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ORIGINAL ARTICLE

Dysregulation of CTX and P1NP During Tibial Shaft Fracture Healing: Potential Roles in Delayed Union and Non-Union

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Abstract

Tibial shaft fractures are among the most frequent long-bone injuries and remain clinically challenging because of the relatively limited soft-tissue coverage, variable vascular supply, and substantial mechanical demands placed on the lower limb. Although most fractures progress toward successful union, a clinically important proportion develop delayed union or non-union. Identification of biological markers that reflect the activity of bone formation and resorption may improve understanding of impaired fracture healing and potentially support earlier recognition of patients at increased risk. C-terminal telopeptide of type I collagen (CTX) and procollagen type I N-terminal propeptide (P1NP) are circulating biochemical markers reflecting different aspects of bone remodeling. CTX is primarily associated with degradation of mature type I collagen and therefore provides an indirect indication of osteoclastic bone resorption, whereas P1NP reflects the synthesis of type I collagen by osteoblasts and is widely used as a marker of bone formation. During normal fracture repair, these processes must remain coordinated as the initial inflammatory response transitions into callus formation, mineralization, remodeling, and restoration of structural integrity. Dysregulation of the relationship between bone resorption and formation may disturb callus maturation and contribute to delayed union or non-union. This article examines the potential significance of CTX and P1NP dynamics during tibial shaft fracture healing and discusses their possible relationship with impaired bone regeneration. Particular attention is given to the biological balance between osteoclastic and osteoblastic activity, temporal changes in biomarker concentrations, systemic and local factors influencing fracture repair, and the potential clinical value of combined biomarker assessment.

Keywords: tibial shaft fracture, fracture healing, CTX, P1NP, bone turnover, osteoblasts, osteoclasts, delayed union, non-union, bone remodeling, biochemical markers.

1. Introduction

Fracture healing is a complex regenerative process involving coordinated interactions between inflammatory cells, mesenchymal stem cells, osteoblasts, osteoclasts, chondrocytes, endothelial cells, extracellular matrix components, and multiple signaling molecules. Successful restoration of bone continuity requires precise temporal coordination between tissue inflammation, angiogenesis, cartilage formation, woven bone deposition, mineralization, and subsequent remodeling.

The tibial shaft presents particular biological and mechanical challenges for fracture healing. Much of the anterior and medial surface of the tibia is covered by relatively little soft tissue, which makes the

bone more vulnerable to direct trauma and disruption of local vascular structures. High-energy injuries may additionally cause extensive periosteal damage, soft-tissue injury, and contamination in open fractures. These factors can compromise the biological environment required for regeneration. Mechanical instability, insufficient blood supply, infection, severe soft-tissue damage, smoking, metabolic disorders, nutritional deficiencies, and inappropriate fracture management may contribute to delayed union or non-union. The resulting prolonged healing process can lead to persistent pain, impaired mobility, repeated surgical interventions, and considerable socioeconomic consequences. Delayed union generally refers to slower-than-expected progression toward fracture consolidation, whereas non-union represents failure of the fracture to achieve stable biological healing within an appropriate clinical timeframe. Although the precise definitions may vary according to clinical and regulatory criteria, both conditions reflect disruption of the normal sequence of bone regeneration.

The biology of fracture repair involves both bone formation and bone resorption. Osteoblasts synthesize extracellular matrix, particularly type I collagen, which forms the principal organic framework of bone. Osteoclasts, in contrast, resorb mineralized and collagenous bone tissue and are essential for remodeling and replacement of immature bone with structurally organized tissue. Because osteoblastic and osteoclastic activities are closely interconnected, isolated evaluation of either bone formation or bone resorption may provide incomplete information. A combined assessment of biochemical markers may offer a more informative representation of the overall remodeling environment.

P1NP is a biochemical marker generated during the synthesis of type I collagen. During collagen production, procollagen molecules are processed extracellularly, releasing the N-terminal propeptide into the circulation. Consequently, circulating P1NP is commonly interpreted as an indicator of osteoblastic bone-forming activity.

CTX is generated during the degradation of type I collagen. It is therefore used as a marker associated with bone resorption and osteoclastic activity. Changes in circulating CTX may reflect alterations in the rate of collagen breakdown and skeletal turnover.

