthrosis, or unfavorable mechanical loading.

Closing the current knowledge gaps will require well-designed longitudinal studies specifically focused on pediatric and adolescent populations, integrating serial collection of synovial fluid and blood with advanced imaging, biomechanical assessments, and long-term clinical outcomes. In this context, the field would greatly benefit from the standardization of biomarker panels and analytical methodologies, enabling cross-study comparisons and the identification of reproducible molecular signatures of risk or recovery. Establishing consensus on core inflammatory, catabolic, and pro-resolving biomarkers in synovial fluid and systemic circulation represents a critical step toward translating mechanistic insights into clinical tools. Ultimately, a deeper understanding of early post-traumatic molecular trajectories in the growing joint may inform targeted monitoring strategies and timely interventions aimed at preventing or mitigating the risk of early-onset post-traumatic degeneration, shifting pediatric knee injury management from a reactive to a truly preventive paradigm.

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CRediT authorship contribution statement

Marco Bigoni: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Marco Crippa:** Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Marco Turati:** Conceptualization, Methodology, Investigation, Formal analysis, Supervision, Writing – original draft, Writing – review and editing. **Ramona Meanti:** Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review and editing. **Giulia Beltrame:** Investigation, Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- • of special interest
- •• of outstanding interest

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