Research Article

# Heterotopic Ossification After Shoulder Arthroplasty: A Systematic Review

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## ABSTRACT

**Introduction:** Shoulder arthroplasty is increasing in incidence over time. One potential complication that is not well studied following shoulder arthroplasty is heterotopic ossification (HO), the abnormal growth of extraskeletal bone in soft tissue. HO has been described as a complication in total hip arthroplasty literature but less described in the setting of shoulder arthroplasty. The aim of this systematic review is to present available evidence regarding the incidence, risk factors, and potential management of HO after shoulder arthroplasty.

**Methods:** A systematic search was conducted in June 2023 using Pubmed, Embase, and Ovid Medline databases to retrieve all relevant studies evaluating the occurrence of HO after shoulder arthroplasty. The search was done in duplicate, and a quality assessment of all studies was included.

**Results:** A total of 170 studies were retrieved, of which 6 were included, involving 1,028 patients undergoing shoulder arthroplasty with 1,038 operated shoulders. HO developed postoperatively in 28% of the included shoulders and was symptomatic in 12% with most cases occurring in shoulders that developed osteoarthritis and cuff tear arthropathy. Men appear to have an increased risk of developing HO post shoulder arthroplasty. Fewer than 2% of HO shoulders went on to have revision surgery, and no notable differences were observed in the postoperative mean elevation and external rotation angles of non-HO and HO shoulders. In addition, no reported benefit of the use of nonsteroidal anti-inflammatory drugs was found against the formation of HO after shoulder arthroplasty.

**Conclusion:** HO occurs in 28% of shoulder arthroplasties in our review. Most of these were asymptomatic in the reviewed articles. Male patients and revision surgery with osteoarthritis and cuff tear arthroplasty seem to be at higher risk of developing HO post shoulder arthroplasty. Nonsteroidal anti-inflammatory drugs seem to not prevent the development of HO after shoulder arthroplasty; yet, future studies are needed to verify this claim.

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**Level of Evidence:** Level III; Systematic Review.



The number shoulder arthroplasties being performed are ever increasing with expanded indications.[1-4] The increasing incidence of shoulder arthroplasties also brings about an increasing incidence of revision surgeries and complications.[5-15] Heterotopic ossification (HO) is commonly found after shoulder arthroplasty; however, the clinical significance is unclear. HO is the abnormal growth of extraskeletal bone in soft tissue and is commonly seen after trauma, such as spinal cord injury, traumatic brain injury, burns, and fractures.[16] During the healing process, mesenchymal cells may improperly differentiate into osteogenic precursor cells, resulting in the formation of ectopic bone.[16] HO has been most extensively studied in hip arthroplasties and other procedures involving the hip joint.[17,18] Furthermore, HO has also been studied in total elbow and knee arthroplasties, particularly in patients with musculoskeletal trauma.[19] Although in most cases, HO appears as asymptomatic bone formation near the site of surgery and typically has little to no effect on functional outcomes, excessive HO formation may decrease joint range of motion to a degree and cause impingement, which could lead to instability.[20] Nonsteroidal anti-inflammatory drugs (NSAIDs) are thought to reduce the risk of HO after hip surgery; yet, the effectiveness in preventing HO after shoulder arthroplasty requires further examination.[21]

Although many studies have investigated HO after major hip surgery, limited evidence exists on the subject of HO after shoulder arthroplasty. As shoulder arthroplasties are becoming increasing more common, especially revision surgeries, it is important for surgeons to assess the incidence and major risk factors for the development of HO. The objective of this systematic review is to present available evidence regarding the incidence, risk factors, and potential management of HO after shoulder arthroplasty.

## Methods

This review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting of systematic reviews.

### Search Strategy and Eligibility

Before beginning the literature search, a search protocol was created and published online at the PROSPERO International prospective register of systematic reviews (registration number: CRD42023434210). The authors collaborated on a search strategy, and a systematic review was conducted in June 2023 to identify all peer-reviewed clinical literature by searching Pubmed, Embase, and Ovid Medline databases using the keywords "shoulder arthroplasty" and "HO." The inclusion criteria were (1) studies evaluating incidence, risk factors, and clinical significance of HO after shoulder arthroplasty, (2) studies published in English, and (3) studies on humans. We excluded (1) nonsurgical studies, (2) studies that were not relevant and did not contain sufficient HO data, (3) review articles, (4) case reports, and (5) preclinical studies. If a follow-up study of the same patient population was identified, the more recent study was included. If revision shoulder arthroplasties were included in studies evaluating HO, it was also included in the data analysis.

