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Clinical Efficacy of Jiegu San External Application Combined with Small Splint External Fixation Following Closed Reduction in Distal Radius Fracture Patients

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Abstract: *Objective:* To explore the clinical efficacy of the external application of Jiegu San combined with small splint external fixation after closed reduction in treating patients with distal radius fracture. *Methods:* A total of 397 cases with distal radius fractures admitted from October 2019 to December 2023 were recruited as study subjects and divided into the control group (n = 180) and the observation group (n = 217) according to the treatment method. The control group was treated with small splint external fixation after closed reduction, while the observation group was treated with Jiegu San external application in addition to small splint external fixation following closed reduction. The clinical efficacy, circumference of the fracture site, and pain level of both groups were observed and compared. *Results:* The total clinical efficacy rate of patients in the observation group (97.70%) was significantly higher than that of patients in the control group (88.88%; P = 0.000). Additionally, the circumference of the fracture site of the observation group was significantly smaller than that of the control group after 3 weeks of treatment (P = 0.000). Moreover, the pain score of the patients in the observation group was significantly lower than that of the control group after 3 weeks of treatment (P = 0.000). *Conclusion:* In the treatment of distal radius fracture, the combination of Jiegu San external application combined with small splint external fixation following closed reduction can effectively improve the clinical efficacy of patients, promote the reduction of swelling, and reduce the pain level of patients, which is worthy of further promotion.

Keywords: Jiegu San; Closed reduction; Small splint external fixation; Distal radius fracture; Clinical efficacy

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1. Introduction

Distal radius fracture is one of the common types of surgical fracture, accounting for nearly 80% of all forearm fractures [1], which is commonly caused by the palm-first position when falling in the clinic. With the accelerated pace of life and the arrival of an aging society, the incidence of this fracture has been increasing yearly [2]. Due

to the close relationship between the distal radius and the wrist joint, its fracture often affects the recovery of the wrist function, which in turn has a serious impact on patients' quality of life [3]. Therefore, enhancing the therapeutic outcomes of distal radius fractures, minimizing the incidence of complications, and improving patients' quality of life are pressing issues in current orthopedic research and clinical work. For closed fractures that do not require surgical treatment, external fixation techniques have been widely used. External fixation is commonly carried out using plaster or splint, which is used to keep the fracture end in the result of reduction to facilitate the healing of the fracture, but too long fixation time and too rigid fixation may lead to the emergence of complications such as joint stiffness and muscle atrophy. As a result, some auxiliary therapeutic means, such as the external application of Jiegu San combined with closed reduction and other traditional Chinese medicine methods, have been gradually applied to the treatment of distal radius fracture, and certain clinical results have been achieved. Thus, this study was carried out to observe the healing status of patients with distal radius fractures treated with Jiegu San external application combined with small splint external fixation following manipulative redundancy, thereby providing a more scientific and effective therapeutic basis and a new clinical plan for the non-operative treatment of distal radius fracture to improve the prognosis of the patients, decrease the number of complications, and enhance the quality of life.

2. Materials and methods

2.1. General information

A total of 397 cases with distal radius fractures admitted between October 2019 and December 2023 were recruited and divided into the control group (n = 180) and the observation group (n = 217) according to the treatment. There was no significance in the basic data statistics of the two groups of patients ($P > 0.05$).

Inclusion criteria: (1) Diagnosed as distal radius fracture by imaging examination (such as X-ray, CT, etc.); (2) Closed fracture; (3) Within 48 hours from the occurrence of fracture to the event of admission to the hospital; (4) No dysfunction of heart, lungs, liver, kidneys and other important organs, and able to tolerate closed reduction and external fixation treatment; (5) Patients or their legal guardian signed an informed consent form, agreeing to participate in this study.

Exclusion criteria: (1) Patients with pathological fractures caused by tumors, osteoporosis, metabolic diseases, etc.; (2) Patients who have been injured for more than 2 weeks, and the fracture ends have obvious scab growth, which is unsuitable for closed reduction; (3) Patients with fracture ends exposed to the external environment, which has the risk of infection; (4) Patients with a history of allergy to the components of Jiegu San or the materials of small splint; (5) Patients with severe systemic disorders, such as heart failure, respiratory failure, severe hepatic and renal insufficiency, etc.; (6) The presence of mental disorders or cognitive disorders; (7) The presence of severe soft tissue contusions at the fracture site.

2.2. Methods

The control group was treated with small splint external fixation after closed reduction. The patient took the sitting or lying position, and according to the type of fracture and displacement, the doctor used appropriate traction, folding top, pressing, and other techniques to restore the fracture end to its normal anatomical position. After the completion of closed reduction, according to the patient's fracture site and stability after reduction, appropriate small splints were chosen, placed on the fracture site of the distal radius, and fixed with a bandage or cloth tape to maintain the stability and alignment of the fracture end. The tightness of the splint was adjusted regularly to ensure the fixation outcomes and avoid discomfort or injury caused by excessive compression.

In the observation group, in addition to the treatment received by the control group, the method of Jiegu

San external application was carried out. The appropriate amount of Jiegu San was taken and mixed with the appropriate amount of 75% alcohol to make a paste. After the completion of closed reduction and repositioning, the Jiegu San paste was applied to the skin of the fracture site, covered with cotton, and gently wrapped with a bandage to immobilize the Jiegu San, keeping it moist, and ensuring its absorption. A small splint bandage was then added. Jiegu San paste was replaced every 2 to 3 days, and the external application site was kept clean and dry to avoid infection and allergy.

2.3. Observation indicators

The clinical efficacy of patients according to their clinical symptom performance, the circumference of the fracture site before and 3 weeks after treatment, and the visual analog scoring (VAS) method for pain level assessment (0–10 points) of both groups were observed and compared.

2.4. Statistical analysis

SPSS 20.0 software was used for statistical processing. Measurement data were expressed as mean ± standard deviation (SD) while count data were expressed as [*n* (%)], and the comparison of the two groups was performed using two-sample *t* or χ^2 tests, with statistically significant differences indicated by *P* values of less than 0.05.

3. Results

3.1. Clinical efficacy

As shown in **Table 1**, the total clinical efficacy rate of patients in the observation group (212/97.70%) was significantly higher than that of the control group (160/88.88%; $\chi^2 = 12.933$, $P = 0.000$).

Table 1. Comparison of clinical efficacy between the two groups [*n* (%)]

Efficacy indicators	Very effective	Effective	Ineffective	Total effective rate
Control group (*n* = 180)	35 (19.44%)	125 (69.44%)	20 (11.12%)	160 (88.88%)
Observation group (*n* = 217)	168 (77.42%)	44 (20.28%)	5 (2.30%)	212 (97.70%)
χ^2				12.933
P				0.000

3.2. Fracture site circumference before and after treatment

Table 2 shows that there was no significant difference between the two group's fracture site circumferences. However, after 3 weeks of treatment, the observation group showed a significantly smaller fracture site circumference as compared to the control group ($P = 0.000$).

Table 2. Comparison of fracture site circumference before and after treatment between the two groups (mean ± SD)

Time	Before treatment	After 3 weeks of treatment
Control group (*n* = 180)	39.61 ± 2.46	31.56 ± 2.05
Observation group (*n* = 217)	39.54 ± 2.53	27.35 ± 1.64
t	0.278	22.730
P	0.781	0.000

3.3. Pain score

Before treatment, the pain scores of both groups were not significantly different ($P > 0.05$), but after 3 weeks of treatment, the observation group had a significantly lower pain score as compared to the control group ($P = 0.000$), as presented in **Table 3**.

Table 3. Comparison of pain scores between the two groups (mean ± SD)

Time	Before treatment	After 3 weeks of treatment
Control group ($n = 180$)	7.68 ± 1.08	3.98 ± 0.72
Observation group ($n = 217$)	7.61 ± 1.07	2.23 ± 0.31
t	0.646	32.375
P	0.519	0.000

4. Discussion

Distal radius fracture is a fracture within 2–3 cm above the articular surface of the distal radius, and this region includes the radial wrist joint surface and the proximal carpal joint surface. The types of fracture can be categorized into extension fracture, flexion fracture, and Barton fracture according to the direction of the fracture line, the direction of displacement of the fracture end, and the degree of fracture. Fractures of the distal radius are mostly caused by traumatic injuries, such as landing on the palm during a fall, automobile accident injuries, sports injuries, etc. In these cases, the direct action of external forces can lead to fractures of the distal radius. The severity and type of fracture depend on the size, direction, and duration of the external force.

In the treatment of distal radius fracture, external fixation with a small splint after closed reduction is a commonly used conservative treatment method [4]. However, this method also has some disadvantages. First, external fixation with a small splint may not be as stable as plaster fixation, especially in the early period after fracture reduction, when the fracture end has not yet formed stable healing, and the fixation effect of the small splint may be affected by the patient's activities or external factors, which may lead to the re-displacement of the fracture end [5]. Secondly, although closed reduction can restore the anatomical alignment of the fracture to a certain extent, its precision and stability have a certain gap compared with surgical incisional reduction, especially for those complex and comminuted fractures, closed reduction may be difficult to achieve the ideal reduction effect. Meanwhile, after small splint immobilization, patients may feel discomfort and pain in the wrist, especially when the initial immobilization is tight, and this discomfort may affect the patient's daily activities and sleep quality. In addition, prolonged minor splint immobilization may lead to complications such as joint stiffness and muscle atrophy. Plus, if immobilization is improper or not adjusted in time, it may also lead to risks such as pressure ulcers and nerve damage. For this reason, it is necessary to combine other treatments with comprehensive treatment, and the external application of bone-splinting has become a good choice.

In this study, the total clinical effectiveness rate of patients in the observation group (97.70%) was significantly higher than that of the control group (88.88%; $P = 0.000$), and the fracture site circumference of the observation group was significantly smaller than that of the control group after 3 weeks of treatment ($P = 0.000$). This indicates that in the treatment of distal radius fracture, the combination of Jiegu San external application and small splint external fixation following closed reduction can effectively improve the clinical efficacy of the patients and promote the reduction of swelling and healing of the patient's tissues. This is because the traditional Chinese medicine components in Jiegu San have the effect of activating blood

circulation, removing blood stasis, and renewing tendons and connecting bones, which can accelerate the blood circulation of the fracture site and provide sufficient nutrition to the fracture end, thus promoting the healing process of the fracture, and this combined treatment can significantly shorten the time of fracture healing and improve the quality of the healing process. Meanwhile, small splint external fixation can effectively fix the fracture end and prevent the fracture from displacement or reoccurrence, and this stable fixation environment provides good conditions for fracture healing and avoids the risk of fracture non-healing or deformity healing caused by unstable fixation [6,7]. In addition, the Jiegu San external application can be individualized according to the patient's specific situation, and the composition and dosage of Jiegu San can be adjusted to achieve the best therapeutic effect. Small splint external fixation can also be flexibly adjusted according to the type and severity of the fracture to ensure stability and comfort of fixation. These studies are consistent with the findings of Xu [8], Xing [9], and others.

This study also found that after 3 weeks of treatment, the pain scores of the observation group were significantly lower than the control group ($P = 0.000$), indicating that in the treatment of distal radius fracture, the combination of Jiegu San external application and small splint external fixation after closed reduction can effectively reduce the degree of patient pain. This is mainly due to the following reasons: Firstly, the components in the Jiegu San have the effect of rapidly relieving pain. When Jiegu San is applied externally to the fracture site, these ingredients can rapidly penetrate the skin and effectively relieve pain [10]. Secondly, compared with oral or injectable medications, topical application of Jiegu San can provide a sustained release of components at the fracture site, maintaining a prolonged soothing effect, which helps patients maintain a lower level of pain throughout the treatment process and promotes recovery. Thirdly, after a fracture, an inflammatory reaction often occurs in the local tissues, leading to swelling and pain. The anti-inflammatory ingredients in Jiegu Sans help to reduce inflammation and pain. Through external application, these ingredients can act more directly on the fracture site and rapidly reduce the inflammatory reaction [11]. Fourthly, small splint external fixation following closed reduction provides a stable fixation environment for the fracture site. Stable fixation reduces friction and movement between fracture ends, thus reducing pain, and this stability also helps protect the surrounding tissues from further injury and pain. Lastly, the Jiegu San external application can promote blood circulation at the fracture site and help eliminate metabolites and inflammatory mediators, thus reducing pain, and good blood circulation is very important for both fracture healing and pain relief.

In conclusion, in the treatment of distal radius fracture patients, the combination of the Jiegu San external application and small splint external fixation following closed reduction can effectively improve the clinical efficacy of patients, promote the reduction of swelling and healing of patients, and reduce the degree of pain, which is worthy of further promotion.

Disclosure statement

The authors declare no conflict of interest.

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Analysis of the Effect of Interlocking Intramedullary Nail Fixation on Treating Bone Nonunion After Extremity Trauma Fracture

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Abstract: *Objective:* To analyze the effect of interlocking intramedullary nail fixation on treating bone nonunion after extremity trauma fracture. *Methods:* 80 patients with bone nonunion after extremity trauma fracture were selected and divided into two groups according to different treatment methods, each group having 40 cases. The control group performed compression plate fixation, and the observation group performed interlocking intramedullary nail fixation. A comparison of surgical indexes, bone metabolism indexes, and surgical effects was done. *Results:* The observation group had shorter operation time and postoperative hospitalization time, the levels of various bone metabolism indexes were higher than those of the control group one month after operation, and the total effective rate of the operation was higher than that of the control group ($P < 0.05$). *Conclusion:* Interlocking intramedullary nail fixation is more effective in the treatment of post-traumatic fracture of the extremities with bone nonunion.

Keywords: Traumatic fracture of extremity; Bone nonunion; Interlocking intramedullary nail fixation

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1. Introduction

Extremity trauma fracture is a high-prevalence disease in orthopedics, which can cause more complications, such as bone nonunion. Generally, in extremity trauma fractures, the fracture site can be reset and healed after internal fixation treatment, but some patients have poor healing, i.e., bone nonunion occurs [1]. For the clinical treatment of bone nonunion after extremity trauma fracture, compression plate fixation is the most common therapy with a more satisfactory effect but a long postoperative recovery time. The interlocking intramedullary nail fixation utilizes the principle of elastic fixation, which is highly stable [2]. In this paper, we will analyze the therapeutic effect as well as the effective rate of this therapy in the post-traumatic fracture of the extremities with bone nonunion, including a total of 80 patients in the study.

2. General information and methods

2.1. General information

A total of 80 cases of patients with bone nonunion after extremity trauma fracture were screened (admission date was from January 1, 2022 to December 31, 2023), and divided into 40 cases in the control group and 40 cases in the observation group according to the different treatment methods. In the control group, there were 23 male patients and 17 female patients, with ages ranging from 24 to 63 (45.05 ± 8.17) years old, of which 13 were fibula fractures, 11 were ulnar-radial fractures, and 9 and 7 were femur and humerus fractures, respectively. In the observation group, the ratio of male to female was 25:15, the age range was 22–64 (45.11 ± 8.40) years, and the fibula, ulnar-radial, femur, and humerus fractures corresponded to 14, 10, 10, and 6 cases in that order. $P > 0.05$ when comparing the data of the two groups.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) clear trauma history and diagnosed as bone nonunion after extremity trauma fracture after relevant examination; (2) treated with open reduction and internal fixation, with an interval of more than 9 months between the last time and the current time of treatment; (3) patients with good communication and cooperation; and (4) patients with complete general information.

Exclusion criteria: (1) belonging to pathological fracture; (2) patients with other serious diseases; (3) patients with other bone diseases or serious infection of fracture end; (4) patients with mental diseases.

2.3. Methods

After the admission of the two groups of patients, they were subjected to routine examination and combined with the actual situation, a reasonable selection of fixation materials was done to ensure that there was no allergy, the specific treatment methods are as follows:

The compression plate fixation surgical treatment was implemented for 40 patients in the control group. The patient was assisted to lie supine on the surgical bed and a routine anesthesia operation was carried out. A 10 cm size incision was performed at the fracture end, separating the skin tissue layer by layer; after the separation of the broad fascia and the surrounding tissues, periosteotomy treatment and appropriate peeling were carried out to prevent excessive damage to the periosteum, revealing the discontinuous end of the bone in the field of vision, the original internal fixation was cleared away. After the scar at the fracture end was treated accordingly, it was polished, rinsed, and reset, and then the plate was placed in parallel and fixed with cortical bone screws. The incision was sutured, and the operation was completed.

40 patients in the observation group underwent interlocking intramedullary nail fixation. The position and anesthesia method were the same as that of the control group, the length of the incision was about 8 cm, and the fracture ends were separated layer by layer to reveal the fracture ends. After some cleaning, the sclerotic bone was removed with a bone knife, and the fracture ends were polished to the trapezoidal cross-section after marrow expansion. The intramedullary nails were examined after reset and they were grooved with hollow drills, and then inserted to determine the accurate position; the locking nails were taken to lock the proximal and distal ends, and then they were fixed, cleaned, and sutured.

2.4. Observation indexes

(1) Comparison of surgical indicators: The surgical indicators included operation time and postoperative hospitalization time.

(2) Comparison of bone metabolism indexes: The indexes included epidermal growth factor (EGF), osteocalcin (BGP), osteoprotegerin (OPG), alkaline phosphatase (ALP), applying enzyme-linked

immunosorbent assay test before and one month after surgery.

(3) Comparison of surgical effects [3]: The surgical effect three months after the operation was judged by the fracture healing. If there is no compression pain and percussion pain at the fracture end, the fracture is healing well, and the fracture line is under 1 cm, it is excellent, i.e. "highly effective"; there is slight pain at the fracture end, the fracture is healing relatively well, a cloudy scab is formed, and the fracture line is under 2 cm and below, it is good, i.e. "effective"; severe pain at the fracture end, poor healing, no bone scab, fracture line above 2 cm, it is poor, i.e. "ineffective." Total effective rate = highly effective + effective.

2.5. Statistical methods

SPSS version 25.0 statistical software was used to analyze the comparative data. Measurement data were measured using mean ± standard deviation (SD), indicated by *t*-test; count data were measured using [n (%)], indicated by χ^2 test; and $P < 0.05$ was used to indicate that the comparative data were statistically significant.

3. Results

3.1. Surgical indicators

As shown in **Table 1**, the operation time and postoperative hospitalization time of the observation group were shorter than that of the control group, $P < 0.05$.

Table 1. Surgical indicators (mean ± SD)

Group	Number of cases (*n*)	Surgical time (minutes)	Post-operative hospitalization (days)
Control group	40	139.56 ± 15.17	14.18 ± 3.20
Observation group	40	126.15 ± 13.34	11.15 ± 2.27
t	-	4.198	4.884
P	-	0.000	0.000

3.2. Bone metabolism indexes

As presented in **Table 2**, compared with the preoperative bone metabolism indexes of the two groups of patients, the difference was not significant, $P > 0.05$; and in comparison with one month after the operation, the levels of all bone metabolism indexes of the observation group were higher than those of the control group, $P < 0.05$.

Table 2. Bone metabolism indexes (mean ± SD)

Group	Number of cases (*n*)	EGF (pg/ml)		BGP (ng/L)		OPG (μg/L)		ALP (mmol/L)	
		Preoperative	One month after surgery	Preoperative	One month after surgery	Preoperative	One month after surgery	Preoperative	One month after surgery
Control group	40	0.65 ± 0.13	0.87 ± 0.13	44.15 ± 5.27	53.36 ± 5.14	2.49 ± 0.41	3.32 ± 0.28	93.15 ± 7.45	145.59 ± 8.57
Observation group	40	0.68 ± 0.11	0.95 ± 0.12	44.29 ± 5.14	59.54 ± 5.57	2.45 ± 0.38	4.59 ± 0.36	93.24 ± 7.18	161.45 ± 10.18
t	-	1.114	2.860	0.120	5.157	0.453	17.612	0.055	7.538
P	-	0.269	0.005	0.905	0.000	0.652	0.000	0.956	0.000

3.3. Surgical effects

As shown in **Table 3**, the total surgical effectiveness rate of the observation group was higher than that of the control group, $P < 0.05$.