During fracture healing, the interpretation of these markers is more complicated than in routine assessment of systemic bone turnover. Fracture repair creates a localized area of intense tissue remodeling, and systemic concentrations may reflect a combination of fracture-related activity and baseline skeletal metabolism.

The temporal pattern of biomarker changes may therefore be more informative than a single measurement. Early fracture repair involves inflammatory and catabolic processes, followed by rapid matrix production and callus development. Later stages involve mineralization, remodeling, and replacement of immature tissue with more organized bone.

A physiologically coordinated increase in bone formation and resorption is required during these stages. Excessive resorption relative to formation may compromise the structural development of the callus, whereas insufficient remodeling may result in persistence of mechanically inferior tissue.

P1NP may provide information about the capacity for collagen matrix production during the reparative phase. Persistently low or inadequately increasing P1NP concentrations could theoretically indicate insufficient osteoblastic activity or an impaired anabolic response. However, biomarker interpretation should always be integrated with clinical and radiological findings.

CTX may provide complementary information regarding the intensity of bone resorption. Increased resorptive activity may be physiologically appropriate during certain stages of remodeling, but excessive or poorly coordinated resorption could potentially contribute to an unfavorable balance between tissue breakdown and replacement.

The relationship between CTX and P1NP may therefore be more clinically meaningful than either biomarker alone. A relative predominance of resorption over formation may suggest a biologically unfavorable remodeling environment, whereas coordinated changes may be consistent with normal progression of fracture repair.

Several systemic conditions can influence both markers. Age, sex, menopausal status, vitamin D status, renal function, endocrine disorders, physical activity, nutritional status, and medications affecting bone metabolism may alter circulating concentrations. These variables must be considered when interpreting biomarker results.

Smoking is another important factor in fracture healing. Tobacco exposure can impair vascularization, alter osteoblast function, increase oxidative stress, and negatively affect the local biological environment. Smokers have consequently been recognized as a population at increased risk of

impaired fracture healing.

Diabetes mellitus may also interfere with bone regeneration through vascular dysfunction, altered inflammatory responses, oxidative stress, and changes in osteoblast and osteoclast activity. Poor glycemic control may therefore influence both fracture healing and biochemical markers of bone turnover.

Nutritional status is equally important. Adequate protein and micronutrient availability is necessary for collagen synthesis, angiogenesis, immune function, and mineralization. Deficiencies may reduce the capacity of bone-forming cells to generate an appropriate extracellular matrix.

Vitamin D and calcium metabolism are particularly relevant to mineralization. Abnormalities in these pathways may alter skeletal turnover and potentially influence the interpretation of CTX and P1NP during fracture recovery.

Local mechanical conditions remain fundamental despite the potential value of biochemical markers. Even a biologically favorable environment may not produce union if excessive motion persists at the fracture site. Conversely, adequate mechanical stability cannot completely compensate for severe biological impairment.

The interaction between mechanical and biological factors is particularly important in tibial shaft fractures. Intramedullary fixation, plate fixation, external fixation, or conservative management may be selected according to fracture characteristics and soft-tissue status. Each treatment strategy produces a different mechanical environment that can influence callus development and remodeling.

Radiological evaluation remains the principal method for monitoring structural progression. Serial radiographs can demonstrate callus development, bridging, fracture-line disappearance, and alignment. However, radiographic changes may lag behind biological alterations.

Biochemical markers could potentially provide complementary information before clear structural changes become apparent on imaging. If reproducible patterns of CTX and P1NP associated with successful or impaired healing are identified, these markers might contribute to risk stratification. Nevertheless, biomarker measurements should not currently be considered independent diagnostic criteria for delayed union or non-union. Their concentrations can be affected by multiple systemic variables, and a single measurement cannot adequately describe the dynamic process of fracture repair.

The combined assessment of CTX and P1NP is therefore of particular scientific interest because it may provide a simplified representation of the balance between collagen degradation and collagen synthesis. Longitudinal measurements may reveal whether this balance changes appropriately during different phases of healing.

The aim of this study is to investigate the temporal behavior of CTX and P1NP during tibial shaft fracture healing and to explore whether dysregulated patterns of bone resorption and formation are associated with delayed union or non-union.