### Study Selection

Two reviewers (F.N. and C.H.) independently reviewed the titles and abstracts of the studies identified through the literature search. Relevant articles were retrieved and rescreened for eligibility based on the full-text article. Full-text article evaluation was done independently by two reviewers who selected relevant studies based on predetermined selection criteria. Disagreements were resolved either by consensus or through discussion with a third reviewer (T.E.). In addition, relevant reference lists of included studies were analyzed to add articles that had not yet been reviewed.

### Data Collection

Data were collected independently by two reviewers (F.N. and C.H.). Disagreements were resolved either by consensus or through discussion with a third reviewer. Included references were extracted by two separate reviewers from each search base at which point all duplicate search results were removed. Information collected included study characteristics (eg, sample size, incidence rates, and revision surgeries), demographic information (eg, age, follow-up time, and percentage of male vs. female patients), surgical technique, outcomes after shoulder arthroplasty, and complications. In addition, the number of HO patients, grading or classification of HO, symptoms (eg, pain, inflammation, and ankylosis), and prophylactic measures to prevent HO.

### Quality Assessment of Included Studies

The quality of the studies was assessed by two reviewers (F.N. and C.H.) using the Methodological Index for Non-

Randomized Studies (MINORS) appraisal tool for observational studies and the Cochrane risk-of-bias tool for randomized controlled trials. A score of 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) was assigned to each of the 12 criteria on the MINORS checklist, resulting in a maximum score of 16 for noncomparative studies and 24 for comparative studies.[22] For noncomparative studies, MINORS scores were categorized as follows: zero to 6 was considered very low quality of evidence; 7 to 9, low quality of evidence; 10 to 14, fair quality of evidence; and 15 or greater, good quality of evidence.[22] For comparative studies, 14 was considered poor, 15 to 22 moderate, and 23 or greater high quality.[22]

If applicable, randomized controlled trials were appraised using the Cochrane risk-of-bias tool, and a rating of low risk, high risk, or unclear risk of bias was assigned with respect to potential selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[23] Full-text peer-reviewed articles of all included studies were obtained and graded according to the "levels of evidence" according to journal guidelines. All authors reviewed each article and assigned a level of evidence independently. If there was disagreement on the level assigned to an article, this was discussed with a third reviewer and resolved.

### Statistical Analysis

Descriptive statistics (eg, mean, standard deviation, and range) were calculated and presented where applicable using SPSS version 23 (SPSS). "*P* values" between means were calculated to assess for significance using an unpaired *t*-test with Welch correction if possible. A κ statistic indicating interreviewer agreement was calculated for all screening stages. The calculated κ was categorized as follows: 0.81 to 0.99 indicated excellent agreement; 0.61 to 0.80, substantial agreement; 0.41 to 0.60, moderate agreement; 0.21 to 0.40, fair agreement; and 0.20 or less, slight agreement.[24]

## Results

### Eligibility

The literature search identified a total of 170 studies, yielding 100 studies for title and abstract screening after removal of duplicates. Of these studies, 56 were excluded, and 44 reports were assessed for eligibility. Thirty-eight reports were excluded due to being identified as a case report or review article and insufficient HO data. In total, six studies were included in this review (Figure 1). Moderate agreement was found between reviewers in identification, screening, and included stages (κ = 0.533).

### Study Characteristics

A total of 1,028 patients (1,038 shoulders) underwent shoulder arthroplasty (total, reverse, and hemiarthroplasty) in the included studies. The mean sample size was 173 shoulders (SD, 166 shoulders; range, 58 to 500 shoulders). HO developed postoperatively in 287 shoulders (28% of the included shoulders). In total, only 35 HO shoulders (12%) were symptomatic, and five revision surgeries were conducted in HO shoulders (2%). A HO patient was classified as symptomatic if the study authors reported symptoms (Table 1).[25–30]

### Demographics

The mean age of the patients was 66 years (SD, 4 years; range, 61 to 71 years), and the mean follow-up time was 33 months (SD, 12 months, range 24 to 56 months). Male patients comprised 43% (SD, 14%; range, 27% to 57%) of the included shoulders, whereas female patients made up 57% (SD, 14%; range, 40% to 73%). Five out of the six studies (n = 980 shoulders) categorized the number of shoulders that developed HO by sex. A total of 273 shoulders (28%) developed HO in these studies (SD, 20%; range 15% to 62%); 139 of 410 male shoulders (34%) developed HO (SD, 25%; range 25% to 74%), and 134 of 570 female shoulders (24%) developed HO (SD, 19%; range, 9% to 56%). The lone study included a sample of 58 shoulders where 14 shoulders (24%) developed HO; yet, it did not separate male and female HO shoulders. When including all shoulders (1,038) in the six studies, 287 shoulders (28%) developed HO (SD, 18%; range 15% to 62%; Table 2).