Table 3. Surgical effects [n (%)]

Group	Number of cases (*n*)	Ineffective	Effective	Highly effective	Total effective rate
Control group	40	9 (22.50)	17 (42.50)	14 (35.00)	31 (77.50)
Observation group	40	2 (5.00)	11 (27.50)	27 (67.50)	38 (95.00)
χ^2	-	-	-	-	5.165
P	-	-	-	-	0.023

4. Discussion

Bone nonunion after extremity trauma fracture refers to the situation in which the fracture end is not healed nine months after extremity trauma fracture surgery, the pain is more intense, the healing of the fracture place is greatly affected, and the limb function cannot be restored for a while. Bone nonunion requires prompt fixation treatment, applying pressure to the fracture end. In the past, the effect of the compression plate internal fixation therapy was still ideal, but it produced the effect of stress masking, affecting fracture healing and recovery of limb function [4]. Interlocking intramedullary nail fixation therapy is less invasive and has fewer complications, which makes it more effective in the treatment of bone nonunion. This study showed that the observation group had a shorter operation time and postoperative hospitalization time than the control group, indicating that interlocking intramedullary nail fixation therapy is faster compared with compression plate fixation, which is more conducive to the patient's postoperative recovery and achievement of the discharge standard.

Bone nonunion affects the blood supply to the end of the bone, and subsequently, the bone repair ability is reduced. In severe cases, the bone completely loses its repair ability, which means that the bone scab cannot be formed naturally, the fracture recovery is delayed, and the limb function recovery is also poor. Among the bone metabolism indexes, EGF is a key index to promote tissue repair, BGP affects bone healing, OPG regulates the proliferation and differentiation of mesenchymal cells, which in turn promotes the proliferation of chondrocytes and osteoblasts, and the level of ALP reflects the metabolic status of the fracture site [5,6], and these levels have a direct impact on the healing of fractures. The result data in this article showed that the bone metabolism index levels of patients in the observation group were higher than those of the control group one month after surgery, indicating that the surgical method of the observation group is conducive to improving the level of bone metabolism, which is favorable to the recovery of limb function [7]. Comparing the surgical results of the two groups, the total effective rate of 95.00% in the observation group is higher than that of the control group, which shows that the treatment efficacy of the observation group is better. In the past, the internal fixation therapy of the compression plate could fix the fracture end, however, it is necessary to fix the two ends of the fracture, greatly influencing the blood flow to the fracture end, which is inconducive to the healing of the fracture. In addition, the bending stress is relatively large, and the rehabilitation training is hindered in the later stage; moreover, when performing the fixation with the steel plate, its effect will be gradually weakened in the period of fracture resorption [8], which is prone to secondary fracture. The principle of interlocking intramedullary nail fixation therapy is elastic fixation and good biomechanics; after the pressure is applied, it can prevent the displacement or rotation of the bone, which can help the healing of the fracture. In addition to its good flexibility [9], high adaptability, and no effect on the subsequent rehabilitation exercise, the treatment technique

can also prevent excessive impact on the blood supply of the fracture end tissues; there is less pain and there are sufficient nutrients to promote the healing of the fracture, and gradually restore the bone metabolism [10]. Overall, the healing effect is ideal, with light trauma and less impact, it stimulates the formation of bone scabs, the fracture ends can have a rapid and good recovery, and limb function is gradually enhanced.

5. Conclusion

In summary, it can be seen that the application of interlocking intramedullary nail fixation in the treatment of post-traumatic fracture of the extremities with bone nonunion has high efficiency and is worthy of promotion.

Disclosure statement

The authors declare no conflict of interest.

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Analysis of the Effect of Minimally Invasive Locking Plate Internal Fixation on Fracture Healing and Functional Recovery in Patients with Proximal Humerus Fractures

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Abstract: *Objective:* To investigate the effect of minimally invasive locking plate internal fixation on fracture healing and functional recovery in patients with proximal humerus fractures. *Methods:* 98 patients with proximal humerus fractures admitted to the hospital from August 2021 to July 2023 were selected and divided into the control group (n = 49) and the observation group (n = 49) according to the lottery method. The control group implemented conventional treatment, and the observation group implemented minimally invasive locking plate internal fixation. The treatment effect and complications, surgery-related indexes, and functional recovery of the shoulder joint in the two groups were compared. *Results:* Compared with the control group, the observation group (97.96%) had a better therapeutic effect than the control group (73.47%) (χ^2 = 12.000, P < 0.05); the complication rate of the observation group (2.04%) was lower than that of the control group (18.37%) (χ^2 = 7.127, P < 0.05); the fracture healing rate of the observation group (97.96%) was higher than that of the control group (81.63%) ($\chi2$ = 7.127, P < 0.05). The operation time of the observation group (74.25 ± 10.30 minutes) was shorter than that of the control group (115.63 ± 20.30 minutes) (t = 12.725, P < 0.05), the intraoperative bleeding of the observation group (177.30 ± 19.63 ml) was less than that of the control group (306.63 ± 30.62 ml) (t = 24.890, P < 0.05). The fracture healing time was shorter in the observation group (12.30 ± 2.30 weeks) than in the control group (16.23 ± 2.66 weeks) (t = 7.823, P < 0.05), and the hospitalization time was shorter in the observation group (9.30 ± 0.99 days) than in the control group (12.66 ± 2.20 days) (t = 9.749, P < 0.05). Compared with the control group, the pain, muscle strength, activity function, and activity score of the observation group were significantly different (t = 6.398, 12.817, 8.386, 7.892, P < 0.05); compared with the control group, the observation group's abduction, forward flexion, external rotation, internal rotation, and posterior rotation were significantly different (t = 3.042, 2.843, 3.633, 4.669, 9.176, P < 0.05). *Conclusion:* Minimally invasive locking plate internal fixation for proximal humerus fracture can adjust its surgery-related indexes, increase the patients' shoulder joint mobility, enhance the shoulder joint function, improve the fracture healing rate and therapeutic effect, and reduce the complications, which is worth recommending in clinical practice.

Keywords: Minimally invasive locking plate internal fixation; Proximal humerus fracture; Fracture healing; Functional recovery

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1. Introduction

Humerus fracture is a common surgical disorder with a high incidence at present. It is mostly caused by trauma, in which proximal humerus fracture is half of the incidence of humerus fracture. Traditional manipulative treatment of proximal humerus fracture is mostly based on screw internal fixation. As the surgical operation is highly invasive and adverse to postoperative prognosis, it has a certain value in improving the condition of proximal humeral fractures [1]. With the continuous development of medical technology in recent years, minimally invasive surgery has been widely popularized, with the advantages of low trauma and bleeding, etc. Minimally invasive locking plate internal fixation is an effective means of treating this disease, which is of great significance for the improvement of patients' clinical symptoms [2,3]. The aim of this study is to investigate the application value of minimally invasive locking plate internal fixation for patients with proximal humerus fracture, and the treatment results of 98 patients included in the study are reported as follows.

2. Clinical data and methods

2.1. Clinical data

98 patients with proximal humerus fractures admitted to our hospital from August 2021 to July 2023 were taken as the study subjects and divided into the control group and the observation group according to the lottery method. There were 30 males and 19 females in the control group, ranging in age from 20–89 years old, with a mean value of 54.50 ± 10.22 years old; there were 15 cases in senior high school, 24 cases in junior high school, 10 cases in junior college and above. There were 29 males and 20 females in the observation group, their ages ranged from 21–89 years old, with a mean age of 55.00 ± 11.63 years old; there were 16 cases in high school, 25 cases in junior high school, and 8 cases in college and above. The basic data of the two groups were comparable ($P > 0.05$). Inclusion criteria included patients with proximal humerus fracture with complete data; patients meeting the indications for surgery; proximal humerus fracture diagnosed by imaging. Exclusion criteria were patients with proximal humerus fracture combined with psychiatric disorders; patients with fuzzy consciousness; patients with other diseases such as liver, kidney, and cardiac diseases; and those who withdrew from the study halfway.

2.2. Methods

The control group was treated conventionally. The patients were given tracheal intubation anesthesia and kept in a supine position, with appropriate shoulder padding. An incision was made down the anterior edge of the deltoid muscle to the edge of the deltoid muscle and the length of the incision was 10–12 cm. The subcutaneous skin was incised layer by layer, and blunt separation of the pectoralis major muscle deltoid muscle gap was done to ensure that the fracture end of the humerus was completely exposed. Prying and traction reset were performed to assess the effect of the reset in the humerus after removing the lateral locking plate and screws of the greater tuberosity, and then it was cleaned with irrigation fluid, leaving the plate and the screw. Afterward, the incision was cleaned with a flushing solution, drains were left in place, and the incision was closed.

The observation group was treated with minimally invasive locking plate internal fixation. Maintaining the supine position with an appropriately padded shoulder, a longitudinal incision was made, blunt separation of the deltoid muscle, retraction, nodal groove, shoulder abduction, and internal rotation were done to promote fracture reset. Under fluoroscopic guidance, the humeral neck stem angle was restored and the unstable tuberosity fracture block was temporarily fixed with Kirschner wires. The plate channel was created, subsequently, the plate was inserted and the proximal end was fixed to assess the effect of reduction and fixation. This was followed by incision irrigation treatment, drainage management, and incision closure.

2.3. Observation indexes

2.3.1. Treatment effects and complications

The therapeutic effect was determined by highly effective, effective, and ineffective. Highly effective referred to the significant improvement of patients' shoulder joint mobility and function compared with that before treatment; effective referred to the certain improvement of patients' shoulder joint function and mobility compared with that before; ineffective referred to no change in patients' shoulder joint function and mobility compared with that before. Treatment effect = Highly effective + Effective / 49 × 100%. The evaluation of complications included the indicators of incision infection, joint dysfunction, femoral head necrosis, and poor fracture healing.

2.3.2. Surgery-related indexes

Surgery-related indexes included the evaluation of operation time, intraoperative bleeding, fracture healing time, and hospitalization time in both groups.

2.3.3. Shoulder joint recovery

Shoulder joint recovery was divided into shoulder joint mobility and shoulder joint function. The higher the shoulder function score, the better the functional recovery. Shoulder joint mobility included abduction (0–180°), forward flexion (0–180°), external rotation (0–90°), internal rotation (0–90°), and posterior extension (0–50°).

2.4. Statistical analysis

SPSS20.0 software was used to analyze the research data in the observation and control groups, and the measurement data conforming to normal distribution was described by mean ± standard deviation (SD), and *t*-test was performed; the count data was expressed by the number of cases and percentage, and the comparison between groups was performed by χ^2 test. The difference was considered statistically significant at $P < 0.05$.

3. Results

3.1. Effect of surgical treatment and complications

Compared with the control group, the observation group (97.96%) had a higher treatment efficiency than the control group (73.47%) ($\chi^2 = 12.000$, $P < 0.05$), and the complication rate of the observation group (2.04%) was lower than that of the control group (18.37%) ($\chi^2 = 7.127$, $P < 0.05$); the fracture healing rate of the observation group (97.96%) was higher than that of the control group (81.63%) ($\chi^2 = 7.127$, $P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of surgical treatment effects and complications between the two groups [*n* (%)]

Groups	Treatment effects				Complications					Fracture healing rate
	Highly effective	Effective	Ineffective	Effective rate of treatment	Incision infection	Joint dysfunction	Poor fracture healing	Necrosis of the humeral head	Complication rate	
Observation group ($n = 49$)	40	8	1	97.96	0	0	1	0	2.04	97.96
Control group ($n = 49$)	11	25	13	73.47	2	3	1	3	18.37	81.63
χ^2	-	-	-	12.000	-	-	-	-	7.127	7.127
P	-	-	-	0.001	-	-	-	-	0.007	0.007

3.2. Surgery-related indexes

The operation time of the observation group (74.25 ± 10.30) was shorter than that of the control group (115.63 ± 20.30) (t = 12.725, P < 0.05), the intraoperative bleeding of the observation group (177.30 ± 19.63) was less than that of the control group (306.63 ± 30.62) (t = 24.890, P < 0.05); the postoperative fracture healing time of the observation group (12.30 ± 2.30) was shorter than that of the control group (16.23 ± 2.66) (t = 7.823, P < 0.05), and the hospitalization time of the observation group (9.30 ± 0.99) was shorter than that of the control group (12.66 ± 2.20) (t = 10.532, P < 0.05), as presented in **Table 2**.

Table 2. Comparison of surgery-related indexes between the two groups (mean ± SD)

Groups	Surgical time (minutes)	Intraoperative bleeding (ml)	Fracture healing time (weeks)	Hospitalization time (days)
Observation group (n = 49)	74.25 ± 10.30	177.30 ± 19.63	12.30 ± 2.30	9.30 ± 0.99
Control group (n = 49)	115.63 ± 20.30	306.63 ± 30.62	16.23 ± 2.66	12.66 ± 2.20
t	12.725	24.890	7.823	10.532
P	< 0.05	< 0.05	< 0.05	< 0.05

3.3. Recovery of shoulder joint

After the intervention, compared with the control group, the pain, muscle strength, activity function, and activity score of the observation group were significantly different (t = 6.398, 12.817, 8.386, 7.892, P < 0.05); the observation group had abduction, forward flexion, external rotation, internal rotation, and posterior rotation. Compared with the control group, the difference was significant (t = 3.042, 2.843, 3.633, 4.669, 9.176, P < 0.05), as shown in **Table 3**.

Table 3. Comparison of shoulder joint function scores (mean ± SD, points)

Groups	Pain		Muscle strength		Activity function		Activity score	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group (n = 49)	9.20 ± 0.96	14.30 ± 2.02	8.30 ± 1.30	14.30 ± 1.33	11.30 ± 1.52	17.30 ± 1.63	23.30 ± 2.36	33.30 ± 3.02
Control group (n = 49)	9.26 ± 0.89	11.63 ± 2.11	8.63 ± 1.25	11.02 ± 1.20	11.36 ± 1.36	14.63 ± 1.52	23.63 ± 2.66	29.02 ± 2.30
t	0.321	6.398	1.281	12.817	0.206	8.386	0.650	7.892
P	> 0.05	< 0.001	> 0.05	< 0.001	> 0.05	< 0.001	> 0.05	< 0.001

Groups	Abduction		Forward flexion		External rotation		Internal rotation		Posterior rotation	
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention
Observation group (n = 49)	9.20 ± 1.33	125.30 ± 12.66	12.30 ± 2.30	144.30 ± 14.52	45.30 ± 4.25	64.30 ± 6.52	12.30 ± 1.55	65.30 ± 6.55	20.30 ± 2.66	40.30 ± 4.22
Control group (n = 49)	9.31 ± 1.26	117.63 ± 12.30	12.63 ± 2.30	136.33 ± 13.20	45.88 ± 4.82	59.63 ± 6.20	12.63 ± 1.63	59.33 ± 6.10	20.63 ± 2.55	32.66 ± 4.02
t	0.420	3.042	0.710	2.843	0.632	3.633	1.027	4.669	0.627	9.176
P	> 0.05	< 0.01	> 0.05	< 0.01	> 0.05	< 0.001	> 0.05	< 0.001	> 0.05	< 0.001

4. Discussion

Proximal humerus fracture is a harmful disease, which also affects the joint function of patients. The application of conventional screw fixation for proximal humerus fractures has a certain significance in improving patients' clinical symptoms and quality of life scores [4,5]. However, there are some limitations, and the large amount of bleeding may threaten the patient's safety. The application of conventional screw fixation treatment has disadvantages of surgical invasiveness, extensive exposure, extensive stripping, serious ischemic symptoms of the humeral head, and poor functional recovery of the shoulder joint, thus affecting the patient's prognosis. Minimally invasive locking plate internal fixation is the treatment of choice for the treatment of proximal humerus fractures, with the understanding of the anatomy of the proximal humerus as well as the discovery of internal fixation, it offers a significant advantage for the popularity and development of minimally invasive surgery [6,7]. The steel plate applied in minimally invasive locking plate internal fixation is small and can enter the muscle tissue, which has less impact on the patient's soft tissues, and the combination of plate and locking screw fixation normalizes the patient's local blood supply and contributes to fracture healing [8,9]. The plate used in minimally invasive locking plate internal fixation has good biomechanical stability and anchoring force, which can accelerate fracture healing as well as joint function recovery.

The results of this study showed the observation group (97.96%) had a higher treatment efficiency than the control group (73.47%) ($\chi^2 = 12.000$, $P < 0.05$), and the complication rate of the observation group (2.04%) was lower than that of the control group (18.37%) ($\chi^2 = 7.127$, $P < 0.05$); the fracture healing rate of the observation group (97.96%) was higher than that of the control group (81.63%) ($\chi^2 = 7.127$, $P < 0.05$). It can be seen that the implementation of minimally invasive locking plate internal fixation for patients with proximal humerus fracture significantly reduces the complications and improves the fracture healing rate and treatment effect. This is mostly because the fixation of the locking screw and plate promotes pressurization and stabilization of the whole fracture site, reduces the manipulation of the plate and maintains the normal blood supply to bone and periosteum, accelerates the fracture healing rate, and promotes the improvement of the treatment effect, ensures the stability of fixation within a certain range, and reduces the complications.

After the intervention, compared with the control group, the pain, muscle strength, activity function, and activity score of the observation group were significantly different ($t = 6.398$, 12.817, 8.386, 7.892, $P < 0.05$); the observation group had abduction, forward flexion, external rotation, internal rotation, and posterior rotation. Compared with the control group, the difference was significant ($t = 3.042$, 2.843, 3.633, 4.669, 9.176, $P < 0.05$). The implementation of minimally invasive locking plate internal fixation in patients with proximal humerus fracture accelerates the functional recovery and mobility of the shoulder joint in patients. In minimally invasive locking steel plate internal fixation, the screw and locking steel plate have biomechanical characteristics of angular stability. It accelerates the fixation of fracture through the locking formation of anchoring force and resistance to pull-out force to improve the functional recovery of the shoulder joint and increase joint mobility [10,11]. The operation time of the observation group (74.25 ± 10.30) was shorter than that of the control group (115.63 ± 20.30) ($t = 12.725$, $P < 0.05$), the intraoperative bleeding of the observation group (177.30 ± 19.63) was less than that of the control group (306.63 ± 30.62) ($t = 24.890$, $P < 0.05$); the postoperative fracture healing time of the observation group (12.30 ± 2.30) was shorter than that of the control group (16.23 ± 2.66) ($t = 7.823$, $P < 0.05$), and the hospitalization time of the observation group (9.30 ± 0.99) was shorter than that of the control group (12.66 ± 2.20) ($t = 10.532$, $P < 0.05$). Proximal humerus fracture should be fully assessed preoperatively to evaluate the patient's orthopedic injury, assisted by relevant examinations; minimally invasive locking plate internal fixation is done to fix the locking screws and steel plate, to maintain a normal blood supply of the bone and the periosteum under the steel plate, to reduce the damage of relevant tissues

of the patient, to improve the stability, and adjust the surgical indexes. To ensure the surgical effect, it is also necessary to make full use of the role of the locking plate suture holes, comminuted fracture blocks, rupture of the joint capsule, displaced large nodes of the suture; the plate is fixed in a reasonable position and not too close to the proximal end; locking screws of moderate length should be selected to avoid locking screws into the joint, affecting the patients with proximal humerus fractures in the early exercise and functional recovery; after the operation, the patients with proximal humerus fractures should be instructed to carry out early functional exercise to accelerate fracture recovery. This study has some limitations, including a small sample size and a short study period, which may affect the quality of the study. Further study needs to increase the sample size of patients with proximal humerus fracture according to the actual situation and extend the study period, as well as ensure that the professional skills of the researchers meet the requirements and have a wealth of experience of more than 6 years.

5. Conclusion

In conclusion, the application of minimally invasive locking plate internal fixation for proximal humerus fracture can adjust its surgery-related indexes, increase the patients' shoulder joint mobility, enhance their shoulder joint function, improve the fracture healing rate and therapeutic effect, and reduce the complications, which is worthy of recommendation.

Disclosure statement

The authors declare no conflict of interest.

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The Potential Therapeutic Role of Curcumin in Osteoporosis Treatment Based on Multiple Signaling Pathways

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Abstract: Osteoporosis is a common bone disease that occurs when the body makes too little bone, loses too much bone, or both. This makes the bones weak and more likely to break. Scientists are studying how to treat osteoporosis using natural substances found in food and medicine. One of these substances is curcumin, which comes from the roots of plants in the ginger family. Curcumin has different components like phenols, terpenes, and flavonoids. Research shows that curcumin can help treat osteoporosis by affecting how cells in the bones grow and change. It can also interfere with the signals that tell the body to make more bone or break down bone. This helps to prevent and treat osteoporosis in multiple ways. Studying how curcumin works against osteoporosis can help us find new ways to prevent and treat this condition.

Keywords: Signaling pathway; Osteoporosis; Curcumin; Therapeutic role

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1. Introduction

As the population ages, osteoporosis has become one of the top chronic diseases in China. Osteoporosis occurs when bone mass is reduced and fractures occur due to an imbalance between bone-forming and bone-resorbing cells. Achieving normal peak bone mass is crucial in preventing osteoporosis. Maintaining a balanced diet, regular menstrual cycles, and exercise are essential for optimal bone density. Curcumin, derived from *Curcuma* plants, has antioxidant and anti-inflammatory properties that can combat oxidative stress and promote osteoblast differentiation [1].