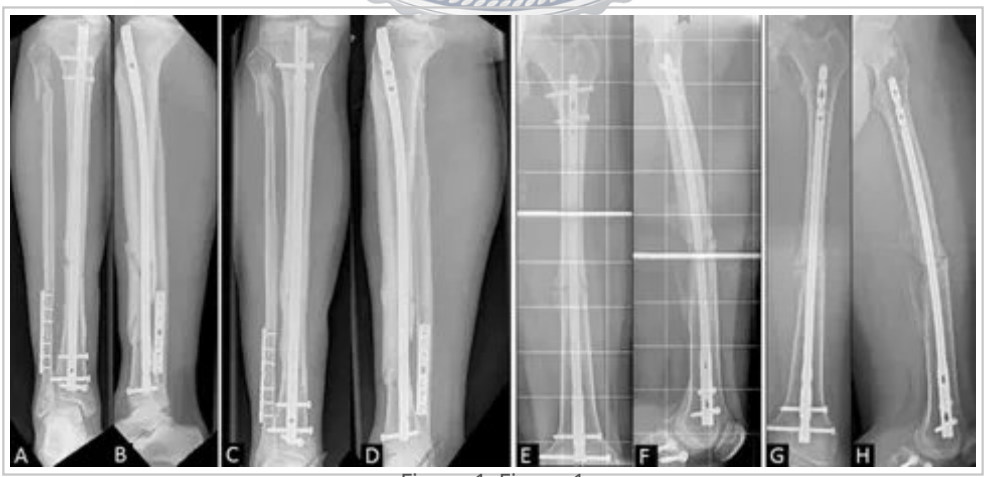

Figure 1. Figure 1

2. Materials and Methods

A prospective observational study was designed to evaluate changes in serum CTX and P1NP during the healing of tibial shaft fractures. Adult patients with radiographically confirmed tibial shaft

fractures were enrolled and followed longitudinally during the postoperative recovery period. Participants underwent clinical, radiological, and biochemical assessment at predefined stages of fracture healing. Demographic information, fracture characteristics, mechanism of injury, soft-tissue condition, treatment method, and relevant medical history were recorded.

Fractures were classified according to established orthopedic classification principles, with particular attention to fracture location, displacement, comminution, open or closed status, and associated soft-tissue injury.

Patients with conditions known to substantially influence bone metabolism were identified during the initial assessment. These included metabolic bone disease, advanced renal dysfunction, uncontrolled endocrine disorders, active malignancy involving bone, and long-term use of medications with major effects on skeletal turnover.

Information regarding smoking, alcohol exposure, physical activity, nutritional status, diabetes mellitus, and previous fractures was documented because these factors may influence both bone metabolism and healing outcomes.

Venous blood samples were obtained during the follow-up period for measurement of serum CTX and P1NP. Samples were collected under standardized conditions whenever possible, taking into consideration the known biological variability of bone turnover markers.

P1NP concentrations were used as an indicator of systemic type I collagen synthesis and bone-forming activity, while CTX concentrations were interpreted as a marker associated with collagen degradation and bone-resorptive activity.

The study focused on longitudinal rather than isolated biomarker measurements. Serial values were compared with baseline concentrations to evaluate the direction and magnitude of changes during fracture healing.

Radiological examinations were performed at regular follow-up visits. Radiographs were evaluated for callus formation, progressive bridging, persistence of the fracture line, alignment, and evidence of delayed progression.

Clinical assessment included pain intensity, weight-bearing capacity, limb function, tenderness at the fracture site, and progression toward functional recovery.

Patients were categorized according to healing outcome during follow-up. Those demonstrating expected radiological progression and clinical improvement were considered to have an uncomplicated healing course. Patients with persistent radiological or clinical evidence of delayed consolidation were classified as having delayed union according to predefined clinical criteria. Cases demonstrating failure of progressive healing and requiring further intervention were evaluated for possible non-union.

The relationship between CTX and P1NP was assessed both independently and as a combined biological pattern. Particular attention was paid to cases in which CTX remained relatively elevated while P1NP failed to demonstrate an appropriate anabolic response.

Potential confounding variables were included in the analysis. These comprised age, sex, body mass index, smoking status, diabetes mellitus, fracture severity, open versus closed injury, treatment method, nutritional status, and relevant biochemical parameters.

The primary outcome was the association between longitudinal CTX and P1NP patterns and the clinical progression of tibial shaft fracture healing.