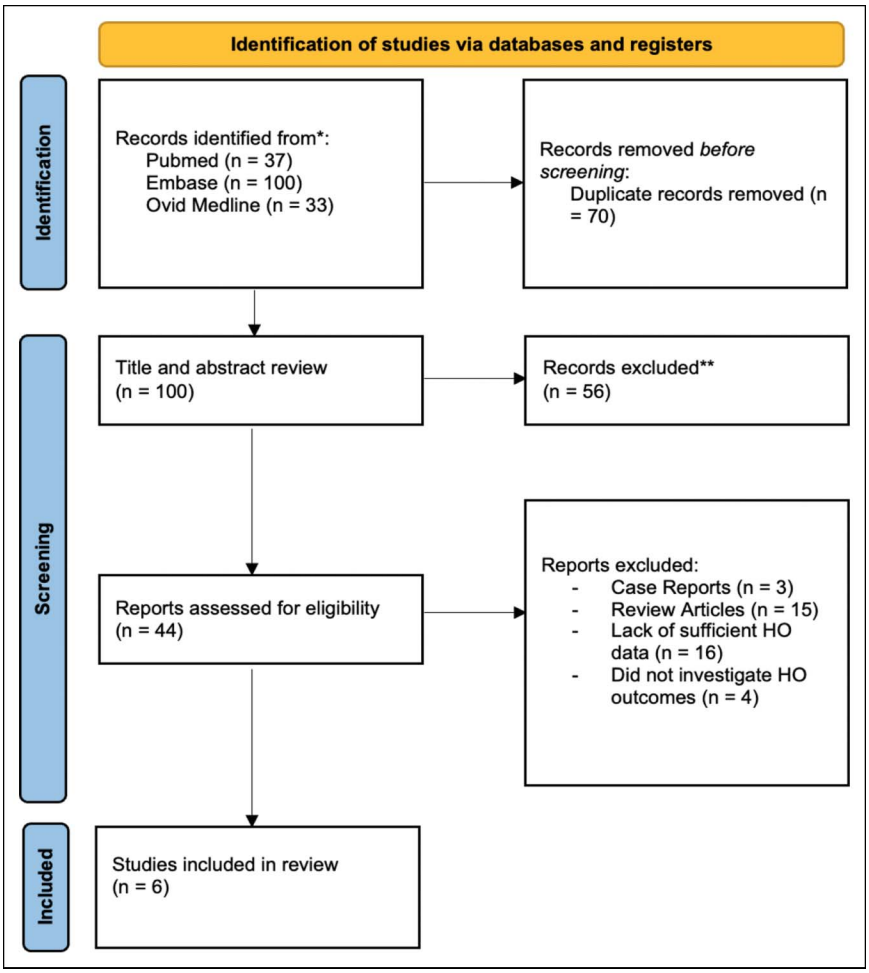
### Study Quality

All six included studies were retrospective case series studies that evaluated HO outcomes after shoulder arthroplasty. These studies were noncomparative in design, and their quality was assessed using the MINORS score. Most of the studies had clearly stated aims, prospective collection of data, and end points and follow-up periods appropriate to the study aim. However, almost all studies failed to perform an unbiased assessment of the study end points, as well as prospectively calculate the study size. The included articles are characterized by the mean MINORS score, level of evidence, and study quality.

### Classifications

HO classification was reported in five of the six studies (n = 896 patients and 906 shoulders). Three studies used

## Figure 1




Flowchart showingincluded studies. HO = heterotopic ossification



the Kjaersgard-Andersen grading scale, which is classified as follows: grade I, ossifications occupying less than 50% of the space; grade II, ossifications occupying more than 50% of the space but no roentgenographic bridge; and grade III, ossifications roentgenographically bridging the space.[26] The other two studies used custom grading methods. Ko et al[27] used a newly graded proposed grading system, which measures the size of any