MAPK (mitogen-activated protein kinase) pathway can be switched on by various extracellular stimuli and regulates processes like cell growth, stress response, and inflammation [2]. There are specific pathways in the MAPK signaling pathway associated with diseases like osteoporosis. NF-κB (nuclear factor kappa B) regulates immune cells and inflammation and is a target for anti-inflammatory and anti-cancer drugs. The PI3K-AKT (phosphatidylinositol 3-kinase-protein kinase B) pathway is involved in physiological processes and diseases like obesity, diabetes, and cancer. These pathways have characteristic targets for osteoporosis, and curcumin can

act on these targets to treat osteoporosis [3].

2. Curcumin

Curcumin is a highly pleiotropic natural polyphenol compound isolated from the rhizome of *Zingaceae* and *Araceae*. Widely consumed as an herb, dietary spice, and food colorant, it has a long history and has received increasing attention due to its multiple pharmacological effects, mainly anti-inflammatory and antioxidant [4]. Curcumin, due to its special structural characteristics, has a variety of biological activities, it not only has the effects of the inhibition of platelet aggregation, anti-thrombotic, anti-cancer, antibacterial, antiviral, and other effects, and can antagonize inflammatory media, but it also can clear oxygen-free radicals in the body, enhance antioxidant capacity, and improve superoxide dismutase, glutathione peroxidase, and so on [5].

3. The pathogenesis of osteoporosis

Osteoporosis is a bone condition characterized by reduced bone tissue and an increased risk of fractures. It can be primary, caused by factors like aging, or secondary, caused by other conditions or medications. In women, menopause is the main cause of primary osteoporosis due to the loss of ovarian function and estrogen deficiency. Bone mineral density can be influenced by the consumption of phenols, which act as antioxidants and protect against oxidative damage to bone cells [6]. So far, numerous studies have demonstrated that curcumin significantly contributes to regulating the signaling pathways that mediate osteoporosis.

4. Mechanism of action of curcumin against osteoporosis based on multiple pathways

4.1. Wnt/β-catenin signaling pathway

The Wnt signaling pathway is highly conserved and plays a crucial role in various biological processes. Mammalian cells contain 19 Wnt proteins, divided into Wnt1 and Wnt5a [7]. These proteins interact with Frizzled receptors and LGR5/6 complexes to enhance their functionality. There are two Wnt signaling pathways: classical, mediated by β-catenin, and non-classical, which includes the Wnt/Ca^{2+} and Wnt/Planar Cell Polarity pathways. The Wnt/Ca^{2+} pathway modulates intracellular calcium levels, while the Wnt/Planar Cell Polarity pathway regulates cellular behaviors like migration and morphological polarization. These pathways operate as receptor-mediated signaling pathways regulated by G-proteins and activate downstream stress kinases to participate in cytoskeleton remodeling and cell adhesion [8]. The β-catenin protein plays a crucial role in the Wnt signaling pathway. Its abnormal expression is linked to various diseases, including tumors. When Wnt signaling is off, β-catenin is degraded. However, when Wnt signaling is on, β-catenin accumulates in the nucleus and activates the expression of target genes [9].

4.1.1. Wnt/β-catenin signaling pathway and the occurrence of osteoporosis

The Wnt signaling pathway is crucial for bone growth and development and is linked to diseases such as osteoporosis and certain tumors [10]. It regulates the growth, differentiation, and apoptosis of mesenchymal stem cells and influences the balance between adipogenesis and osteogenesis. Increased Wnt signaling can lead to decreased bone resorption by facilitating the expression of osteoprotegerin in osteoblasts [11]. In specific situations, increased Wnt signaling can potentially lead to decreased osteoclastogenesis and bone resorption. This is achieved by facilitating the expression of osteoprotegerin in osteoblasts. Osteoprotegerin (OPG)

functions as a binding site for RANKL, diverting its interaction with receptors, thereby inhibiting the binding of RANKL to its receptor (RANK) on osteoclast precursors. As a result, osteoclast differentiation and activity are suppressed, leading to decreased bone resorption.

4.1.2. Mechanism of curcumin regulating Wnt pathway in osteoporosis

Turmeric root contains curcumin, which has antioxidant and anti-inflammatory properties. It affects the Wnt signaling pathway, important for treating osteoporosis, and promotes bone health. Studies have shown that curcumin enhances the nuclear translocation of β-catenin and ameliorates bone mineral loss [12]. In addition, it has been found that the mRNA expression level of Wnt/β-catenin in glucocorticoid (GC)-induced osteoporosis model rats is significantly down-regulated, and curcumin intervention can increase serum osteocalcin level (OCN) and decrease C-terminal peptide (CTX) of type I collagen. The mRNA expression levels of alkaline phosphatase (ALP), Runx2, and osteoblast transcription factor (Osx) were up-regulated. ALP and OCN in cells were markers of bone formation, and CTX was known as a marker of bone resorption. It can be seen that curcumin influences the regulation of osteoporosis.

4.2. NF-κB signaling pathway

NF-κB is a protein that regulates the survival, activation, and differentiation of certain immune cells. It can impact cells of the innate immune system and T cells involved in inflammation. Targeting NF-κB can potentially develop drugs with anti-inflammatory and anticancer properties [13].

4.2.1. Role of NF-κB signaling pathway in osteoporosis

NF-κB plays a role in regulating genes related to osteoporosis. TNF-α and oxidative stress are linked to its activation. Estrogen deficiency can also lead to increased inflammation and osteoporosis. In addition, the NF-κB signaling pathway, which is involved in regulating the inflammatory response, is modulated by estrogen to activate estrogen receptors alpha and beta (ERα and β). In women who have reached menopause, an increase in the production and secretion of pro-inflammatory cytokines such as TNF-α and IL-6 was observed. Estrogen deficiency increases circulating FSH levels, which promotes the secretion of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, thus inducing osteoporosis.

4.2.2. Regulation of NF-κB signaling pathway by curcumin in osteoporosis

Curcumin can assist in the treatment of osteoporosis by reducing inflammation and promoting bone health. Studies have shown that it can help in the growth of new blood vessels and prevent bone loss in diabetes-induced osteoporosis. Moreover, curcumin has been found to decrease factors involved in cell activity and reduce inflammation. In experimental studies with mice using a cellular oxidative stress model, curcumin was found to reduce the expression of phosphorylated p65 (p-p65), transcription of phosphorylation factors, and inhibit the expression of IL-6 and RANKL.

4.3. MAPK signal pathway

Signals between a cell's surface and nucleus are transmitted by MAPK, a cluster of protein kinases that can be triggered by external factors like hormones, pressure, and attachment. MAPK is a crucial component in this process. MAPK is named because it is identified by the activation of cultured cells in response to mitogen stimulation such as growth factors. The MAPK pathway exhibits a conserved tertiary kinase pattern across various species, ranging from yeast to humans. The pathways consist of three protein kinases, MAP3K, MAP2K, and MAPK, which transmit signals through phosphorylation [14]. **Figure 1** depicts the formation and

differentiation of the MAPK/Erk signaling pathway and the cascade of MAPK.

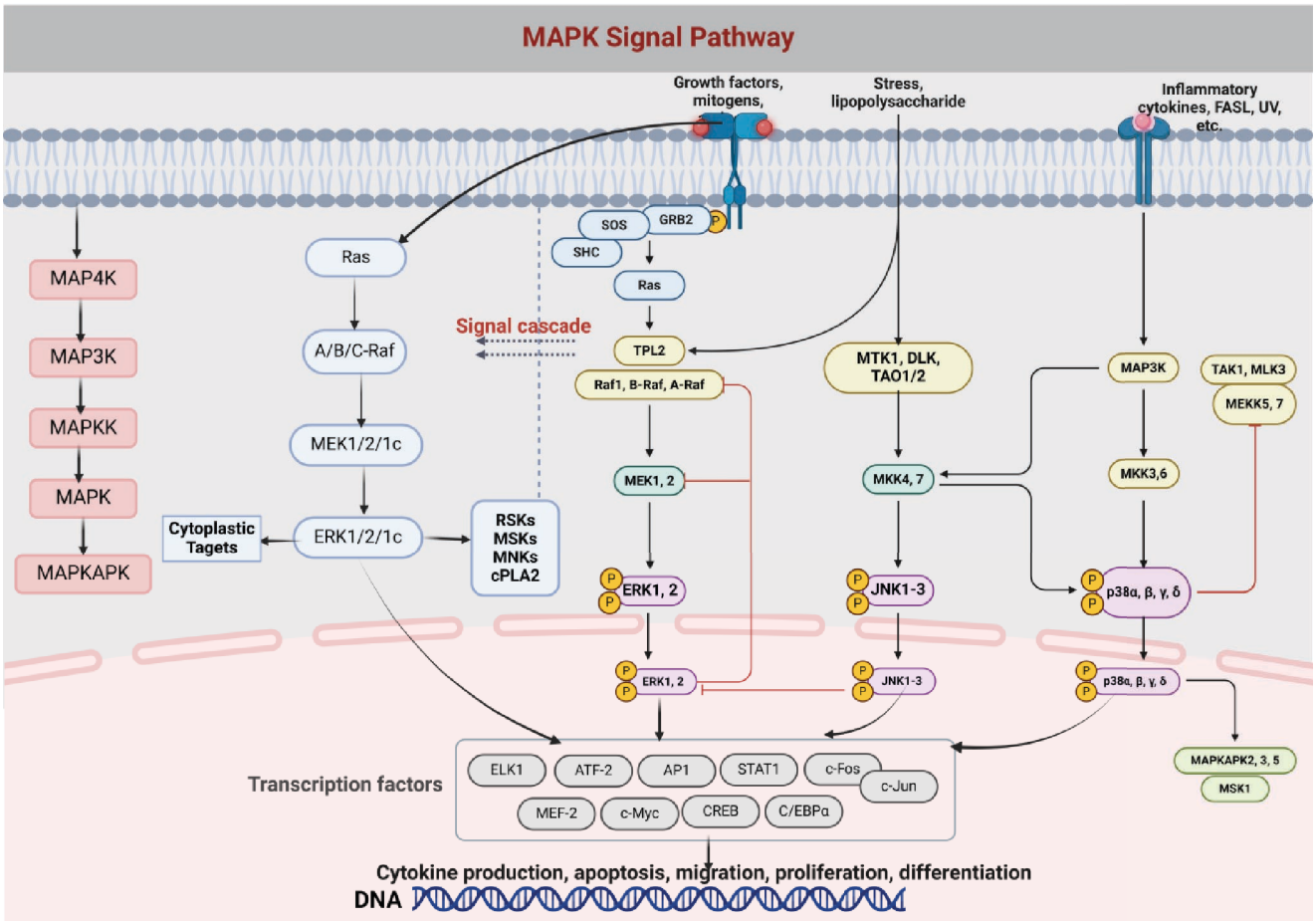

Figure 1. MAPK, mitogen-activated protein excitation, MAPK exists in the cytoplasm and can be translocated to the nucleus to catalyze the phosphorylation of dozens of cytoplasmic proteins and many nuclear transcription factors.

4.3.1. Relationship between MAPK signaling pathway and osteoporosis

Op-related factors, such as RANKL, OPG, parathyroid hormone (PTH), bone morphogenetic protein (BMP), TGF-β, IL-1, IL-6, TNF-α, and estrogen, primarily correlate with the MAPK signaling pathway. Notably, pretreatment with the p38 inhibitor SB203580 hindered osteoblast proliferation, implying a significant role of the p38 pathway in enhancing Kobophenol A-induced osteoblast proliferation [15]. These findings suggest that estrogen aids in bone formation by activating the MAPK pathway, thereby counteracting osteoporosis development [15]. However, it is worth noting that an increase in caspase-3 and caspase-9 mRNA expression was also observed. Dexamethasone, a synthetic glucocorticoid, negatively regulates the expression of p-PI3K and p-AKT. This suppression of the PI3K/AKT signaling pathway in osteoblasts and MC3T3-E1 cells leads to a significant upregulation of glycogen synthase kinase (GSK)-3β. Consequently, dexamethasone inhibits cell proliferation and triggers apoptosis. These effects make dexamethasone a viable therapeutic option for osteoporosis caused by glucocorticoids.

4.3.2. Curcumin interferes with osteoporosis and MAPK signaling pathway

Various studies have shown that curcumin has a positive impact on the p38 MAPK signaling pathway, which leads to its anti-inflammatory, neuroprotective, and apoptotic effects. Curcumin is known to reduce the phosphorylation level of p38 MAPK, making it a potential treatment for osteoporosis. Additionally, it activates

the downstream MAPK pathway [16]. These results effectively inhibit the formation and differentiation of osteoclasts in mouse models *in vitro* experiments. Thus, it can be seen that curcumin can achieve the goal of treating osteoporosis by acting on the MAPK signaling pathway.

5. Conclusion and perspectives

This study summarized several signaling pathways affecting osteoporosis in recent years and integrated the mechanism of curcumin in the treatment of the disease. It was found that curcumin can reduce inflammation, inhibit osteoclast differentiation and proliferation, promote osteoblast growth, and reduce oxidative stress in bone tissue by regulating signaling pathways such as NF-κB, Wnt/β-catenin, PI3K/Akt, and MAPK. The multi-target, multi-pathway, and multi-level mechanism of curcumin in the treatment of osteoporosis was revealed, but the specific cross-target and multi-signaling pathways of curcumin are still limited and need to be further studied.

Disclosure statement

The author declares no conflict of interest.

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Upper Cervical Spine Injuries — A Secondary Publication

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Abstract: *Objectives:* Based on anatomical knowledge of the upper cervical spine, it is necessary to be familiar with the classification, diagnosis, and treatment strategies currently used clinically for upper cervical spine injuries. *Summary of literature review:* Upper cervical spine injuries are major injuries with potentially fatal consequences. The occipitocervical junction, which is composed of several structures, protects the brain and cranial nerves. We need to know the mechanism of each type of damage, and in particular, we must understand the anatomy of the occiput, atlas, and axis, as well as the definitions of landmarks of the positional relationships among all structures. *Materials and methods:* This study reviewed the latest literature on upper cervical spine injuries. *Results:* In occipital condyle fractures and atlanto-occipital injuries, we should understand how to evaluate instability and the treatment methods according to each classification. In atlas injuries, it should be evaluated whether the transverse atlantal ligament has been damaged. In axis fractures, it is necessary to understand the surgical method according to the shape of the odontoid fracture. *Conclusions:* Knowledge of soft tissue and bony structural relationships in the upper cervical spine is required for the diagnosis and treatment plan of upper cervical injuries.

Keywords: Upper cervical spine injury; Occipitocervical junction; Atlas; Axis; Odontoid

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1. Introduction

The occipitocervical junction is a complex structure between the skull and the upper cervical spine. It provides stability during complex movements at the occipitocervical junction. It protects the brain stem and cranial nerves and provides a stable cerebrovascular blood supply. It consists of the atlantooccipital joint, the atlantoaxial joint, and several intrinsic and extrinsic ligaments. It has a large range of motion, but fewer supportive structures compared to other parts of the body, and damage to the upper and lower extremities can lead to devastating complications such as paralysis [1]. 25% of all injuries are associated with head injuries and 40% with nerve injuries. In high-energy trauma patients, injury to the occipitocervical junction should always be suspected. In addition, in elderly patients and those with narrow spinal canals, even mild hyperextension injury can cause spinal cord injury [2]. Therefore, for proper diagnosis and treatment, it is necessary to classify, diagnose, and clinically treat injuries based on the anatomical features of the upper cervical spine.

2. Diagnosis and assessment

2.1. Understanding the anatomical structures

The occiput and atlas perform rotational movements through several joints. These are shallow condyloid joints, providing some bony stability to the occipitocervical junction. The dens of the axis form a synovial joint with the posterior part of the anterior arch of the atlas. Laterally, a pair of synovial joints create the bony articulation of C1–C2. Intrinsic ligaments are structured from anterior to posterior as follows: the anterior atlantooccipital membrane, apical and alar ligaments, the superior band of the longitudinal ligament, and the tectorial membrane. Behind these structures are the dura mater, spinal cord, and posterior atlantooccipital membrane. The tectorial membrane is the cranial extension of the posterior longitudinal ligament, connecting the posterior part of the axis to the foramen magnum. The cruciate ligament connects the posterior surface of the dens to the anterior arch of the atlas via the transverse atlantal ligament, and the vertical fibers extend from the foramen magnum to the axis. The alar ligaments connect the dens of the axis to the occipital condyles. Extrinsic ligaments also contribute to the stability of the occipitocervical junction, including the nuchal ligament, anterior longitudinal ligament, and the elastic fibers of the ligamentum flavum [3].

The sagittal plane movement of the upper cervical spine mainly occurs through the occipitocervical joint (15–20°), while rotational movement primarily occurs through the atlantoaxial joint (50° on each side) [4].

2.2. Initial assessment and diagnosis

Damage to the occipitocervical junction and subsequent structural instability can have devastating consequences, therefore, high-energy injuries should be assessed for instability. In addition, the initial examination for motor, sensory, and type of injury should be performed to determine the severity of neurological injury, and the American Spinal Injury Association's guidelines (ASIA) and the Advanced Trauma Life Support guidelines (ATLS) should be used to assess the severity of neurological injury and prognosis.

Despite the increased diagnostic sensitivity due to cervical spine CT, a single cross-table lateral radiograph remains the first radiographic examination to be performed. The evaluation involves assessing the basion, opisthion, occipital condyles, odontoid process, atlas, and axis for fractures and structural relationships, as well as evaluating changes in and consistency of the atlantooccipital and atlantoaxial joints [5]. In patients suspected of having severe ligament injuries, a supine radiograph taken immediately after the injury might result in false negatives due to gravity and muscle contraction. It is also necessary to assess for prevertebral soft tissue swelling. This can also be evaluated through a simple lateral radiograph, with normal ranges being considered as less than 10 mm at the nasopharyngeal space at C1, less than 5 mm at the retropharyngeal space at C3, and less than 22 mm at the retropharyngeal space at C6 (less than 14 mm in children) [6]. However, simple radiographic imaging alone may be limited in directly assessing the atlantooccipital and atlantoaxial joints. Therefore, for the alignment assessment of the occipitocervical junction, indirect evaluation can be performed through correlation assessment of the following anatomical indicators using CT as a reference. McRae's line is an imaginary line drawn from the anterior to the posterior point of the foramen magnum in the median sagittal plane of the skull. Normally, the odontoid process should be positioned less than 5 mm below this line. If it exceeds this line, basilar invagination can be diagnosed. McGregor's line is an imaginary line drawn from the posterior edge of the hard palate to the lowest point of the occipital bone's base curve. If the tip of the odontoid process invades this line by more than 4.5 mm, basilar invagination can be diagnosed [7]. The Wackenheim line is a downward line extending from the clivus to the upper cervical spine and should be located 1–2 mm from the tip of the odontoid process. If the odontoid process intersects the Wackenheim line, basilar invagination can be diagnosed. The atlanto-dens interval (ADI) is the distance from the anterior cortical bone of the odontoid process to the posterior cortical bone of the anterior arch of C1, with a normal range of within 3 mm. If it is 3–5 mm, transverse atlantal ligament injury and C1–2

instability should be suspected. Additionally, the posterior cortical bone of the atlas and the anterior cortical bone of the axis should form parallel lines, and if the space available for the cord (SAC) between the posterior cortical bone of the odontoid process and the anterior cortical bone of the posterior arch of the atlas is 13 mm or less, it is defined as a narrow spinal canal (**Figure 1**).

Through open mouth view (open mouth view) and coronal CT, if the lateral mass displacement on both sides is 7 mm or more based on the relationship of the odontoid process, lateral mass of C1, and the odontoid process, transverse ligament injury can be suspected (rule of Spence) (**Figure 2**). After these initial screening tests and evaluations, further assessments should be conducted. It is also important to note that the information obtained from flexion-extension radiographs in trauma patients is limited and may actually increase the risk of neurological damage, so it is not recommended [8].

Other imaging tests along with CT scans are the primary diagnostic test for cervical spine injuries along with plain radiographs. MRI may also be used to evaluate spinal cord injury and cervical spine anatomy. MRI is difficult to obtain if neurological deficits are present, a spinal cord contrast CT may be performed.