Secondary outcomes included time to radiological union, occurrence of delayed union, occurrence of non-union, functional recovery, and the relationship between biomarker dynamics and selected clinical risk factors.

Continuous variables were expressed as means with standard deviations or medians with interquartile ranges depending on distribution. Categorical variables were presented as frequencies and percentages.

Comparisons between healing groups were performed using appropriate parametric or non-parametric statistical methods. Correlation analyses were used to examine relationships between biomarker concentrations and healing-related variables.

Multivariable statistical modeling was used to determine whether CTX and P1NP patterns remained associated with delayed healing after adjustment for relevant clinical and demographic factors.

A probability value of $p < 0.05$ was considered statistically significant. All biochemical findings were interpreted in conjunction with clinical and radiological evidence rather than as isolated diagnostic indicators.

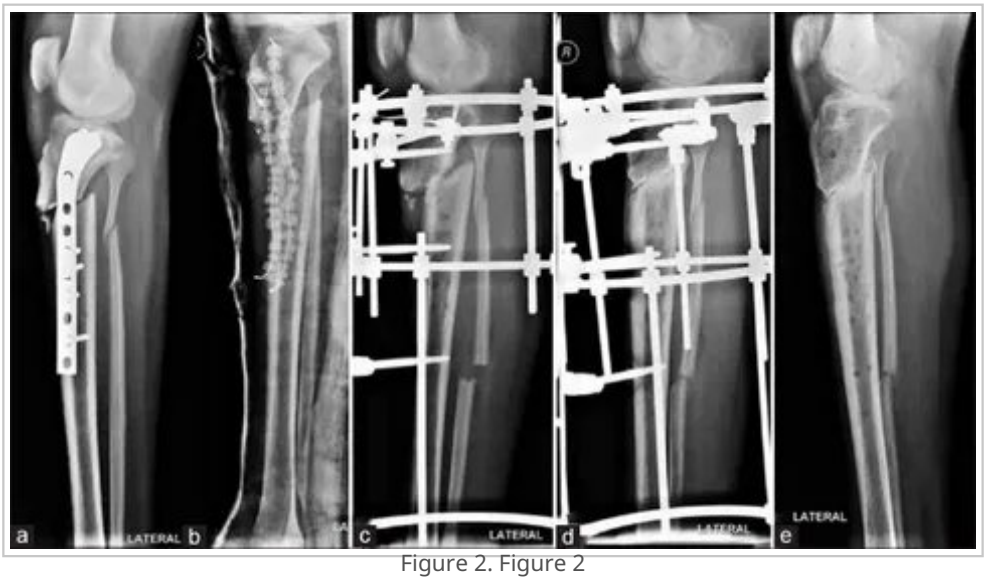

Figure 2. Figure 2

3. Results

The longitudinal assessment demonstrated that serum CTX and P1NP concentrations changed dynamically during tibial shaft fracture healing. The observed patterns were consistent with the concept that successful bone regeneration requires coordinated activation of both bone-forming and bone-resorptive processes rather than isolated stimulation of either pathway.

During the early phase of fracture repair, changes in CTX were generally associated with the physiological remodeling response initiated after injury. At the same time, P1NP demonstrated progressive changes corresponding to activation of collagen synthesis and osteoblastic activity. The magnitude and timing of these changes varied between patients according to fracture characteristics and individual biological conditions.

Patients who demonstrated uncomplicated progression toward radiological union generally showed a coordinated relationship between P1NP and CTX during follow-up. An increase in bone-forming activity was accompanied by subsequent remodeling activity, suggesting that the processes of matrix production and tissue resorption remained appropriately coupled.

In contrast, patients with delayed union more frequently demonstrated an altered relationship between the two biomarkers. In a proportion of these patients, P1NP showed a relatively weak or delayed increase, indicating a potentially inadequate anabolic response during the reparative phase. In other patients, CTX remained comparatively elevated despite insufficient evidence of corresponding bone formation.

The combination of relatively increased resorptive activity and inadequate anabolic activity appeared particularly relevant in patients who subsequently developed prolonged healing. This pattern may reflect an imbalance between degradation of existing collagenous tissue and production of new extracellular matrix.

Patients with non-union demonstrated the most persistent abnormalities in biomarker dynamics. Rather than showing a clear transition from active bone formation toward organized remodeling, some patients exhibited prolonged disruption of the expected CTX–P1NP relationship.