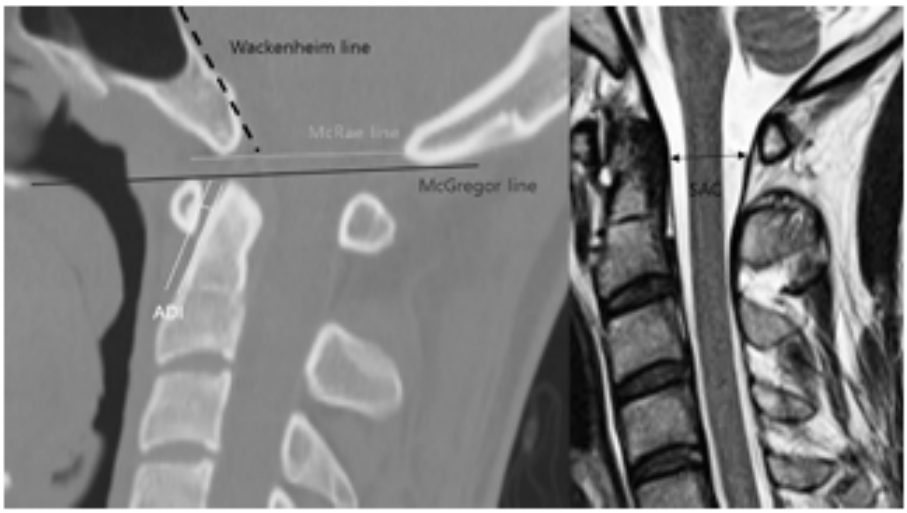

Figure 1. Cervical computed tomography and magnetic resonance imaging (midsagittal cut). Dotted line: Wackenheim line, red line: McRae line, blue line: McGregor line, yellow line: atlanto-dens interval (ADI), black arrow: space available for the cord (SAC).

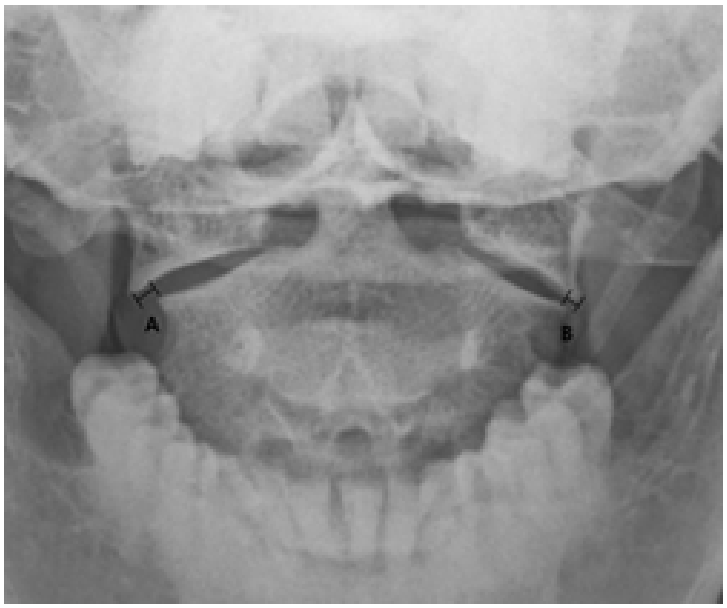

Figure 2. Cervical open-mouth view. The sum of A and B is the lateral mass displacement.

3. Diagnosis and treatment according to injury

3.1. Occipital condyle fracture

To diagnose an odontoid process fracture, cervical CT is used as the primary examination, and plain radiographs can also be referenced, although they are relatively less sensitive. Anderson and Montesano classified odontoid process fractures into the following three types (I: Impacted type; II: Fracture involving the base of the skull; III: Avulsion fracture of the alar ligament) [9]. Types I and II are generally stable and can be treated conservatively by wearing a rigid cervical brace for 6–8 weeks. For type III, it is necessary to confirm whether there is instability indicating cranio-cervical dissociation. If there is no cranio-cervical dissociation, a halo vest can be worn for 12 weeks. If dissociation is present, it is an indication for surgery, and occipitocervical fusion can be performed. Therefore, the presence of a type III fracture alone is not an indication for surgery; rather, the confirmation of associated dissociation should be considered for surgical intervention.

Meanwhile, in a study by Van der Burg *et al.*, the union rate, clinical outcomes (Neck Disability Index, NDI; Neck Pain and Disability Scale, NPAD), and range of motion were analyzed for 39 patients with fractures of the odontoid process (Type I: 4, Type II: 16, Type III: 19) [10]. Among the 39 patients, no significant differences were found in NDI ($P = 0.34$ & 0.98) and NPAD ($P = 0.44$ & 0.46) based on the classification and treatment. Additionally, there were no significant differences in the range of motion when comparing isolated odontoid fractures with those accompanied by cervical fractures. Except for one patient, all 25 patients who completed radiographic follow-up showed bone union at the final follow-up. Therefore, the study concluded that conservative treatment of odontoid process fractures, regardless of the fracture type, results in satisfactory bone union and clinical outcomes. The Anderson classification was reported to have little clinical relevance.

3.2. Atlantooccipital dislocation

Diagnosis of atlantooccipital dislocation can be made by measuring Power's ratio and the basion-axis interval (BAI) and basion-dens interval (BDI) on CT. The basion-dens interval, which is the distance between the basion and the tip of the odontoid process, is considered normal if it is 12 mm or less. Similarly, the basion-axis interval, which is the vertical distance from the basion to the anterior cortex of the axis, is also considered normal if it is 12 mm or less. If either the BAI or BDI exceeds 12 mm, dislocation should be suspected. Additionally, a Power's ratio of 0.9 or less on CT may indicate anterior dislocation of the atlantooccipital joint (**Figure 3**). In cases of severe occipitocervical joint dislocation with neurological deficits, reduction and the application of a halo vest may be performed, but this is only for temporary stabilization and surgical fixation will be required later. The halo vest should be applied carefully to avoid excessive traction. According to Traynelis' classification, type I is anterior displacement, type II is vertical displacement, and type III is posterior displacement.

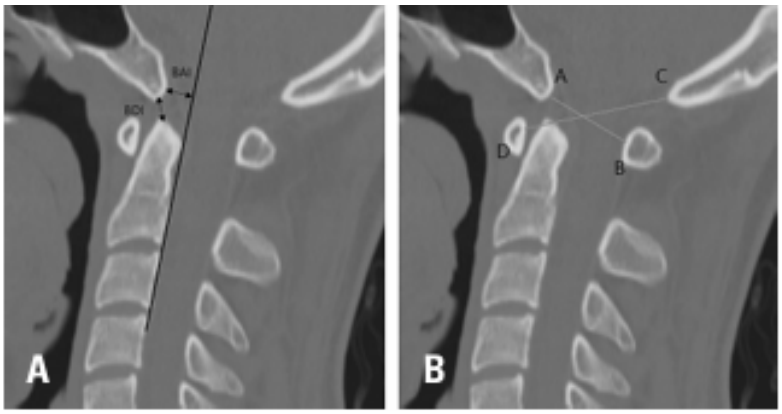

Figure 3. (A) Basion-dens interval (BDI), Basion-axis interval (BAI). (B) Power's ratio: AB/CD (A: basion, B: posterior spinolaminar line of the atlas, C: opisthion, D: anterior arch of the atlas).

Harborview classification focuses more on the degree of instability rather than the direction of displacement and divides it into three categories with therapeutic implications. Type 1 involves minimal or no displacement and is typically unilateral; in such cases, it may be deemed sufficient to treat with orthoses, as ligamentous support to maintain occipitocervical alignment is considered adequate. Type 2 injuries show positive traction testing (partial or complete), indicating instability requiring surgical fixation. Type 3 injuries exhibit severe instability with malalignment of the occipitocervical junction (greater than 2 mm deviation from normal ranges in BAI and BDI). In these cases, there is a high mortality rate and often significant neurological deficits. Surgery requires posterior fixation from the occiput to at least C2 [11].

Furthermore, if a craniocervical dislocation is confirmed, vascular injury assessment is necessary. In a study by Kazemi *et al.*, among 28 patients with craniocervical dislocation, 14 had cerebrovascular injuries, with a total of 25 cerebrovascular injuries reported (12 carotid artery injuries and 13 vertebral artery injuries) [12]. Depending on the presence of cerebrovascular injuries, preoperative and postoperative management and surgical plans may change. Therefore, it is necessary to evaluate cerebrovascular injuries, such as through angiography, in patients suspected of having such injuries (**Figure 4**).

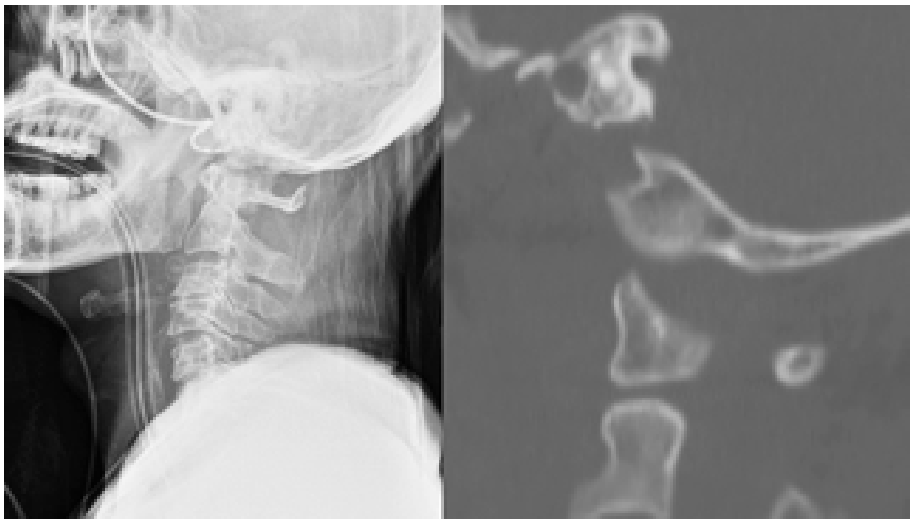

Figure 4. A 63-year-old man who had been in a motorcycle accident. The image shows the dislocation of the occipital condyle.

3.3. Atlas fracture

Degeneration of the zygapophyseal joints can cause a fracture of the articular process and may injure the transverse ligament, leading to transverse atlantal ligament (TAL) disruption. Falls are the most common cause, and spinal cord injury at C1 is rare due to the wider spinal canal at this level. It is associated with other cervical spine injuries in 50% of cases, with the hangman's fracture being the most frequent. Diagnosis involves open-mouth radiographs and CT scans of the facet joints, measuring the degree of lateral displacement of the C1 lateral masses relative to C2. A total lateral mass displacement (LMD) of more than 7 mm raises suspicion of TAL injury, while less than 5.7 mm suggests a lower likelihood of TAL injury (**Figure 2**). However, Woods *et al.* evaluated the accuracy of the "rule of Spence" through 11 cadaveric studies, finding that an average lateral mass displacement of 3.2 mm (± 1.2 mm) observed in experiments using high-resolution/high-speed cameras resulted in TAL injury, and analysis showed a significant likelihood of TAL injury when lateral mass displacement exceeded 3.8 mm ($P < 0.001$). Therefore, lateral mass displacement is not a reliable independent indicator of TAL injury, and diagnosis through MRI should take precedence over it, utilizing it as a supplementary measure [13].

When there is a single transverse process fracture and no damage to the transverse process ligament, stability can be assessed, so evaluation of the transverse process ligament is essential in determining the treatment plan. Evaluation of the transverse process ligament is necessary for determining the treatment plan because if there is no damage to the transverse process ligament in the case of a sole transverse process fracture, stability can be assessed. Evaluation of the ligament and confirmation of injuries such as avulsion fractures by MRI and CT are necessary. If the type of fracture is stable and the transverse process ligament is intact, conservative treatment with a rigid brace can be performed for 6–12 weeks. When a transverse process ligament tear is confirmed, surgical treatment is indicated, and fusion surgery can be performed. There have been reported cases of satisfactory results without fusion of the upper cervical spine through compression osteosynthesis using C1 lateral mass screws in cases of unstable Jefferson fractures, but a long-term follow-up analysis is required (**Figure 5**) [14].

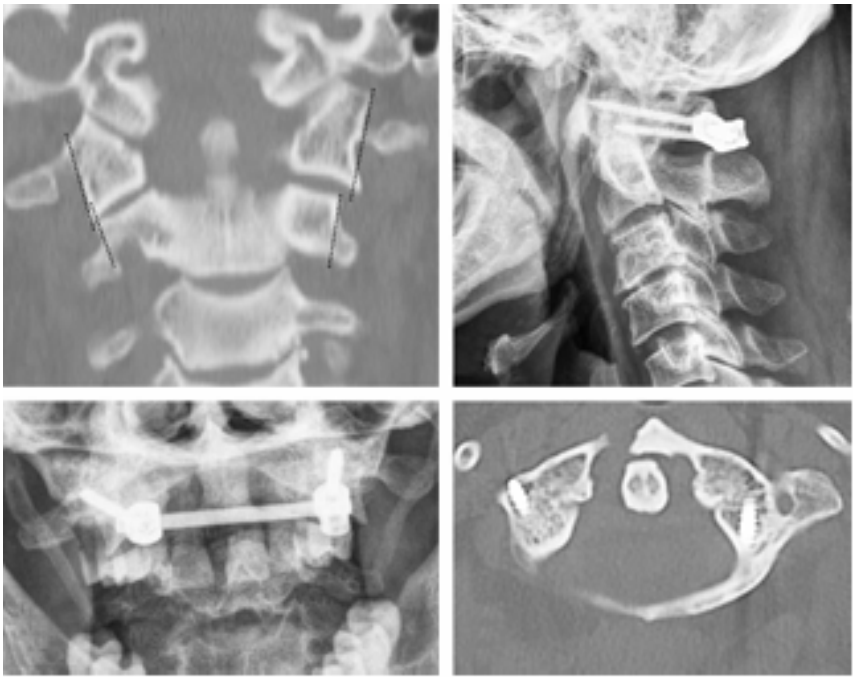

Figure 5. A 59-year-old woman who had been in a slip-down injury. The image shows rupture of the transverse atlantal ligament and lateral mass displacement. Compressive reduction and osteosynthesis using C1 lateral mass screw fixation were performed.

3.4. Transverse annulus ligament damage

Injuries and head trauma resulting from overestimation and falls primarily occur when the occiput hits the ground. In cervical spine curvature images, if the occipital-atlantal interval is between 5 to 10 mm, transverse atlantal ligament (TAL) injury is diagnosed, while if it is above 10 mm, TAL rupture is diagnosed and requires surgical intervention. According to the classification by Dickman using horizontal plane CT, type 1 involves a rupture of the TAL itself and requires surgical stabilization via C1–2 fusion, while type 2 involves a lateral mass fracture of C1 and can be treated conservatively with Halo vest application (**Figure 6**).

3.5. Atlantoaxial rotatory subluxation

Three types of instability in the subaxial cervical spine are recognized. Type A is characterized by rotational subluxation in the horizontal plane, type B involves translational instability due to lateral facet injury, and type

C involves bilateral facet dislocation with vertical instability. Each type may also exhibit overlapping features. Type A is predominantly non-traumatic and presents with rotational subluxation. Subaxial cervical spine rotational subluxation is classified into four categories by Fielding & Hawkins classification, characterized by symptoms such as dysphagia and limitation of cervical motion range (**Figure 7**). Subluxation is asymmetrically projected on simple radiographs, showing a typical "winking sign" which aids in diagnosis [15]. Treatment includes wearing a cervical collar for one week followed by one week of bed rest if onset is less than a week, hospitalization with halo traction and cervical collar for 4–6 weeks if it persists for 1–4 weeks, and possible fusion if it lasts for more than 4 weeks. If conservative management fails, surgical intervention through a posterior approach may be necessary (**Figure 8**).

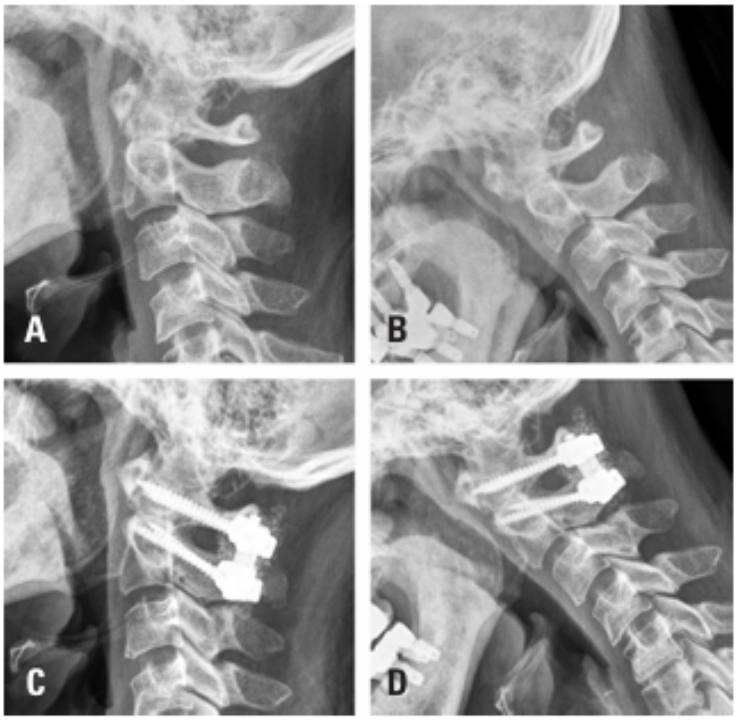

Figure 6. Plain radiographs of a 48-year-old woman after a pedestrian traffic accident. (A, B) Preoperative flexion and extension view. The atlas-dens interval was increased on the flexion view. (C, D) Postoperative flexion and extension view. Stabilized atlas-dens interval is noted.

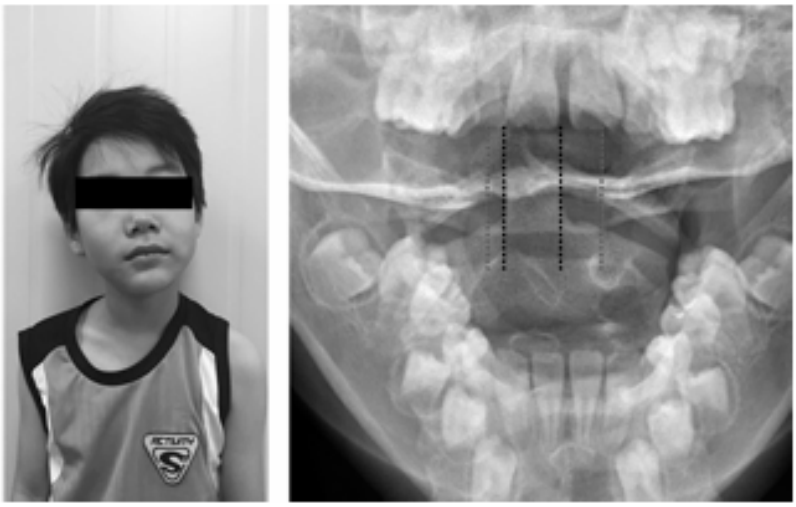

Figure 7. An 8-year-old boy with an asymmetric posture due to atlantoaxial rotatory subluxation.

Figure 8. Holter traction for atlantoaxial rotatory subluxation.

3.6. Odontoid fracture

Odontoid fractures account for 10–15% of all cervical spine injuries, and 75% of pediatric cervical spine injuries. Mechanistically, anterior displacement is observed in flexion injuries, while posterior displacement is observed in extension injuries. According to Anderson and D'Alonso, it can be classified into three types. Type 1 is an oblique fracture at the spinous process of the odontoid due to avulsion of the supraspinous ligament. Type 2 involves a fracture through the body of the odontoid with a high risk of nonunion due to vascular compromise. Especially when the displacement is more than 5 mm, angulation is more than 10 degrees, there is posterior displacement, or the patient is over 50 years old, the risk of nonunion is high. Type 2 fractures can be further classified according to the direction of the fracture line using the Grauer classification. Type 2A has no or minimal displacement and no comminution, 2B has a fracture line extending from anterior to posterior, and 2C has a fracture line extending from anterior to posterior. Anterior screw fixation is indicated for type 2B fractures, while posterior fusion is indicated for type 2C fractures (**Figure 9**). Contraindications for anterior screw fixation include type 2C fractures, concurrent unstable vertebral fractures, suspicion of pathological fractures, and nonunion of odontoid fractures. Type 3 involves an extension fracture to the C2 vertebral body, which can occur at various locations in the C1–2 joint complex, with a 90% union rate with conservative treatment.

On the other hand, in a study by Andre *et al.*, despite the conservative treatment using a halo vest, there is still a high rate of non-union in the elderly. Therefore, for the elderly, fixation surgery using two screws is also recommended to reduce the possibility of non-union. Additionally, after assessing the fracture status and vertebral artery, C1–2 fusion surgery may also be considered [16,17].

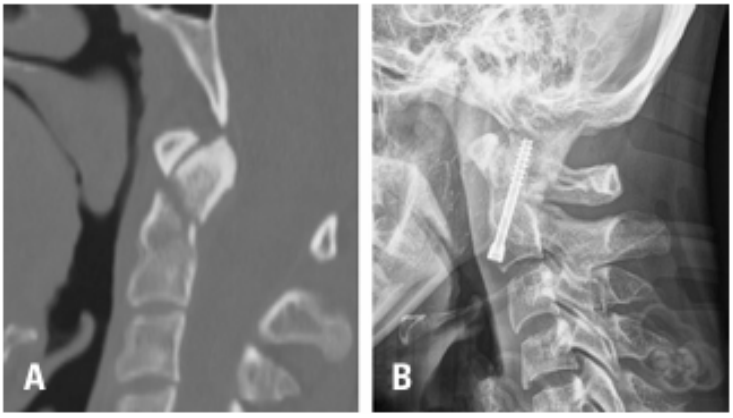

Figure 9. A 37-year-old woman who had been in a fall down injury. (A) Type IIB odontoid fracture. (B) Postoperative radiograph of anterior screw fixation.

3.7. Traumatic spondylolisthesis of the axis

Traumatic spondylolisthesis of the axis is the second most common axis fracture (38%) and generally occurs due to hyperextension and axial loading. It is also called Hangman's fracture and involves bilateral pedicle fractures of the axis with separation of the axis pedicle and body [18]. According to the classification by Levine and Edwards, Type 1 exhibits minimal displacement (< 3 mm) and typically requires rigid cervical collar immobilization for 12 weeks. Type 2 involves horizontal displacement of 3 mm or more accompanied by angulation, resembling Type 1 on lateral views but showing more than 3 mm of displacement on upright radiographs after collar application, necessitating treatment with a halo vest for 12 weeks. Type 2A is a flexion-distraction injury without horizontal displacement but with a horizontal fracture line, potentially with more posterior displacement and possible C2–3 disc and posterior longitudinal ligament injuries. Treatment involves conservative management with a halo vest for 12 weeks. Type 3 involves C2–3 facet dislocation, often requiring surgical intervention as closed reduction is not achievable. Surgery involves posterior approach reduction of the dislocated facet followed by fusion of C1–3 or C2–3. Preoperative MRI evaluates disc injury, and if present, anterior discectomy and fusion followed by posterior reduction can be performed [19-21].

4. Conclusion

To diagnose and treat various upper cervical injuries effectively, understanding the correlation between adjacent soft tissues and osseous structures is necessary. Based on this understanding, establishing a treatment direction is essential. Additionally, anticipating fatal outcomes through early appropriate screening tests is crucial.

Disclosure statement

The authors declare no conflict of interest.

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A Comparative Study of Trochanteric Fractures Treated with Hip Hemiarthroplasty or Proximal Femoral Nail — A Secondary Publication

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Abstract: *Objective:* The aim of this study was to compare the clinical and functional outcomes of patients treated with partial hip prosthesis (PHP) or double lag screw proximal femoral nailing (PFN) for unstable femoral intertrochanteric region fractures. *Material and method:* In this study, the data of 101 patients who developed grade 3-4-5 femoral intertrochanteric fractures according to the Evans-Jensen classification between 2019–2020 and were treated with cemented PHP or double screw PFN were evaluated retrospectively. The patients were evaluated in terms of postoperative follow-up time, age, gender, trauma side, American Anesthesia Society Anesthesia Risk Scale (ASA), number of comorbid diseases, total hospitalization time, amount of intraoperative bleeding, duration of surgery, and postoperative complications. *Results:* 101 patients evaluated within the scope of the study were divided into groups of 51 patients who underwent PHP (Group 1) and 50 patients who underwent PFN (Group 2). When the results were compared in terms of mean length of hospital stay, duration of surgery, amount of intraoperative bleeding, and postoperative 1-year mortality, the results were found to be statistically significant. *Conclusion:* Our study results showed that the PFN method has clinical advantages over PHP. The PFN technique is a method that can be applied quickly and safely.

Keywords: Hip fractures; Intramedullary nailing; Arthroplasty

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1. Introduction

Today, the incidence of hip fractures in the elderly population continues to increase each year with the increase in life expectancy [1]. In the elderly population, more low-energy hip fractures caused by traumas occur in the intertrochanteric region with a rate of up to 50% [2]. Because of the high morbidity and mortality after the fracture, the main aim of treatment is to obtain a stable fracture fixation in the shortest time, mobilize the patient, and transition to normal life [3]. In the treatment planning phase, fracture pattern and morphology are taken into consideration. The integrity of the posteromedial calcar is evaluated and the fracture is accepted as stable or unstable [4]. Evans-Jensen classification is the preferred classification for intertrochanteric fractures

depending on the fracture configuration, and trochanter major and minor integrity [5]. The dynamic hip screwing (DHS) method, which is considered the gold standard in stable fracture patterns, has been associated with high failure rates in unstable fracture patterns [6]. These results have led to the development of intramedullary nail designs that can provide more biomechanically stable fixation in unstable fracture patterns [7]. In addition, in severe osteoporosis or comminuted fractures, arthroplasty should be considered in addition to proximal femoral nailing (PFN) [8]. Early loading and mobilization, good functional outcome, and avoidance of osteosynthesis-related failure have been considered advantages of arthroplasty [9]. In addition, disruption of posteromedial calcar integrity and comminuted fractures may adversely affect the results of treatment with arthroplasty [10]. In addition, there may be an increased risk of mortality and complications related to the cement used in arthroplasty treatment [11]. The aim of this study was to compare the clinical and functional results of PFN and cemented partial hip prosthesis (PHP) in the treatment of unstable FITC in a geriatric population.

2. Materials and methods

2.1. Subjects and evaluation criteria

The study data were collected in accordance with the Declaration of Helsinki after obtaining ethics committee approval (Gaziantep University Ethics Committee dated August 18, 2021 and reference number 2021-274). The data of 201 patients operated for FITC between 2019 and 2020 were analyzed retrospectively. Inclusion criteria were as follows: being over 65 years of age, presenting due to a simple fall, type 3,4,5 fracture according to Evans-Jensen fracture classification, PHP or PFN as the treatment method, and being operated within the first 48 hours after trauma. Patients whose follow-up data were not available, who had additional injuries, pathological fractures, and neurological deficits were excluded from the study. The patients included in the study were divided into group 1 treated with cemented PHP and group 2 treated with PFN. The groups were evaluated in terms of postoperative follow-up time, age, gender, side of trauma, American Society of Anaesthesia Anaesthesia Risk Scale (ASA), number of comorbid diseases, total length of stay, amount of intraoperative bleeding, operative time, and postoperative complications. were evaluated. Patients who died within 1 year postoperatively were included in the calculation of the mortality rate. Clinical and functional outcomes were analyzed using the Barthel activity index (BI) and Harris hip scoring (HHS).

2.2. Surgical technique

All patients in the study were operated on within 48 hours after preoperative anesthetic preparation. Patients were operated on by orthopedic surgeons in our department and implant choice was randomized. All patients received 40 milligrams of low molecular weight heparin prophylaxis once a day for 1 month preoperatively and postoperatively. In addition, antibiotic prophylaxis with a single dose of 1 gram cefazolin 1 hour preoperatively and 1 gram intravenous cefazolin 4 times a day for 24 hours postoperatively was used. All patients who underwent PFN were operated in the lateral decubitus position using a double lag screw PFN system with fluoroscopic reduction control. Two 7.3 mm parallel lag screws were inserted into the femoral head and advanced 5 mm into the subchondral space (**Figure 1**). All patients who underwent PHP were operated on in the lateral decubitus position with a posterolateral approach. In cases where arthroplasty was preferred, the femoral stem was placed using cement. In addition, 1 plug was used in all cases to prevent the escape of the cement to the distal femur. A bipolar cemented prosthesis and trochanteric hook plate system was used if necessary considering the intraoperative trochanteric major integrity (**Figure 2**). Drains were placed in the patients in the PHP group for 24 hours postoperatively. All patients underwent a rehabilitation program with a physiotherapist starting from the 1st postoperative day. Patients were mobilized with the help of a walker by giving a tolerable load.

2.3. Statistical analysis

Descriptive statistics of the study data were presented as the mean and standard deviation for continuous variables and frequency and percentage for categorical variables. In terms of continuous variables, two groups (PHP and PFN) Independent samples *t*-test was used to compare the preoperative and postoperative values of the same numerical variable, and paired samples *t*-test was used to compare the preoperative and postoperative values of the same numerical variable. The chi-square test was also used to analyze the relationships between categorical variables. All analyses were performed using SPSS (version 22, IBM Company). $P < 0.05$ was considered significant.

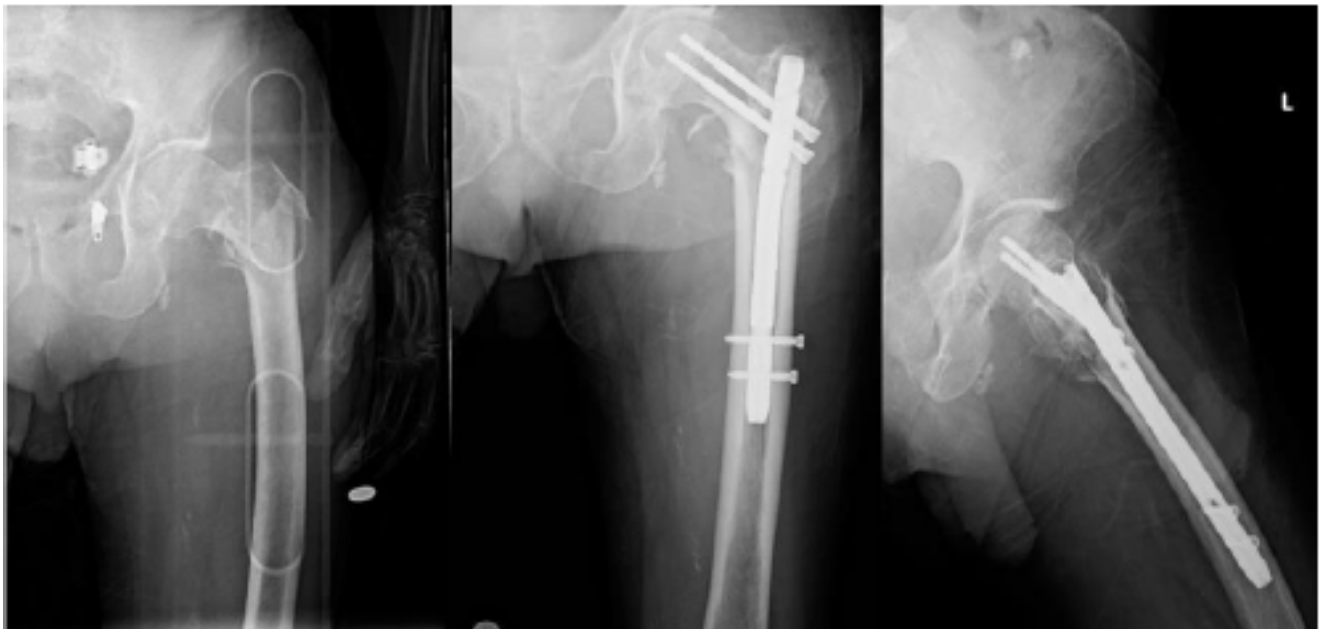

Figure 1. Preoperative and postoperative radiographs of a 90-year-old male patient after proximal femoral nailing

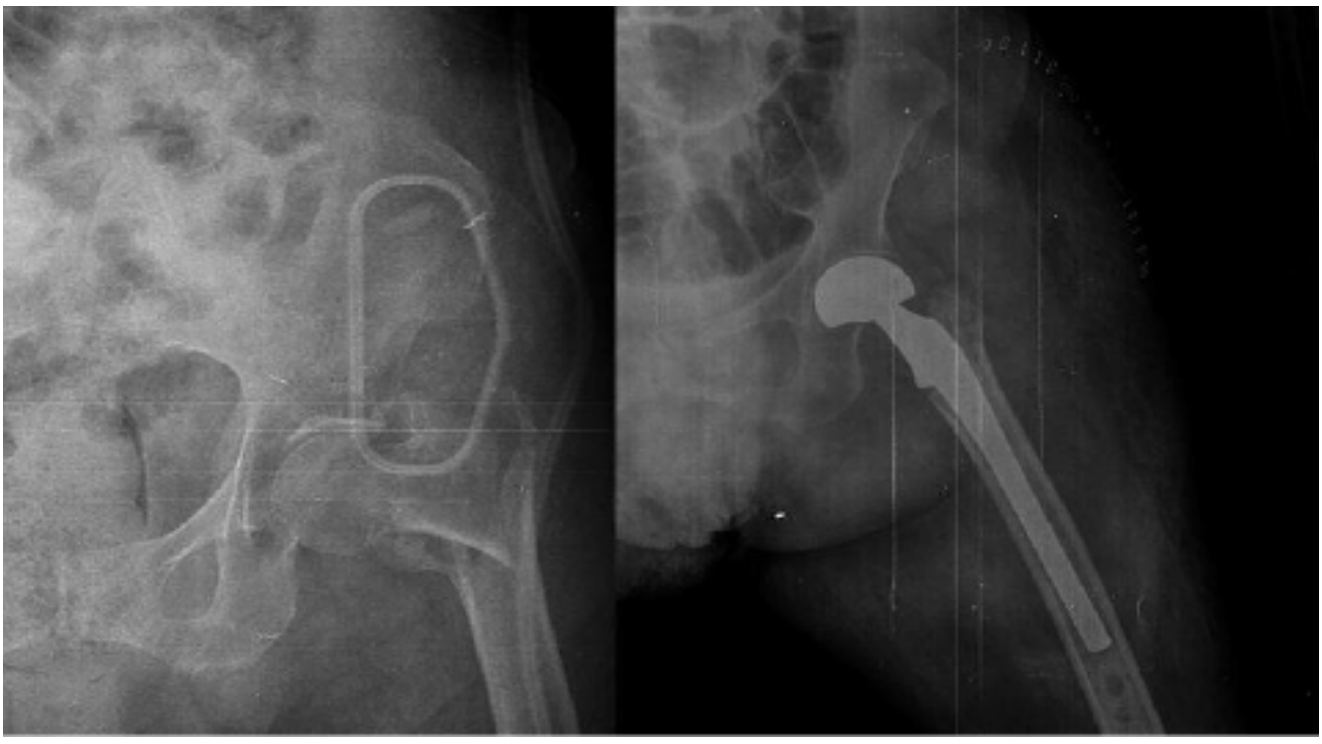

Figure 2. Preoperative and postoperative radiographs of an 85-year-old female patient after bipolar hemiarthroplasty

3. Findings

The data of 101 patients who met the study criteria were analyzed. Eleven of 51 patients (21.5%) in group 1 and 8 patients (16%) in group 2 died within the first 1 year and these patients were included in the mortality rates. The mean age of the patients in the study was 81.86 years (65–94) and the mean follow-up period was 19.86 months (12–28). 43 patients (52.43%) had right-sided trauma and 39 patients (47.56%) had left-sided trauma. 65 (79.26%) of the patients were female and 17 (20.74%) were male. Other demographic data and follow-up data of the study groups are shown in **Table 1**. Postoperative complications are given in **Table 2**. The mean total hospitalization time was 9.6 ± 4.94 days (4–24) in group 1 and 6.3 ± 3.57 (2–19) days in group 2, and the difference between the groups was statistically significant ($P = 0.01$). The difference in the amount of intraoperative bleeding and duration of surgery between the groups was statistically significant ($P = 0.00$, $P = 0.01$). The results were statistically significant when the 3rd month mean values of BI were compared ($P = 0.01$). When BI and HKS scoring values were evaluated statistically according to the groups, the results were not statistically significant.

Table 1. Distribution of demographic data by groups

	Variables	PHP (Group 1)	PFN (Group 2)
	Number of patients	40	42
	Post-op follow-up time (month)	20.25 (12–26)	19.50 (12–28)
	Patient age	82.25 (67–92)	81.50 (65–94)
Trauma side	Right	21 (52.5%)	22 (47.6%)
	Left	19 (47.5%)	20 (42.4%)
Gender	Male	8 (20%)	9 (21.43%)
	Female	32 (80%)	33 (78.57%)
ASA score	2	1 (2.5%)	3 (7.1%)
	3	5 (12.5%)	3 (7.1%)
	4	30 (75%)	31 (73.9%)
	5	4 (10%)	5 (11.9%)
Accompanying disease	0	8 (20%)	8 (19%)
Number of diseases	1	15 (37.5%)	12 (28.6%)
	2	9 (22.5%)	10 (23.9%)
	3	6 (15%)	9 (21.4%)
	4	2 (5%)	3 (7.1%)

Table 2. Clinical scoring and complication values between groups

Variables	PHP (Group 1)	PFN (Group 2)	*P* value
Total hospitalization time (days)	9.6 ± 3.26 (4–24)	6.3 ± 2.73 (2–19)	0.010
Post-op first-year mortality	11 (21.5%)	8 (16%)	0.036
Pre-op Barthel	87.5 ± 1.92 (80–95)	85 ± 2 (80–95)	0.863
3-day post-op Barthel	70 ± 4.43 (50–75)	64.5 ± 3.08 (50–70)	0.010
12-day post-op Barthel	78.50 ± 4.93 (55–95)	76.5 ± 4.70 (50–85)	0.064
Harris hip score	78.7 ± 5.30 (45–80)	80.5 ± 4.09 (55–85)	0.075

Complications	Peritoneal disease	1 (2.5%)	0	-
	Deep vein thrombosis	1 (2.5%)	1 (2.3%)	-
	Splenic vein occlusion	1 (2.5%)	0	-
	Infection	2 (5%)	1 (2.3%)	-
	Mechanical complications	-	3 (7.1%)	-
	Intra-op bleeding	370 ± 24.25 (300–480)	180 ± 22.52 (70–260)	0.000
	Duration of surgery	75 ± 8.12 (65–84)	45 ± 3.89 (35–52)	0.010

4. Discussion

The aim of treatment in intertrochanteric fractures is to mobilize the patient in a short time and to enable the patient to reach the functional capacity of his/her previous life and to avoid possible complications [12]. In addition, the elderly patient population requires consideration of the duration of surgery, the potential for intraoperative side effects, the amount of intraoperative bleeding, and the risk of morbidity and mortality in the postoperative period in terms of the selection of the ideal surgical technique [13]. The mean age of the patients in our study was 81.86 years (65–94), 65 (79.26%) were female and 17 (20.74%) were male. A meta-analysis has shown that the mean age ranged between 79.4 and 83.7 years and the proportion of females ranged between 82% and 50% [14]. The high number of female patients in the study groups may be explained by increased bone fragility due to osteoporosis in the postmenopausal period [15]. In addition, the number of comorbidities and ASA scoring risks were similar between the groups in our study, which indicates that we can make comparisons between the study groups. When the intraoperative bleeding amounts were analyzed, the mean intraoperative bleeding was 370 (300–480) ml in group 1 and 180 (70–260) ml in group 2. In addition, the mean operation time was 75 (65–84) minutes in group 1 and 45 (35–52) minutes in group 2. According to the results, the amount of bleeding was higher and the operation time was longer in the group in which PHP was performed. Korkmaz *et al.* [16] reported the mean operation time as 95 minutes in the group in which PHP was performed and 61.8 minutes in the group in which PFN was performed, but they showed that there was more bleeding and need for blood transfusion in the group in which PCP was performed. Luo *et al.* [17] showed that the mean amount of bleeding in the PFN group was 100 ml, the mean amount of bleeding in the PHP group was 300 ml and a longer operation time was needed in the PHP group. The results showed that PFN is a technically less invasive method. We think that this accelerates the patient's return to normal life. In addition, less bleeding reduces the need for blood transfusion and the risk of transfusion-related complications decreases. When total hospitalization duration was analyzed, the mean value was found to be 9.6 (4–24) days in group 1 and 6.3 (2–19) days in group 2 and this difference was statistically significant. Tang *et al.* [18] reported the mean hospitalization time as 14 days in the group in which PHP was performed and 11 days in the group in which PFN was performed. Kim *et al.* [19] reported the mean hospitalization time as 14 days in the PHP group and 8 days in the PFN group. The data in the literature show that the PFN technique provides closed fixation without opening the fracture line with less incision and shorter surgery [20]. This leads to less dressing follow-up and faster recovery of the patient's general condition. As a result, a shorter hospitalization period is required. In terms of clinical scores, BI values at 3 months postoperatively were statistically significantly higher in group 1. This shows that PHP has the advantage of early mobilization and the ability to give more BI and HHS at 12 days post-operation. When we look at the monthly values, even though the clinical scoring values were higher in group 2 patients who underwent the PFN technique, there was no statistically significant difference. Ju *et al.* [21] performed a

meta-analysis on randomized controlled trials and found that the results of the PCS after PHP and PFN were similar in 5 studies. Regarding the complications, postoperative peroneal nerve injury was observed in 1 patient (2.5%) in group 1 and returned to normal at postoperative 6th month. One patient (2.5%) showed signs of DVT in the lower extremity during hospitalization and received medical treatment. SVO was diagnosed in one patient (2.5%) and controlled with medical treatment. In one patient (5%), superficial infection findings were observed and oral antibiotics and dressing follow-up were sufficient. In group 2, 1 patient (2.3%) had lower extremity DVT findings and medical treatment was sufficient. One patient (2.3%) had superficial infection findings and oral antibiotic treatment was sufficient. Two patients (4.7%) had Z-effect and screw revision was performed. In one patient (2.3%), loss of reduction was observed in postoperative follow-up and revision surgery was performed. In our study, the results were similar between the groups in terms of infection and DVT risk. Koyuncu *et al.* [22] found that Z-effect is a specific mechanical complication of PFN with a rate of 1.8–11%. Yu *et al.* [23] compared the results of PHP and PFN in patients with unstable intertrochanteric fractures and reported that PFN had a higher risk of mechanical complications and the early mobilization advantage of PHP reduced the risk of complications. In addition, the risks of hip dislocation, aseptic loosening, peroneal nerve palsy, intraoperative death, cardiac rhythm problems, and cement-related complications should be considered after PHP [24]. In our study, 11 patients (21.56%) in the group in which PHP was performed and 8 patients (16%) in the group in which PFN was performed died within the first 1 year. Görmeli *et al.* [25] found 1-year mortality rates of 25.3% in the group in which PHP was performed and 11.7% in the group in which PFN was performed. In line with this information, it is possible to say that although PHP has the advantage of mobilization in the early period, it may cause an increase in the risk of mortality in the long term. This study has some limitations. Firstly, the study was retrospective and retrospective data were investigated. In addition, although the group demographic data were similar, the patients were randomly selected. Moreover, inclusion criteria were carefully determined in terms of homogeneity of the study and patients were evaluated accordingly.