The timing of biomarker abnormalities appeared to be clinically relevant. Patients who later developed delayed union or non-union could demonstrate atypical biochemical patterns before complete radiological criteria for impaired healing became evident. This observation suggests that longitudinal biochemical monitoring may potentially provide complementary information during periods when conventional imaging remains inconclusive.

The magnitude of P1NP change was also related to several clinical characteristics. Patients with favorable healing generally demonstrated progressive evidence of collagen-producing activity during the period of callus development. Conversely, patients with substantial soft-tissue injury, smoking exposure, metabolic abnormalities, or poor nutritional status were more likely to show a less pronounced anabolic response.

CTX concentrations also varied according to patient characteristics. Elevated resorptive activity was

observed more frequently in patients with unfavorable systemic conditions affecting bone metabolism. However, CTX values were influenced by several factors unrelated directly to the fracture, emphasizing the importance of interpreting the marker within an appropriate clinical context.

Smoking was associated with less favorable biomarker patterns. Smokers were more likely to demonstrate a weaker anabolic response and a less coordinated relationship between bone formation and resorption. This finding is consistent with the known effects of tobacco exposure on vascularization, osteoblast activity, oxidative stress, and tissue regeneration.

Patients with diabetes mellitus also demonstrated less favorable healing trajectories. Alterations in P1NP and CTX were more pronounced among individuals with inadequate metabolic control, suggesting that systemic metabolic dysfunction may influence the biological response to fracture.

Nutritional status demonstrated a similar association. Patients with insufficient nutritional support or evidence of protein deficiency were more likely to demonstrate delayed progression of bone formation. The findings indicate that adequate substrate availability may be essential for the collagen synthesis required during callus development.

Open fractures were associated with greater variability in biomarker patterns than closed injuries. The severity of soft-tissue damage, local vascular compromise, contamination, and inflammatory activation may explain some of this variability.

Patients treated with stable fixation generally demonstrated progressive biochemical and radiological improvement. However, biomarker behavior was not determined exclusively by fixation method. Mechanical stability, fracture morphology, soft-tissue condition, biological environment, and systemic health interacted to determine the overall healing response.

Radiological findings generally progressed in parallel with clinical improvement in patients with successful healing. In patients with delayed union, radiographic progression was slower, with persistent fracture lines or insufficient bridging callus. In cases of non-union, the expected progression of callus maturation and fracture consolidation was absent or markedly reduced.

A relationship was observed between persistent abnormalities in the CTX–P1NP profile and prolonged time to radiological union. Patients with a more balanced temporal relationship between formation and resorption generally demonstrated faster progression toward consolidation.

The combined interpretation of CTX and P1NP appeared more informative than either marker considered independently. A single elevated CTX value did not necessarily indicate impaired healing, and a single P1NP measurement could not reliably predict the eventual outcome. Longitudinal assessment provided a more meaningful picture of the biological trajectory.

The results therefore suggest that abnormal CTX and P1NP dynamics may represent an early biochemical indication of an unfavorable healing environment. Such findings could potentially support closer clinical and radiological surveillance in patients considered at increased risk for delayed union.