5. Conclusion

In this study, we compared the clinical and functional results of two surgical methods, PFN and PHP, in the treatment of unstable femoral intertrochanteric fractures. Our results showed that the results of treatment with PFN are superior to PHP in unstable fractures. In unstable intertrochanteric fractures, the PFN technique has the advantages of rapid application, less intraoperative bleeding, and shorter operation time. On the other hand, although PHP allows early motion and mobilization, it should be considered that it may be associated with increased mortality rates in the long term.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

Data collection and processing: Orhan Büyükbebeci, Savaş Güner, Burçin Karslı
Analysis and interpretation: Savaş Güner, Bahri Bozgeyik, Kamil İnce
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Bioceramics: A Potential Biomaterial for Hard Tissue Repair

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Abstract: In the past two decades, significant progress has been made in the biomaterials field aimed at developing calcified tissues and facilitating tissue regeneration. The increasing demand for innovative biomaterials capable of replacing damaged tissues, enhancing the body's regenerative capacity, and promoting efficient calcification in hard tissues is primarily motivated by the rising number of elderly individuals afflicted with age-related ailments. Bioceramics, such as calcium phosphates, bioactive glasses, and glass ceramics, exhibit considerable potential in closely mimicking the structure of original calcified tissues when constructing scaffolds for repairing, restoring, reconstructing, or regenerating diseased body parts. These biomaterials have shown promising applications in calcified tissue engineering in recent years. This review covers the fundamental requirements of bioceramics for biomedical purposes and provides an extensive examination of the latest developments in bioceramics and composites, encompassing tissue engineering and drug delivery. The review concludes by underscoring the need for future research endeavors, particularly in the realm of fabricating scaffolds for tissue engineering utilizing nanotechnology.

Keywords: Biomaterial; Bioceramics; Bioinert ceramics; Bioactive ceramics; Tissue engineering

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1. Introduction

Hard tissue repair refers to the process of healing and regenerating bone and other hard tissues in the body after injury or damage. This process involves a series of complex biological events that aim to restore the structure and function of the affected tissue. During hard tissue repair, specialized cells called osteoblasts are recruited to the site of injury to produce a new bone matrix. This matrix serves as a scaffold for new bone formation. In addition, blood vessels grow into the area to provide oxygen and nutrients necessary for tissue regeneration. Factors such as age, nutrition, and the extent of the injury can influence the speed and success of hard tissue repair. For more severe injuries or in cases of certain medical conditions, additional interventions such as bone grafts or surgical procedures may be necessary to facilitate the healing process. Overall, hard tissue repair is a dynamic and highly regulated process that plays a crucial role in maintaining the structural integrity of the skeletal system and supporting overall mobility and functionality. Researchers continue to explore new

technologies and treatment strategies to improve the outcomes of hard tissue repair and enhance patient recovery.

Hard tissue repair, also known as bone repair, refers to the process by which the body restores damaged or fractured bone tissue to its original structure and function. This process involves a series of biological events orchestrated by specialized cells and signaling molecules. The following is a simplified overview of the steps involved in hard tissue repair:

(1) Hematoma formation: When a bone is fractured, blood vessels within the bone and surrounding tissues are damaged, leading to bleeding. This results in the formation of a hematoma (a blood clot) at the site of injury.

(2) Inflammatory phase: The hematoma triggers an inflammatory response, where immune cells, such as neutrophils and macrophages, migrate to the site of injury. These cells remove debris and damaged tissue, creating a clean environment for repair.

(3) Soft callus formation: Within a few days, cells called chondroblasts start to produce a soft callus made of cartilage at the fractured site. This serves as a temporary scaffold to stabilize the fracture.

(4) Hard callus formation: Over the next several weeks, osteoblasts begin to produce new bone tissue, gradually replacing the cartilaginous callus with a harder, woven bone structure. This process is called osteogenesis.

(5) Bone remodeling: The hard callus is eventually remodeled into mature lamellar bone through a process called bone remodeling. Osteoclasts remove excess bone tissue, while osteoblasts deposit new bone, resulting in the restoration of the bone's original shape and strength.

Several factors can influence the rate and success of hard tissue repair, including the extent of the injury, the patient's age and overall health, and the presence of any underlying medical conditions. In some cases, surgical intervention may be required to realign the fractured bone fragments or provide additional support, such as screws, plates, or bone grafts, to facilitate proper healing. Physical therapy and rehabilitation are often recommended following bone repair to restore function and mobility to the affected area.

Hard tissue repair often requires the use of various materials to support and facilitate the healing process. These materials can be synthetic or natural, and they serve different purposes depending on the specific needs of the patient and the type of injury. Some common materials used in hard tissue repair are as follows:

(1) Bone grafts: Bone grafts are perhaps the most common material used in hard tissue repair. They can be sourced from the patient's own body (autograft), a donor (allograft), or synthetic materials (alloplastic grafts). Bone grafts provide a scaffold for new bone growth and can help stimulate bone regeneration in cases of large defects or non-healing fractures.

(2) Bioceramics: Bioceramic materials, such as calcium phosphate ceramics (e.g., hydroxyapatite), are widely used in hard tissue repair due to their biocompatibility and ability to integrate with the surrounding bone tissue. These materials can be used as bone substitutes, coatings for implants, or scaffolds for tissue engineering applications.

(3) Metal implants: Metal implants, such as titanium and its alloys, are commonly used in orthopedic surgeries to stabilize fractures and provide mechanical support to the healing bone. These implants are typically designed to mimic the mechanical properties of bone and can remain in the body permanently or be removed once the bone has healed.

(4) Biodegradable polymers: Biodegradable polymers, such as polylactic acid (PLA) and polyglycolic acid (PGA), are used in the fabrication of scaffolds and implants for hard tissue repair. These materials gradually degrade over time, allowing for the gradual replacement of the implant with new bone tissue.

(5) Collagen matrices: Collagen-based materials, derived from natural sources such as bovine or porcine collagen, are often used in tissue engineering and regenerative medicine applications. Collagen matrices provide a supportive environment for cell attachment, proliferation, and differentiation, promoting the formation of new bone tissue.

(6) Platelet-rich plasma (PRP): PRP is a concentration of platelets derived from the patient's own blood, which contains growth factors that can stimulate tissue repair and regeneration. PRP is sometimes used in conjunction with other materials, such as bone grafts or bioceramics, to enhance their osteogenic properties and accelerate the healing process.

(7) Bioactive glasses: Bioactive glasses, such as silicate-based glasses, have the ability to bond with bone tissue through the formation of a hydroxycarbonate apatite layer, which promotes osseointegration. These materials are often used in bone graft substitutes and dental applications.

These materials can be used alone or in combination with each other, depending on the specific requirements of the patient and the nature of the injury. The choice of material depends on factors such as biocompatibility, mechanical properties, degradation kinetics, and the desired outcome of the treatment.

For hard tissue repair, materials commonly used include:

(1) Ceramics: Ceramics such as hydroxyapatite and tricalcium phosphate, are biocompatible and mimic the mineral composition of bone.

(2) Metals: Metals like titanium and stainless steel, are often used for load-bearing applications due to their strength and durability.

(3) Polymers: Polymers such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG), are biodegradable and can provide temporary support during tissue regeneration.

(4) Composite materials: Combining two or more material types, such as ceramic-polymer composites, can offer a balance of mechanical strength and biocompatibility.

(5) Scaffolds: Scaffolds made from natural or synthetic materials provide a framework for cell attachment and tissue growth, aiding in the regeneration of hard tissues.

(6) Biomimetic materials: Biomimetic materials are designed to mimic the structure and function of natural tissues, promoting better integration and regeneration.

(7) Bioactive materials: Bioactive materials incorporate growth factors or other bioactive molecules to stimulate tissue regeneration and promote healing.

These materials play a crucial role in various applications, including bone grafts, dental implants, and orthopedic surgeries, to facilitate the repair and regeneration of hard tissues in the body.

To diminish the dependence on tissue and organ transplants, novel materials have been engineered to function as implants or scaffolds for damaged organs, promoting the regeneration of various tissues. These advancements have emerged in response to the treatment of organ or tissue injuries stemming from diseases or various forms of physical, chemical, or biological harm. A global concern is the development of novel biomaterials to enhance human life standards through the replacement of malfunctioning organs or the regeneration of tissue using scaffolds. The need for biomaterials that can replace, regenerate, and restore soft and hard tissues including skin, bones, cartilage, blood vessels, and even organs has grown dramatically as the population has grown exponentially. Many materials are now being employed in regenerative medicine, including materials for bioimaging to track the progression of illness, drug delivery vehicles, and porous scaffolds for tissue engineering structures. Several organic and inorganic materials have been specifically developed and used as scaffolds for tissue regeneration and medication administration [1].

Biomaterials for hard tissue repair play a crucial role in regenerative medicine, as they provide structural

support and promote tissue regeneration in damaged or diseased tissues such as bones and teeth. These biomaterials can be synthetic or natural in origin, and they are designed to mimic the properties of the native tissue to enhance healing and integration. Some commonly used biomaterials for hard tissue repair include:

(1) Calcium phosphate ceramics: These biomaterials, such as hydroxyapatite and tricalcium phosphate, are biocompatible and bioactive, making them ideal for bone regeneration. They can be used as bone graft substitutes or coatings for implants to promote osseointegration.

(2) Collagen-based materials: Collagen, a naturally occurring protein present in connective tissues, is frequently utilized in tissue engineering owing to its biocompatible nature and capacity to facilitate cell proliferation and tissue rejuvenation. Collagen scaffolds are applicable in the restoration of bone and cartilage, as well as in various dental procedures.

(3) Polymers: Synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG) are commonly used for hard tissue repair due to their tunable properties, biodegradability, and biocompatibility. These materials can be used for drug delivery, scaffolds, and implants in bone and cartilage regeneration.

(4) Bioglass: Bioglass is a bioactive glass material that can stimulate bone formation and integrate with surrounding tissues. It is often used in dental applications, as well as in bone grafts and implants for repairing bone defects.

(5) Composite materials: Composite biomaterials combine different materials to enhance their properties for hard tissue repair. For example, calcium phosphate nanoparticles can be incorporated into polymer scaffolds to improve mechanical strength and bioactivity for bone regeneration.

Overall, biomaterials for hard tissue repair play a critical role in regenerative medicine by providing support and promoting tissue regeneration in damaged or diseased tissues. Researchers continue to explore new biomaterials and combinations to improve outcomes for patients in need of hard tissue repair.

Many definitions for biomaterial have been proposed and endorsed. The term biomaterial could be defined as “a systemically, pharmacologically inert substance designed for implantation within or incorporation with a living system” [2] or “a nonviable material used in a medical device, intended to interact with biological system” [3]. In this definition, the word “medical” would be removed, and the term becomes more applicable and broader suggested above. According to the National Institute of Health, USA, the biomaterial is defined as “any substance or combination of substances, other than drugs, synthetic or natural in origin, which can be used for any period of time, which augments or replaces partially or totally any tissue, organ or function of the body, in order to maintain or improve the quality of life of the individual” [3]. A complementary definition is necessary while dealing with the understanding of biomaterials is “biocompatibility.” It is defined as “the ability of a material to perform with an appropriate host response in a specific application” [3]. Furthermore, biomaterials should exhibit an acceptable host response, which in tissue engineering applications translates to strong resistance to bacterial colonization, blood clotting, and biofilm formation while promoting the natural healing process. Without a doubt, biomaterials improve human life quality and prolong the lives of many individuals annually. There are countless and unparalleled uses for biomaterials in the treatment of human illnesses when compared to alternative therapies and treatments. It comprises prosthetic limbs and arteries, skin replacements, scaffolds for ocular tissue engineering and contact lenses, and bone substitutes. Therefore, as the world’s population grows faster than ever, there is a growing need for biomaterials. By 2021, the value of the global biomaterials market is expected to reach USD 149.17 million. At a compound annual growth rate of 16.0%, this market is projected to grow from USD 70.90 billion in 2016 to USD 149.17 million in 2021. The expansion is dependent upon a number of factors, including the global increase in hip and knee replacement surgeries, the

market for implants, the prevalence of growing illnesses, advances in tissue engineering, and the quick aging of the population. Additionally, the biomaterial types—such as polymers, metals, or ceramics—as well as the area and use of the material in treatment determine the market's growth [4]. The demand for ceramic biomaterials, such as orthopedic implants, which are now on the market, is enormous and accounts for over 1.5 million units annually globally at a cost of $10 billion.

Bioceramics are a class of biomaterials that have shown great promise for hard tissue repair, particularly in bone and dental applications. These materials are biocompatible, bioactive, and have similar mechanical properties to natural bone, making them ideal for use in repairing and regenerating damaged or diseased hard tissues. One of the most well-known bioceramics used for hard tissue repair is hydroxyapatite (HA), which is the main mineral component of natural bone. HA is osteoconductive, meaning it promotes the growth of new bone tissue, and is often used in bone grafts and dental implants. Another commonly used bioceramic is calcium phosphate, which can also promote bone formation and has been used in bone cement and coatings for orthopedic implants. Bioceramics can be used in a variety of forms, including powders, granules, scaffolds, and coatings, and can be tailored to have specific properties depending on the application. For example, bioceramic scaffolds can be designed to have a porous structure that mimics the natural architecture of bone, allowing for better integration with surrounding tissue and promoting new bone growth. Overall, bioceramics have shown great potential for hard tissue repair and have been used successfully in a wide range of clinical applications. Continued research and development in this field are likely to lead to further advancements in the use of bioceramics for repairing and regenerating hard tissues. This paper reveals the overview of bioceramics and its classification and application for hard tissue repair.

2. Overall classification of biomaterials

Biomaterials can be classified in various ways based on their composition, properties, and intended applications. An overall classification of biomaterials is presented as follows:

(1) Natural biomaterials:
   (a) Biological: Derived from living organisms, such as collagen, alginate, chitosan, silk, and hyaluronic acid.
   (b) Mineral: Naturally occurring minerals used in biomedical applications, such as hydroxyapatite and calcium phosphate.

(2) Synthetic biomaterials:
   (a) Polymers: Synthetic polymers designed for biomedical use, including polyethylene glycol (PEG), poly(lactic-co-glycolic acid) (PLGA), polyethylene terephthalate (PET), and polyvinyl alcohol (PVA).
   (b) Ceramics: Inorganic, non-metallic materials like alumina, zirconia, and bioglass.
   (c) Metals: Metallic biomaterials like titanium, stainless steel, cobalt-chromium alloys, and nickel-titanium alloys.
   (d) Composites: Combination of two or more materials, such as polymer-ceramic composites or metal-polymer composites.

2.1. Functional biomaterials

Bioactive materials are materials that elicit a specific biological response at the interface of the material and biological system, such as bioactive glasses and ceramics. Bioinert materials are materials that do not elicit a significant immune response or biological reaction, often used in applications where long-term

stability and compatibility are critical, such as certain metals like titanium and some polymers like PTFE (polytetrafluoroethylene). Bioresorbable materials are materials that degrade and are absorbed by the body over time, such as certain polymers (e.g., PLGA) and ceramics (e.g., tricalcium phosphate).

Derived biomaterials:

(1) Decellularized extracellular matrices (ECMs): ECMs obtained by removing cellular components from tissues or organs, leaving behind the extracellular matrix, which can serve as a scaffold for tissue regeneration.

(2) Extracellular vesicles (EVs): Small membrane-bound vesicles secreted by cells that contain bioactive molecules, such as proteins, nucleic acids, and lipids, which can be used for therapeutic purposes.

Nanostructured biomaterials:

(1) Nanoparticles: Nanoscale materials with unique properties, such as enhanced surface area and reactivity, used for drug delivery, imaging, and tissue engineering.

(2) Nanofibers: Fibrous materials with diameters on the nanometer scale, often used as scaffolds for cell growth and tissue regeneration.

This classification system helps in organizing biomaterials based on their characteristics and functions, aiding researchers and clinicians in selecting the most appropriate materials for specific biomedical applications.

The biocompatibility of the materials is the basis for the first classification of biomaterials. The ability of a substance to be recognized by or accepted by the surrounding tissues and organs in the human body is known as biocompatibility. Biocompatibility refers to the ability of a material to perform its desired function within a specific application without eliciting an adverse biological response in the body. In other words, a biocompatible material is one that is compatible with living tissues and does not cause harm or induce a significant immune reaction when in contact with biological systems. Biocompatibility is a critical consideration in the design and development of biomaterials for medical devices, implants, drug delivery systems, and tissue engineering scaffolds.

Several factors influence the biocompatibility of a material:

(1) Chemical composition: The chemical composition of a material plays a significant role in determining its biocompatibility. Materials that closely mimic the composition of natural tissues are often more biocompatible. For example, biodegradable polymers derived from natural sources like collagen or hyaluronic acid are generally well-tolerated by the body.

(2) Physical properties: Physical properties such as surface roughness, porosity, stiffness, and mechanical strength can affect how a material interacts with biological tissues. For instance, a rough surface may promote better cell adhesion and tissue integration, while excessive stiffness or flexibility may cause tissue irritation or failure.

(3) Degradation kinetics: For bioresorbable materials, the rate of degradation and the by-products formed during degradation are critical factors in determining biocompatibility. Ideally, degradation should occur at a controlled rate, allowing for tissue regeneration without causing inflammation or toxicity.

(4) Surface characteristics: Surface properties such as wettability, charge, and the presence of functional groups can influence protein adsorption, cell adhesion, and tissue response. Modifying the surface of a material through techniques like surface coating, plasma treatment, or biomolecule conjugation can improve its biocompatibility.

(5) Immunogenicity: Some materials may trigger an immune response when implanted in the body, leading to inflammation, foreign body reactions, or rejection. Minimizing the immunogenicity of biomaterials through appropriate surface modifications or using materials with low immunogenicity, such as

biocompatible polymers, is essential for long-term implant success.

(6) Bioactivity: Bioactive materials have the ability to interact with biological systems and promote specific cellular responses, such as cell attachment, proliferation, and differentiation. Bioactive materials can enhance tissue integration and regeneration, improving overall biocompatibility.

(7) Sterility: Ensuring the sterility of biomaterials is crucial to prevent infection and adverse reactions when implanted or used in contact with biological fluids or tissues.

Overall, achieving biocompatibility requires a thorough understanding of the interactions between biomaterials and biological systems, as well as careful consideration of material properties, design, and fabrication techniques. Biocompatibility testing, including *in vitro* assays, animal studies, and clinical trials, is often conducted to evaluate the safety and performance of biomaterials before their use in medical applications. Stated differently, implants made of natural or synthetic materials should not cause negative tissue reactions or immune system responses in humans. Using a categorization system based on biocompatibility, the materials can be classified as follows.

2.2. Bioinert materials

Any substance that, when in touch with physiological systems, causes little unfavorable reaction to the host tissue or organs in the human body is referred to as a bioinert biomaterial. Dental implants made of stainless steel, titanium, alumina, partly stabilized zirconia, polyethylene, and bioinert alumina are examples of this category. Tissue integration occurs via the implant because the biomaterial is functionally wrapped in a fibrous capsule.

Bioinert materials for hard tissue repair are those that do not elicit a significant immune response or adverse reactions when implanted in the body. These materials are often used in applications where long-term stability and compatibility are critical. While they may not actively promote tissue regeneration, they provide mechanical support and stability to facilitate the natural healing process. Some examples of bioinert materials commonly used in hard tissue repair are described below:

(1) Titanium and titanium alloys: Titanium and its alloys, such as Ti-6Al-4V, are widely used in orthopedic and dental implants due to their excellent biocompatibility, corrosion resistance, and mechanical properties. Titanium implants provide structural support for bone fixation and can integrate with the surrounding bone tissue through osseointegration.

(2) Stainless steel: Stainless steel alloys, such as 316L stainless steel, are commonly used in orthopedic implants, fracture fixation devices, and dental instruments. Stainless steel implants provide mechanical strength and stability while minimizing the risk of corrosion and adverse tissue reactions.

(3) Cobalt-chromium alloys: Cobalt-chromium alloys, such as Co-Cr-Mo, are used in orthopedic implants, including hip and knee prostheses, due to their high strength, wear resistance, and biocompatibility. These alloys provide durable and long-lasting support for hard tissue repair.

(4) Polyethylene (PE): Ultra-high molecular weight polyethylene (UHMWPE) is often used as a bearing surface in joint replacement implants, such as hip and knee prostheses. While not completely bioinert, UHMWPE has been extensively studied and modified to improve its wear resistance and biocompatibility *in vivo*.

(5) Polytetrafluoroethylene (PTFE): PTFE, commonly known as Teflon, is a fluoropolymer with low friction and excellent chemical resistance. PTFE coatings are sometimes applied to orthopedic implants to reduce friction and wear, although their use in direct contact with bone tissue is limited.

(6) Alumina (Al_2O_3) and Zirconia (ZrO_2): Ceramic materials such as alumina and zirconia are used in hard

tissue implants, particularly in dental applications. These materials are biocompatible, wear-resistant, and can be fabricated into highly precise components for dental crowns, bridges, and dental implants.

While bioinert materials play a crucial role in hard tissue repair by providing mechanical stability and support, they may not actively participate in the regeneration process. In some cases, bioactive or bioresorbable materials may be used in conjunction with bioinert materials to enhance tissue integration and promote long-term healing.

Bioinert materials are substances that do not elicit a significant immune response when implanted into the body. They are often used in hard tissue repair procedures due to their compatibility with the human body. Some common bioinert materials used for hard tissue repair include titanium, stainless steel, and certain ceramics like alumina and zirconia. These materials are chosen for their excellent mechanical properties, biocompatibility, and resistance to corrosion. Titanium and stainless steel are frequently used in orthopedic implants due to their strength and durability. Ceramics like alumina and zirconia are favored for dental implants and joint replacements because of their biocompatibility and wear resistance. Bioinert materials play a crucial role in promoting successful hard tissue repair by providing support and stability to damaged bones and joints. Their ability to integrate seamlessly with the surrounding tissues helps in reducing the risk of rejection and complications post-surgery. Overall, bioinert materials are essential in the field of hard tissue repair as they offer a reliable and effective solution for patients in need of bone and joint treatments.

2.3. Bioactive materials

Bioactive biomaterials are found in implant materials, which engage with soft tissue via a stimulation process, leading to a regeneration and healing process. One example is the formation of a physiologically active carbonate apatite (CHAp) layer on the implant through an anion-exchange interaction with bodily fluids, mimicking the chemical and crystallographic properties of bone's mineral component. The greatest examples in this area include synthetic hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$], glass ceramic A-W, bioglass, and bioactive hydroxyapatite coating on a metallic dental implant, surface active bioglass, and bioresorbable tricalcium phosphate implant.

Bioactive materials for hard tissue repair are designed to interact with the biological environment and actively promote tissue regeneration and integration. These materials have properties that facilitate cell adhesion, proliferation, differentiation, and extracellular matrix formation, leading to enhanced healing and functional restoration. Bioactive materials for hard tissue repair are designed to interact with the biological environment and actively promote tissue regeneration and integration. These materials have properties that facilitate cell adhesion, proliferation, differentiation, and extracellular matrix formation, leading to enhanced healing and functional restoration. Bioactive materials commonly used in hard tissue repair include:

(1) Hydroxyapatite (HA): Hydroxyapatite is a naturally occurring mineral form of calcium apatite, which is the main component of bone tissue. Synthetic hydroxyapatite is widely used in orthopedic and dental applications due to its excellent biocompatibility and similarity to natural bone minerals. HA coatings and scaffolds provide a bioactive surface for cell attachment and promote osseointegration with surrounding bone tissue.

(2) Tricalcium phosphate (TCP): Tricalcium phosphate is another calcium phosphate ceramic commonly used in hard tissue repair. TCP is biocompatible, bioresorbable, and osteoconductive, meaning it promotes new bone formation. It can be used as a bone graft substitute, scaffold material, or coating for implants to enhance bone regeneration.

(3) Calcium phosphate ceramics: Calcium phosphate ceramics, such as hydroxyapatite (HA) and tricalcium

phosphate (TCP), mimic the mineral composition of natural bone. They are widely used in bone graft substitutes, bone fillers, and coatings for orthopedic implants. These materials provide a scaffold for new bone formation and promote osseointegration with the surrounding tissue.

(4) Bioactive glass: Bioactive glasses, composed of silica-based or borate-based compositions, have the ability to bond with bone tissue through the formation of a hydroxycarbonate apatite layer. This bioactive interaction stimulates bone growth and facilitates the repair of bone defects. Bioactive glass is used in bone grafts, scaffolds, and coatings for orthopedic and dental applications.

(5) Calcium sulfate: Calcium sulfate, in the form of synthetic gypsum (calcium sulfate hemihydrate), is used as a bone void filler and scaffold for bone regeneration. When implanted in the body, calcium sulfate dissolves and is gradually replaced by new bone tissue. It provides temporary support and stimulates bone healing in defects and fractures.

(6) Polymers with bioactive moieties: Some synthetic polymers are modified with bioactive moieties, such as peptides or growth factors, to enhance their interaction with cells and tissues. These polymers can be used as scaffolds for tissue engineering or as drug delivery vehicles to promote tissue regeneration and repair.

(7) Collagen-based materials: Collagen is a natural protein found in connective tissues and is an essential component of the extracellular matrix. Collagen-based materials, such as collagen sponges, sheets, and hydrogels, are used as scaffolds for tissue regeneration in various applications, including bone repair. Collagen provides a bioactive environment that supports cell adhesion, migration, and tissue remodeling.

(8) Platelet-rich plasma (PRP): Platelet-rich plasma (PRP) is a concentrated form of platelets derived from the patient's own blood. PRP contains growth factors and cytokines that promote tissue repair and regeneration. It is used in conjunction with other biomaterials or as a standalone treatment to enhance the healing of bone fractures, tendon injuries, and soft tissue wounds.

These bioactive materials play a crucial role in promoting the regeneration and repair of hard tissues, such as bone, by providing a conducive environment for cellular activities and tissue growth.

2.4. Bioresorbable biomaterials

Bioresorbable biomaterials for hard tissue repair are designed to degrade over time within the body, gradually being replaced by native tissue as the healing process progresses. These materials offer several advantages, including eliminating the need for implant removal surgeries, reducing the risk of long-term complications, and providing temporary structural support during the healing phase. Some examples of bioresorbable biomaterials commonly used in hard tissue repair are as follows:

(1) Poly(lactic-co-glycolic acid) (PLGA): PLGA is a biodegradable copolymer composed of lactic acid and glycolic acid monomers. It is widely used in orthopedic and dental applications for bone fixation devices, such as screws, pins, and plates. PLGA degrades via hydrolysis into biocompatible by-products (lactic acid and glycolic acid) that are metabolized and excreted by the body.

(2) Polylactic acid (PLA): PLA is a biodegradable polymer derived from lactic acid. It is used in bone fixation devices, scaffolds for tissue engineering, and drug delivery systems. PLA degrades into lactic acid, a naturally occurring compound that can be metabolized and eliminated by the body.

(3) Polyglycolic acid (PGA): PGA is a biodegradable polymer commonly used in absorbable sutures and tissue scaffolds. It degrades rapidly *in vivo* via hydrolysis into glycolic acid, which is metabolized and eliminated by the body. PGA is often combined with other polymers, such as PLA, to modify its

degradation rate and mechanical properties.

(4) Calcium phosphate-based ceramics: Some calcium phosphate ceramics, such as α-tricalcium phosphate (α-TCP) and β-tricalcium phosphate (β-TCP), exhibit bioresorbable properties. These ceramics provide a scaffold for new bone formation and gradually degrade over time as they are replaced by native bone tissue. They are used in bone graft substitutes, scaffolds for tissue engineering, and coatings for orthopedic implants.

(5) Polydioxanone (PDO): PDO is a synthetic bioresorbable polymer used in orthopedic surgery for sutures, anchors, and fixation devices. It degrades via hydrolysis into non-toxic by-products that are metabolized and eliminated by the body. PDO maintains its strength for an extended period before gradually losing mechanical integrity as it degrades.

(6) Bioresorbable magnesium alloys: Magnesium alloys, such as magnesium-calcium (Mg-Ca) and magnesium-zinc (Mg-Zn) alloys, exhibit bioresorbable properties and are being investigated for orthopedic and cardiovascular applications. These alloys degrade *in vivo* via corrosion reactions, releasing magnesium ions that can be utilized by cells for tissue regeneration. However, controlling the degradation rate and addressing potential biocompatibility issues are ongoing challenges in the development of magnesium-based implants.

These bioresorbable biomaterials offer versatile solutions for hard tissue repair, providing temporary support while facilitating natural tissue healing and regeneration. The choice of material depends on factors such as the specific application, required mechanical properties, degradation kinetics, and biocompatibility considerations.

Common applications for bioresorbable materials include implanting them into the body, where they interact with biological fluids, dissolve in the physiological medium, and reabsorb into the body through a variety of metabolic processes, eventually being replaced by newly formed tissue like skin and bone. Appropriate examples are polylactic–polyglycolic acid copolymers and tricalcium phosphate [$Ca_3(PO_4)_2$]. Calcium carbonate, gypsum, and calcium oxide are regarded as bioresorbable biomaterials.

2.5. Natural biomaterials

The biomaterials are divided into natural and synthetic categories according to their source. Additionally, there are two categories of natural biomaterials: those based on proteins and those based on carbohydrates. Composites, metals, ceramics, and polymers make up the categories of synthetic materials.

Natural biomaterials for bone repair are gaining significant attention due to their biocompatibility, bioactivity, and ability to promote tissue regeneration. Several commonly used natural biomaterials for bone repair are described as follows:

(1) Collagen: Collagen is the main protein component of the extracellular matrix in bone tissue. It provides structural support and serves as a scaffold for cell attachment and growth. Collagen-based scaffolds can mimic the natural bone environment, promoting cell adhesion, proliferation, and differentiation.

(2) Hydroxyapatite (HA): Hydroxyapatite is a mineral form of calcium apatite, which is the main inorganic component of bone tissue. It provides strength and rigidity to bones. HA-based biomaterials can enhance bone regeneration by mimicking the mineral composition of natural bone.

(3) Chitosan: Chitosan is derived from chitin, a natural polymer found in the exoskeletons of crustaceans. It has excellent biocompatibility, biodegradability, and antimicrobial properties. Chitosan-based scaffolds can support bone regeneration and have been used in various bone tissue engineering applications.

(4) Alginate: Alginate is a natural polysaccharide derived from brown seaweed. It forms hydrogels in the

presence of divalent cations such as calcium ions. Alginate-based scaffolds can provide a 3D matrix for cell encapsulation and support cell proliferation and differentiation for bone repair.

(5) Gelatin: Gelatin is derived from collagen through hydrolysis and has similar biocompatibility and bioactivity properties. Gelatin-based scaffolds can promote cell adhesion, proliferation, and differentiation, making them suitable for bone tissue engineering applications.

(6) Silk fibroin: Silk fibroin is a natural protein extracted from silkworm cocoons. It possesses excellent mechanical properties and biocompatibility. Silk fibroin-based scaffolds can support bone regeneration by providing a suitable microenvironment for cell growth and tissue formation.

(7) Demineralized bone matrix (DBM): DBM is derived from allograft bone tissue that has been processed to remove minerals while retaining the organic matrix and growth factors. It provides a scaffold for bone regeneration and contains various growth factors that promote osteogenesis.

(8) Decellularized extracellular matrix (ECM): ECM is obtained by decellularizing tissues such as bone, cartilage, or tendon to remove cellular components while preserving the extracellular matrix proteins and growth factors. Decellularized ECM scaffolds can provide a biomimetic microenvironment for cell adhesion, proliferation, and differentiation in bone repair. These natural biomaterials can be used alone or in combination with synthetic materials or growth factors to enhance their properties and tailor them for specific bone repair applications.

Natural biomaterials, also known as allografts from human sources and xenografts from animal sources, are processed and decellularized extracellular matrix of animal tissue. They are utilized as prosthetics. Human dermal allografts are utilized in several organ regeneration processes as well as tissue engineering applications such as biological scaffolds for scar avoidance, dental prostheses, and wound repair. Numerous bioactive ingredients found in these biomaterials promote tissue regeneration and healing, leaving fewer scars behind [5]. Lately, there has been interest in using xenografts made from pig and cow sources as prosthetic heart valves. These grafts or cardiovascular biomaterials have a potential market. It is a transient treatment for tissue regeneration, though, and occasionally it results in serious immunological responses to the host tissue and the spread of illness throughout the host system. Biomaterials called extracellular matrix (ECM) are utilized as scaffolds to repair both soft and hard tissues, including burn injuries and wound healing. The most important component of ECM biomaterials is collagen, which is also obtained from animal tissue, including tendons, and by using recombinant DNA technology. Similar to this, a variety of extracellular proteins, including elastin, fibrin, and fibrinogen, are utilized as a natural biomaterial to create scaffolds for tissue engineering projects. Human hair has recently been shown to contain keratin, and horn meal is the greatest source of protein for use in biomedical applications.

The extracellular matrix's natural protein-based polymers have enormous promise for use in the creation of biomaterials and substrates for tissue engineering, which may repair injured tissue. At the damaged location of an injury, these components may trigger the cell destiny process and cell identification. Collagen, elastin, keratin, and fibrin are the most often utilized materials. Fibrinogen is an extracellular matrix protein that is used to make scaffolds, sponges, hydrogels, and films that are used to treat a variety of connective tissue problems, including those that affect the tendon, ligament, cartilage, bone, and skin. Enzymes such as matrix metal proteinase and serine protease may break down these compounds through tissue healing [6].

Typically, glycosaminoglycan, another essential component of the extracellular matrix of connective tissue, is mimicked by carbohydrate-based biomaterials. In this category, cellulose, chitosan, starch, and alginate are among the most widely used polymers. The structures of these molecules are similar to those of glycosaminoglycan, which is a significant regulator of tissue hydrodynamics [7] and adhesion, migration,

proliferation, and differentiation in cells [8]. These biomaterials can be produced as drug-delivery vehicles, scaffolds, sponges, films, and substrates for tissue engineering. Natural biomaterials do have certain drawbacks, though, including lower mechanical properties, difficulty obtaining the necessary quantity for extraction and purification, cross-contamination with other raw material components that could introduce a pathogen or infect host tissue, and high susceptibility to immunological reactions.

2.6. Synthetic biomaterials

Today, the majority of biomedical devices and implants are made with synthetic biomaterials. because it is simple to modify the chemical, surface, and mechanical characteristics to meet biological needs. Nondegradable and biodegradable biomaterials are two major categories into which synthetic biomaterials may be divided. Materials that are biologically inert and do not interact with the physiological milieu of the human body are referred to as non-degradable materials. The most prevalent example of this type, for instance, are implants, which need to be surgically removed from the human body. Materials that can undergo disintegration or resorption of their metabolic pieces under the influence of physiological responses are considered biodegradable materials. The categorization of synthetic biomaterials, together with their uses and justifications in the medical field, are covered in the section that follows. Metals, polymers, composites, and ceramics are the broad categories into which synthetic biomaterials are divided. In **Table 1**, the benefits and drawbacks of different biomaterials are compiled.

Table 1. Advantages and disadvantages of biomaterials

Materials	Advantages	Disadvantages	Applications
Synthetic polymers (nylon, silicone, polyester and biodegradable polymers)	Resilient, simple fabrication, controlled and tailored properties (mechanical strength, biocompatibility, and biodegradation (for biodegradable polymers), reproducible formulation	Lack of good mechanical strength, deform with time, degradable, lack of microenvironment for cell growth, inflammation due to degradation of polymers, lack of balance between polymer degradation and tissue formation	Suture, blood vessels, hip sockets, intraocular lenses.
Natural polymers (collagen, keratin, chitosan and cellulose)	Biocompatible, cell supportive and biodegradable by enzymes mimics extracellular matrix, trigger signaling mechanism (reactive site and growth factors)	Complex decellularization process, poor biomechanical strength, scar formation	Heart valves, Wound dressings
Metals (Ti and its alloys, Ag, Au, and stainless steels)	Strong, tough, and ductile	Corrosion, dense, expensive cost for fabrication of medical device	Joint replacement, dental root implant, pacers, bone plates, and screws.
Ceramics (alumina, zirconia and hydroxyapatite)	Excellent biocompatible	Brittle, not resilient	Dental and orthopedic Implants
Composites (carbon-carbon, bone cement)	Strong, tailor-made	Difficult to prepare	Dental resin and bone cement

2.6.1. Metals as biomaterials

In orthopedic surgery and dentistry, metals and their alloys are used as load-bearing implants. For load-bearing applications, metallic implants offer excellent tensile strength and fatigue resistance. Metallic implants are employed in the form of wires, screws, fracture fixation plates, and prosthetic joints for the ankles, knees, hips, shoulders, and so on. Furthermore, metallic biomaterials are valuable dental materials and are used in cardiovascular and maxillofacial surgery. The most often utilized metallic implants are made of cobalt-based

alloys, pure titanium and its alloys, and stainless steel. According to McGregor *et al.* [9], metallic implants have corroded in physiological fluids and have released metallic cations such as nickel, chromium, and cobalt. These ions have the potential to cause toxic or hypersensitive reactions, including skin-related diseases, or they may even cause carcinogenesis. Peri-implant bone resorption, often referred to as stress-shielding, is caused by a notable mismatch in Young's modulus between metallic implants, such as SUS 316L or Co–Cr, and hard tissue, such as bone [10]. Titanium and its alloys offer a close elastic modulus with bone hardness and produce a layer of titanium dioxide with a physiological environment to solve this issue. This layer offers improved biocompatibility with the biological surface while providing corrosion protection. Titanium implants have a high specific strength, however, when it comes to screws or plates, they have a low shear strength. Furthermore, according to Sumner *et al.* [11], several of the first generation of titanium alloys released aluminum or vanadium ions into the physiological milieu, resulting in harmful effects [12]. Materials that are thought to be bioinert are metals. Nonetheless, certain metals and alloys reacted toxically when they came into touch with the organs' physiological surfaces. Therefore, a number of studies employing various physical, chemical, and biological techniques are being conducted to modify the surface of metal implants in order to improve their biocompatibility and adaptability with the biological surface [13].