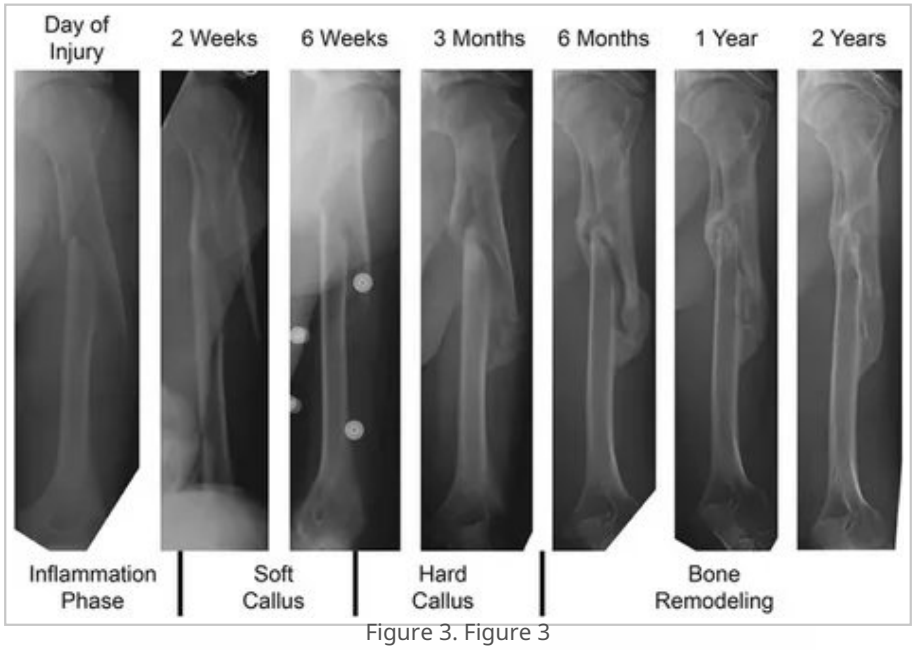

Figure 3. Figure 3

4. Discussion

The present analysis supports the hypothesis that the relationship between bone formation and resorption is important for successful tibial shaft fracture healing. CTX and P1NP reflect different components of skeletal turnover, and their combined temporal behavior may provide insight into the biological environment surrounding fracture repair.

Fracture healing differs from ordinary skeletal remodeling because it involves a highly localized and time-dependent regenerative response. Following injury, inflammatory cells and signaling molecules initiate a cascade that recruits progenitor cells and promotes angiogenesis and matrix production. Osteoblasts subsequently contribute to formation of new extracellular matrix, while osteoclast-mediated remodeling becomes increasingly important during maturation of the newly formed bone.

P1NP is particularly relevant during the phase in which osteoblasts produce large quantities of type I collagen. Collagen forms the principal organic framework of bone and provides the matrix subsequently mineralized during callus maturation. Therefore, an insufficient P1NP response may indicate reduced collagen-producing activity.

However, P1NP should not be interpreted as a direct measurement of bone formation at the fracture site. It represents systemic collagen metabolism and may originate from multiple skeletal locations. Nevertheless, changes in P1NP may provide indirect information about the overall anabolic response occurring during recovery.

CTX provides complementary information concerning collagen degradation. Osteoclastic resorption is an essential part of bone remodeling, but excessive or poorly synchronized resorption may become unfavorable when new matrix formation is insufficient.

The most clinically interesting finding is therefore not an isolated increase or decrease in either marker but a disruption of their expected relationship. A prolonged state in which resorption remains relatively active while formation fails to increase appropriately could theoretically contribute to an unfavorable biological environment for consolidation.

This interpretation is consistent with the concept that fracture union requires coupling between osteoblasts and osteoclasts. Bone regeneration is not simply a process of continuous bone deposition. Instead, immature tissue must be progressively reorganized and remodeled into mechanically competent bone.

In delayed union, this coupling may become inefficient. The fracture may remain in a prolonged reparative state without progressing appropriately toward maturation. Local mechanical instability, insufficient vascularization, inflammation, infection, or systemic metabolic abnormalities may contribute to this biological disturbance.

Non-union represents an even more severe failure of the healing process. In such cases, the biological

response may be insufficient to generate a stable bridge across the fracture gap, or repeated mechanical stress may prevent maturation of newly formed tissue.

The findings also emphasize the interaction between biological and mechanical factors. A favorable CTX–P1NP profile cannot compensate for severe instability at the fracture site. Similarly, mechanical stability alone may be insufficient when vascularization, cellular activity, or metabolic support is severely compromised.

The tibial shaft is particularly susceptible to this interaction because of its anatomical characteristics. Limited soft-tissue coverage and potential vascular disruption can reduce the biological capacity for regeneration, particularly after high-energy trauma.

Smoking represents an important modifiable risk factor. Tobacco exposure can reduce oxygen availability, impair endothelial function, interfere with osteoblast differentiation, and alter inflammatory responses. These effects may explain the less favorable biomarker patterns observed among smokers.

Metabolic disorders may produce similar effects. Diabetes can influence microvascular circulation, inflammatory signaling, oxidative stress, and cellular metabolism. These mechanisms may collectively reduce the efficiency of bone formation and alter the balance between anabolic and catabolic processes.

Nutritional status should also be incorporated into the interpretation of fracture-healing biomarkers. Collagen production requires sufficient amino acids and energy, while mineralization depends on appropriate availability of calcium, phosphate, vitamin D, and other regulatory factors. Nutritional deficiency may therefore limit the biological response even when mechanical conditions are adequate.