2.6.2. Polymers

Polymeric biomaterials are artificial or natural materials designed to interact with biological systems in order to treat, enhance, or repair any kind of tissue found in the human body or its organs. Tissue engineering and regenerative medicine have made substantial use of polymers, a flexible class of biomaterials. The primary characteristic of polymeric biomaterials is their exceptional adaptability in customizing their mechanical, chemical, and physical characteristics by the synthesis or chemical alteration of their functional groups in accordance with the potential for organ or tissue regeneration [14]. Examples of polymeric biomaterials include silicone rubber, polyethylene (PE), acrylic resins, polyurethanes, polypropylene, and polymethylmethacrylate (PMMA) as a cornea replacement. Acrylic bone cement is used in dentistry and orthopedic surgery. The polymer's monomer release, which poisoned the cell, was the constraint. Bioresorbable polymers have potential use as scaffolds for tissue engineering, drug delivery systems, and bioactive scaffolds for tissue regeneration. These break down and are eliminated into the urine since they are biodegradable in the physiological media and participate in the metabolic process. Polyglycolic acid (PGA), polylactide (PLA), and polydioxanone (PDS) are widely utilized as suture materials or resorbable bone fixation devices. Tissue engineering structures made of novel bioactive polymers might replicate several characteristics of the extracellular matrix, including its degradation compatibility. PGA and its copolymers, poly(lactic-co-glycolic acid) (PLGA) and poly-ε-caprolactone (PCL), are examples of common bioactive polymers. Ester bond hydrolysis and bulk erosion are the breakdown mechanisms of these polymers. By adjusting the molecular weight, crystallinity, and copolymer ratio, the rate of degradation may be customized [15].

2.6.3. Composites

The composite can have its mechanical, chemical, biological, and physical characteristics altered to match the tissue's healing processes when it comes to biomaterials. Materials that have two or more different phases separated on a macro scale other than the atomic level are referred to be composites. Fabricating composite for a particular biomedical purpose might change the material's mechanical characteristics. Synthetic composites that are frequently encountered are reinforced plastics and fiberglass. Bone, dentin, cartilage, wood, and extracellular matrix found in connective tissue are examples of natural composites [16].

2.6.4. Ceramics

Tightly packed structures of atoms and ions, ceramics are solid inorganic compounds composed of different proportions via ionic or covalent bonding mechanisms. Open and complicated structures can be created if more needs are needed. These are polycrystalline inorganic non-metallic compounds, which comprise different refractory hydrides and sulfides as well as metallic oxides, silicates, and carbides. Bioceramics, such as bone, teeth, and other calcified tissues, are also found in the human body. Bioceramics, as opposed to other biomaterials, are ceramics that have a remarkable ability to replace or supplement a variety of calcified human body components, particularly bone. In general, ceramics offer materials that are naturally brittle and hard, having a higher Young's modulus than bone. These are extensively employed in biomedical applications, including dental implants, heart valves, and hip prostheses, due to their strong compressive strength, excellent inertness to physiological fluids, and attractive look. In biomedical applications, glasses and glass ceramics are utilized as alternatives to bone. As carbons are compatible with blood in heart valves, they have found applications as biomedical implants. Traditionally, ceramics are quite compressible and have poor tensile strength. Like polymers, the production method affects the mechanical and biological qualities. **Table 2** provides an overview of the use of biomaterials in ceramics.

Table 2. Applications of ceramics biomaterials

Materials used	Application	Materials used	Application
Alumina (Al_2O_3)	Orthopedic load-bearing applications	Trisodium phosphate, calcium and sodium phosphate salts	Temporary bone space fillers
HA, surface-active glasses, and glass ceramics	Coatings for chemical bonding (orthopedic, dental, and maxillary prosthetics)	HA, HA-PLA composites, trisodium phosphate, calcium and phosphate salts, surface-active glasses.	Periodontal pocket obliteration
Al_2O_3, HA, surface-active glasses	Dental implants	Al_2O_3, HA, HA-PLA composites, surface active glasses	Maxillofacial reconstruction
Al_2O_3, HA, HA –autogenous bone composite, HA-PLA composite, surface active glasses	Alveolar ridge augmentations	Bioactive glasses ceramics	Percutaneous access devices
Al_2O_3, HA, surface-active glasses, and glass ceramics	Otolaryngologic applications	PLA-carbon fibers, PLA-calcium/ phosphorus, base glass fibers	Orthopedic fixation devices
PLA-carbon fiber composites	Artificial tendons and ligaments		
Alumina Al_2O_3	Coatings for tissue ingrowth (cardiovascular, orthopedic, dental and Maxillofacial prosthetics)	Zirconia	Femoral heads

The general criteria for the selection of medical applications of ceramics are as follows. When selecting ceramics for medical applications, several criteria need to be considered to ensure their suitability for use in biomedical devices, implants, or other medical purposes.

(1) Biocompatibility: Ceramics must be biocompatible, meaning they should not elicit adverse reactions or toxic responses when in contact with living tissues. They should not cause inflammation, immune responses, or tissue rejection.

(2) Bioactivity: Bioactive ceramics have the ability to form a chemical bond with the surrounding bone tissue, promoting osseointegration and facilitating bone ingrowth. This property is crucial for orthopedic implants and bone substitutes.

(3) Mechanical properties: Ceramics used in medical applications should possess appropriate mechanical properties, including strength, toughness, and elasticity, to withstand physiological loads and stresses. The mechanical properties should match those of the host tissue to prevent implant failure or fracture.

(4) Chemical stability: Ceramics should exhibit chemical stability in the physiological environment, resisting degradation or corrosion over time. This ensures long-term functionality and biocompatibility of the implant or device.

(5) Surface characteristics: The surface of ceramics can influence biological interactions, such as cell adhesion, proliferation, and differentiation. Surface modifications may be necessary to enhance cellular responses and improve the integration of the implant with surrounding tissues.

(6) Wear resistance: For load-bearing applications, ceramics should have high wear resistance to withstand frictional forces and minimize material loss over time. This is particularly important for joint replacements and orthopedic implants.

(7) Radiopacity: Ceramics used in medical imaging or diagnostic applications should have sufficient radiopacity to be visualized on X-rays, CT scans, or other imaging modalities. This enables accurate placement and monitoring of the implant or device.

(8) Manufacturability: Ceramics should be capable of being fabricated into desired shapes and sizes using appropriate manufacturing techniques, such as sintering, machining, or additive manufacturing. The manufacturing process should ensure reproducibility and quality control of the final product.

(9) Cost-effectiveness: The cost of ceramic materials and fabrication processes should be reasonable and justifiable relative to the intended medical application and the benefits provided. Cost-effectiveness considerations are important for the widespread adoption and accessibility of ceramic-based medical devices.

(10) Regulatory compliance: Ceramics used in medical applications must meet regulatory requirements and standards for safety, efficacy, and quality control. Compliance with regulations such as ISO 13485 and FDA regulations in the United States is essential for market approval and commercialization.

By considering these criteria, researchers and manufacturers can select ceramics that meet the specific requirements of medical applications while ensuring safety, efficacy, and patient well-being.

According to El-Meliegy and van Noort [17], the best ceramic materials for biomedical applications should meet the following specifications.

(1) Biocompatibility is the ability of ceramic biomaterials to integrate and react with tissues, as well as how these materials respond to tissues and the physiological environment. It is the most crucial factor to take into account when using bioceramics for tissue engineering and biomedical applications. Coating inert ceramic materials with biocompatible compounds improves their biocompatibility.

(2) All ceramics and glasses that are intended for use in dentistry and biomedicine should have their radioactivity assessed. According to ISO 13356, the materials' radioactivity content should not be more than 1.0 Bq/g of uranium-238.

(3) When using dental biomaterials to replace tooth structure, aesthetics is the primary factor to be taken into account. Ceramics ought to offer a long-lasting and suitable fix for teeth cosmetic restoration. The three visual characteristics of color, translucency, and surface texture are used to assess the aesthetics of dental ceramics. The amount of crystalline material in the ceramics allows for the customization of these qualities.

(4) The determining factor for the caliber of dental applications is the ceramics' refractive index. This has an impact on the ceramics' translucency for dental applications. Better opacity results in a smaller layer of practically used opaque glass ceramic and better concealing power, making more room for the

more transparent aesthetic ceramic layers. By modifying the two-phase content and particle size of the material, the opacity of the ceramics may be regulated. In a similar vein, the refractive index of the ceramics can change their transparency.

(5) When the ceramics reach the biodegradable or acceptable stage, their chemical solubility should be minimal and their solubility in biological fluids should be regulated. According to ISO standard, if the materials are not degradable, their solubility should be low, less than < 100 m g/cm^2 after 16 hours of soaking in 4% boiling acetic acid. **Figure 1** illustrates the ceramics' solubility order. The dissolution rates of monophasic CaP diminish in the following sequence at physiological pH: OHA > CDHA > HA > TTCP > α-TCP > β-TCP [18].

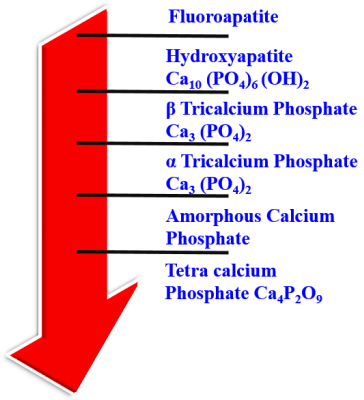

Figure 1. Order of solubility of CaP-based ceramics

(6) Two main aspects influence the mechanical characteristics of ceramics: the magnitude of intrinsic flaws and fracture toughness. To avoid bone loss, osteopenia, or "stress shielding" with the use of bone grafts, the ceramic biomaterial's elastic modulus, tensile strength, fracture toughness, fatigue, and elongation percentage must be as close to the hard tissue as possible, such as bone and other calcified tissue. These characteristics are occasionally linked to ceramic biodegradation. **Figure 2** verifies that porous bioactive ceramics are less potent than cancellous bone and that the bioactive ceramics area is similar to cortical bone's characteristics.

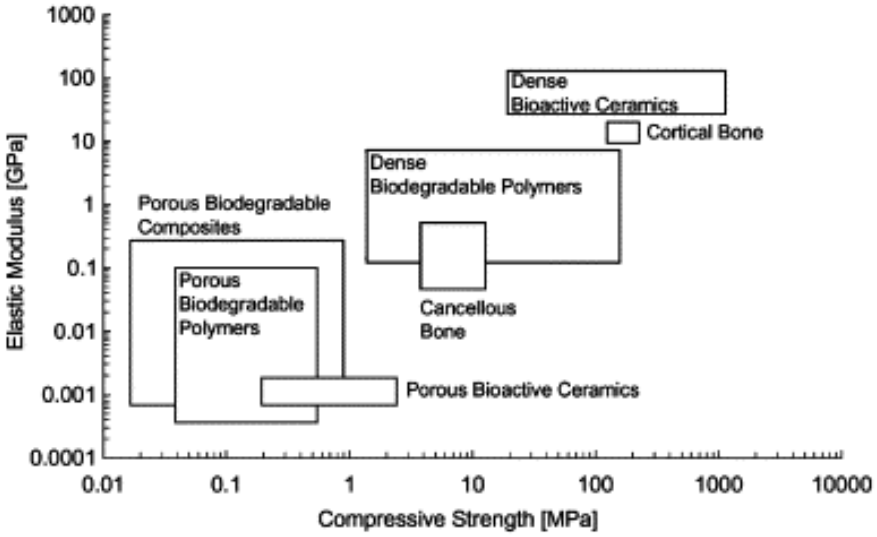

Figure 2. Elastic modulus vs. compressive strength of biodegradable polymers, bioactive ceramics, and composites scaffolds with high porosity (> 75%) and mostly interconnected pore structure [15]

(7) To induce cell fate processes that result in the formation of newly regenerated tissue, the ceramic scaffold's pores and porosity should be optimized. It should also offer a favorable microenvironment for cell proliferation and differentiation, achieving a high mass transfer rate of nutrients, oxygen, and waste metabolic products within the material's structure. For improved cell attachment and proliferation, the ceramic scaffold should also have a wide surface area [19].

(8) Another crucial characteristic in the design of bioceramics is the ceramics' microhardness, which is dependent on the material's surface. The ceramic materials should be easily machined, with little technical difficulty in designing scaffolds with the appropriate dimensions for a given application. The ceramics' other qualities and composition have an impact on this one as well.

(9) The design and production of medical devices, including annealing, covering substrates with glass or glass ceramics, material nucleation, crystallization, etc., depend on the thermal characteristics of the ceramics.

(10) Outstanding osteoconductivity, osteoinductivity, osteogenicity, and osteointegrity are desirable qualities for a bone scaffold composed of ceramic elements.

(11) Another need for ceramic materials is that they should be able to retain their stability throughout storage and function as a medication carrier.

Owing to ceramics' special qualities as biomaterials, treating hard tissue and other calcified tissues using ceramic biomaterials has a significant positive impact on human life and increases lifespan. The many forms of bioceramics, their overview in biomedical and tissue engineering applications, their biological reaction, the benefits of nanofibers and nanoceramics, and some of their processing techniques are all covered in this review paper.

3. Involvement of nanotechnology in the biofabrication of scaffolds for tissue repair

Biofabrication is a cutting-edge technology that combines biology, engineering, and manufacturing to create functional tissues and organs for regenerative medicine applications. One of the key components in biofabrication is the use of scaffolds, which provide structural support for cells to grow and differentiate into the desired tissue types. Nanotechnology has revolutionized the field of tissue engineering by enabling the fabrication of scaffolds with precise control over their physical and chemical properties at the nanoscale. Nanotechnology allows for the design of scaffolds with biomimetic features that mimic the native extracellular matrix, promoting cell adhesion, proliferation, and differentiation. By incorporating nanomaterials such as nanoparticles, nanofibers, and nanotubes into scaffolds, researchers can enhance their mechanical strength, porosity, and bioactivity. Nanotechnology also enables the controlled release of bioactive molecules, growth factors, and drugs from the scaffolds, which can further stimulate tissue regeneration and repair. Overall, the integration of nanotechnology into biofabrication processes holds great promise for the development of advanced scaffolds for tissue engineering applications, with the potential to revolutionize regenerative medicine and personalized healthcare.

Biofabrication is a cutting-edge technology that combines principles of biology, engineering, and materials science to create scaffolds for tissue repair and regeneration. In the context of hard tissue repairs, such as bone or cartilage, biofabrication techniques can play a crucial role in developing scaffolds that mimic the natural extracellular matrix of the tissue, providing structural support and promoting cell growth and tissue formation. Nanotechnology, which deals with materials and structures on the nanometer scale, has revolutionized the field of biofabrication by enabling the precise control of scaffold properties at the molecular level. By incorporating nanoscale features into the design of scaffolds, researchers can enhance their mechanical strength, bioactivity, and biocompatibility, leading to improved outcomes in tissue repair and regeneration. Some of the key

applications of nanotechnology in biofabrication of scaffolds for hard tissue repair include:

(1) Nanofiber scaffolds: Electrospinning techniques can be used to create nanofibrous scaffolds with high surface area and porosity, which are ideal for promoting cell attachment, proliferation, and differentiation. Nanofibers can also be functionalized with bioactive molecules or growth factors to further enhance tissue regeneration.

(2) Nanoparticle-based composites: Nanoparticles can be incorporated into scaffold materials to improve their mechanical properties, bioactivity, and drug delivery capabilities. For example, nanoparticles of hydroxyapatite, a mineral found in natural bone, can be added to scaffold materials to enhance their osteoconductivity and promote bone formation.

(3) Surface modification: Nanotechnology can be used to modify the surface properties of scaffolds, such as roughness, hydrophobicity, and chemical composition, to better mimic the native tissue microenvironment and improve cell-scaffold interactions. Surface modifications with nanoscale features can also help control the release of bioactive molecules and growth factors from the scaffold.

Overall, the integration of nanotechnology into biofabrication processes holds great promise for the development of advanced scaffolds for hard tissue repair. By leveraging the unique properties of nanomaterials, researchers can create scaffolds that closely mimic the structure and function of natural tissues, leading to improved outcomes in regenerative medicine and tissue engineering.

Nanotechnology plays a significant role in the biofabrication of scaffolds for hard tissue repair, particularly in bone tissue engineering. Some key applications of nanotechnology in this field include the following:

(1) Improved mechanical properties: Nanotechnology enables the fabrication of scaffolds with enhanced mechanical properties that closely mimic those of natural bone tissue. By incorporating nanomaterials such as nanofibers, nanoparticles, or nanocomposites into scaffold structures, researchers can strengthen the scaffolds and improve their load-bearing capacity.

(2) Enhanced surface properties: Nanotechnology allows for precise control over the surface properties of scaffolds, such as roughness, porosity, and surface chemistry. Functionalizing scaffold surfaces with nanomaterials or biomolecules can promote cell adhesion, proliferation, and differentiation, leading to improved tissue integration and regeneration.

(3) Drug delivery systems: Nanotechnology-based drug delivery systems can be integrated into scaffolds to provide controlled release of bioactive molecules, growth factors, or drugs at the site of tissue repair. Nanoparticles or nanostructured coatings on scaffold surfaces can release therapeutic agents in a sustained manner, promoting tissue regeneration and reducing inflammation or infection.

(4) Biodegradable nanomaterials: Biodegradable nanomaterials, such as nanofibers or nanoparticles made from polymers or ceramics, can be incorporated into scaffolds to enhance their biocompatibility and degradation kinetics. These nanomaterials can gradually degrade over time, releasing degradation by-products that are non-toxic and easily metabolized by the body.

(5) Nanotopography and nanostructure: Nanotechnology enables the creation of scaffolds with specific nanoscale topographies and structures that mimic the extracellular matrix of natural tissues. Nanotopographic cues can influence cell behavior, including adhesion, migration, and differentiation, leading to improved tissue regeneration and organization.

(6) Bioactive nanoparticles: Nanoparticles loaded with bioactive molecules, growth factors, or signaling molecules can be incorporated into scaffolds to promote specific cellular responses, such as osteogenic differentiation or angiogenesis. These bioactive nanoparticles can enhance the biological functionality of scaffolds and accelerate tissue regeneration.

(7) Nanocomposites: Nanotechnology allows for the development of nanocomposite scaffolds by combining nanomaterials with traditional scaffold materials such as polymers, ceramics, or hydrogels. Nanocomposites can exhibit synergistic properties, including improved mechanical strength, enhanced bioactivity, and controlled release of therapeutic agents, making them ideal for hard tissue repair applications.

(8) 3D printing and nanoscale resolution: Advanced 3D printing techniques, such as stereolithography or direct ink writing, enable the precise deposition of nanomaterials to create scaffolds with complex geometries and nanoscale resolution. This level of precision allows for the fabrication of patient-specific scaffolds tailored to individual anatomies and tissue defects.

Overall, nanotechnology offers versatile tools and techniques for the biofabrication of scaffolds for hard tissue repair, enabling the development of advanced biomaterials with tailored properties and functionalities to promote tissue regeneration and restore function.

4. Conclusion

In conclusion, the development of novel biomaterials plays a crucial role in enhancing human life standards by replacing malfunctioning organs or regenerating tissues. The use of biomaterials for hard tissue repair, such as bioceramics, is essential in promoting tissue regeneration and providing structural support in clinical applications. The classification of biomaterials based on biocompatibility and source, including natural and synthetic materials, highlights the diverse uses and potential for biomaterials in regenerative medicine. New materials have been developed to reduce reliance on tissue and organ transplantation and promote tissue regeneration. These materials, including biomaterials, are used in regenerative medicine to replace, regenerate, and restore soft and hard tissues like skin, bones, cartilage, blood vessels, and organs. Biomaterials for hard tissue repair play a crucial role in regenerative medicine by providing structural support and promoting tissue regeneration in damaged or diseased tissues. Common biomaterials include calcium phosphate ceramics, collagen-based materials, synthetic polymers, bioglass, and composite materials. These materials mimic the properties of native tissue to enhance healing and integration. Researchers continue to explore new biomaterials and combinations to improve outcomes for patients in need of hard tissue repair. These biomaterials are essential for bone regeneration, graft substitutes, and implant applications. Biocompatibility is the basis for the first classification of biomaterials, which is the ability of a substance to be recognized by or accepted by the surrounding tissues and organs in the human body. Bioceramics, a class of biomaterials, have shown great promise for hard tissue repair, particularly in bone and dental applications. They are biocompatible, bioactive, and have similar mechanical properties to natural bone, making them ideal for repairing and regenerating damaged or diseased hard tissues. Bioceramics can be used in various forms, including powders, granules, scaffolds, and coatings, and can be tailored to have specific properties depending on the application.

Disclosure statement

The author declares no conflict of interest.

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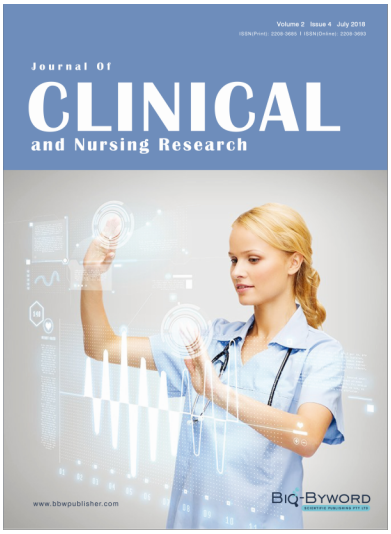

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