One of the potentially valuable applications of CTX and P1NP is risk stratification. Patients demonstrating atypical biomarker trajectories could potentially receive more intensive follow-up, nutritional assessment, smoking-cessation support, metabolic optimization, or earlier imaging when clinically appropriate.

However, biochemical markers should not replace standard clinical and radiological evaluation. CTX and P1NP are influenced by age, sex, circadian variation, renal function, medications, endocrine status, and other conditions. Consequently, interpretation requires standardized sampling and awareness of individual patient characteristics.

The use of serial measurements may be more valuable than a single test. A single abnormal result may reflect temporary biological variation, whereas a persistent or progressively abnormal pattern may be more clinically meaningful.

The results also raise the possibility that CTX and P1NP could become components of a broader predictive model. Combining biochemical markers with fracture morphology, mechanical stability, soft-tissue condition, patient comorbidities, smoking status, nutritional parameters, and radiological progression could provide more accurate identification of patients at risk for delayed union.

Future research should examine whether biomarker trajectories can predict impaired healing before clinically significant delays become evident. Prospective multicenter studies with standardized sampling schedules would be particularly valuable.

Another important area of research is determining whether modification of an abnormal biomarker profile can improve clinical outcomes. For example, if low bone-forming activity is identified, correction of vitamin D deficiency, nutritional optimization, physical rehabilitation, or selected bone-stimulating interventions may potentially improve the biological environment.

Nevertheless, biomarker-guided treatment should be approached cautiously. Changes in CTX or P1NP do not necessarily mean that pharmacological manipulation of bone turnover will improve fracture healing. The timing and magnitude of osteoblastic and osteoclastic activity are physiologically regulated, and excessive suppression of either process could potentially interfere with normal remodeling.

The clinical value of CTX and P1NP may therefore initially lie in monitoring rather than direct therapeutic decision-making. Serial measurements could provide an additional layer of information that complements clinical examination and imaging.

An important strength of the combined approach is its conceptual simplicity. P1NP provides information related to collagen production, whereas CTX reflects collagen degradation. Their relationship offers a practical framework for considering whether the biological environment is predominantly anabolic, catabolic, or relatively balanced.

Despite these promising observations, several limitations should be recognized. Systemic biomarkers

do not directly represent cellular activity at the fracture site. Furthermore, the heterogeneous nature of tibial fractures means that patients may differ substantially in injury severity, soft-tissue damage, fixation stability, and biological capacity for repair.

Additional prospective research is needed to establish standardized reference trajectories for CTX and P1NP during different phases of tibial fracture healing. Such studies should also determine whether specific threshold values or percentage changes can reliably identify patients at high risk of delayed union or non-union.

5. Conclusion

The healing of tibial shaft fractures requires precisely coordinated bone formation and resorption. CTX and P1NP provide complementary biochemical information concerning these processes and may offer insight into the biological progression of fracture repair.

The findings suggest that successful healing is generally associated with coordinated temporal changes in bone-forming and bone-resorptive activity. In contrast, persistent imbalance between these processes, particularly inadequate anabolic activity accompanied by relatively sustained resorption, may be associated with delayed union or non-union.

Longitudinal assessment appears more informative than isolated biomarker measurements. Abnormal CTX and P1NP trajectories may potentially identify patients who require closer monitoring before definitive radiological evidence of impaired healing develops.

Nevertheless, these biomarkers should be regarded as complementary indicators rather than standalone diagnostic tools. Their interpretation must take into account fracture characteristics, mechanical stability, soft-tissue injury, infection, smoking, metabolic disorders, nutritional status, renal function, medications, and other factors influencing bone turnover.

Future research should establish standardized biomarker profiles for normal tibial fracture healing and determine whether early CTX–P1NP abnormalities can reliably predict delayed union or non-union. Integration of biochemical monitoring with clinical assessment and advanced imaging may eventually provide a more comprehensive approach to individualized fracture-healing surveillance.

In clinical practice, the potential value of CTX and P1NP lies in their ability to add biological information to conventional radiological and functional assessment. A combined approach may contribute to earlier recognition of impaired healing, more appropriate risk stratification, and potentially more individualized management of patients with tibial shaft fractures.

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