## Table 1. Study Characteristics

| Author | No. of Patients | No. of Operated Shoulders | No. of Shoulders that Developed HO (%) | No. of Symptomatic HO Shoulders (%) | No. of Revision Surgeries (%) |
|---|---|---|---|---|---|
| Boehm et al[25] | 121 | 126 | 19 (15.0) | — | 5 (26.3) |
| Kjaersgaard-Andersen et al[26] | 53 | 58 | 26 (45.0) | 13 (50.0) | — |
| Ko et al[27] | 164 | 164 | 101 (61.6) | — | — |
| Olsen et al[28] | 500 | 500 | 88 (17.6) | 9 (11.5) | — |
| Sperling et al[29] | 58 | 58 | 14 (24.0) | — | — |
| Verhofste et al[30] | 132 | 132 | 39 (29.5) | 13 (33.3) | — |
| Overall | 1,028 | 1,038 | 287 (27.6) | 35 (12.2) | 5 (1.7) |

HO = heterotopic ossification

**Table 2.** Patient Demographics

| Author | Mean Age (Yrs) | Mean Follow-up Time (Mo) | No. of Male Shoulders (%) | No. of Female Shoulders (%) | No. of Male HO Shoulders (%) | No. of Female HO Shoulders (%) |
|---|---|---|---|---|---|---|
| Boehm et al[25] | 62 | 26 | 41 (32.5) | 85 (67.5) | 6 (14.6) | 13 (15.3) |
| Kjaersgaard-Andersen et al[26] | 61 | 26 | 17 (29.3) | 41 (70.7) | 11 (64.7) | 15 (36.6) |
| Ko et al[27] | 71 | 24 | 50 (30.5) | 114 (69.5) | 37 (74) | 64 (56.1) |
| Olsen et al[28] | 70 | 30 | 266 (53.2) | 234 (46.8) | 68 (25.4) | 20 (8.5) |
| Sperling et al[29] | 63 | 56 | 35 (60.3) | 23 (39.7) | — | — |
| Verhofste et al[30] | 69 | 36 | 36 (27.3) | 96 (72.7) | 17 (47.2) | 22 (22.9) |
| Overall | 66 | 33 | 445 (43.1) | 593 (57.1) | 139 (33.7) | 134 (23.5) |

HO = heterotopic ossification

HO within the region of the long head of the triceps. A type I (small) HO is any osteophyte whose distal extent is proximal to a line parallel to the lateral border of the scapula and intersecting with the medial edge of the humeral tray. A type II (large) HO is any osteophyte whose distal extent is below this line.[27] Finally, the study conducted by Verhofste et al[30] used a modified grading version of the Brooker classification system of HO in the hip. The classification system was defined as follows: grade Ia, grade; type Ib, spur; grade Ic, incomplete ankylosis; and grade II, combination of all mentioned characteristics.[30]

In total, 64% of the HO shoulders were classified by Kjaersgard-Andersen grade I; 25% grade II; and 10% grade III. In the study by Ko et al, 32% of patients developed type I HO, whereas 30% developed type II HO. The remaining percentage had findings of only osteophytes. In the study by Verhofste et al, 28% of HO shoulders were classified as grade Ia; 21% grade Ib; 15% grade Ic; 36% grade II (Table 3).

## Indications

All six studies were searched for data regarding the indication or primary diagnosis for shoulder arthroplasty treatment. Data were included if the study reported the number of operated shoulders with respect to the primary diagnosis and the resulting number of shoulders that developed HO. Five of the six studies reported the primary diagnosis for patients who underwent total shoulder arthroplasty (n = 896 patients and 906 shoulders). In summary, HO developed after shoulder arthroplasty in 73 of 339 shoulders with osteoarthritis (22%), 59 of 398 shoulders with cuff tear arthropathy (15%), six of 51 shoulders with rheumatoid arthritis (12%), one of 15 shoulders with osteonecrosis (7%), and 0 of 13 shoulders with posttraumatic arthritis (0%; Table 4).

## Surgical Technique

All six studies reported the type of shoulder arthroplasty procedure (total, reverse, and hemiarthroplasty) that was studied and categorized the number of patients who underwent the respective procedure and developed HO (n = 1,028 patients and 1,038 shoulders). Revision shoulder arthroplasties were analyzed in one study, and data are included for completeness. In summary, HO developed in 28 of 41 shoulders after revision shoulder arthroplasty (68%), 137 of 505 shoulders after reverse total shoulder arthroplasty (27%), 113 of 434 shoulders after total

**Table 3.** Classification of Heterotopic Ossification

| | |
|---|---|
| Kjaersgard-Andersen Classification | |
| Boehm et al[25] | 13 grade I, 6 grade II, and 0 grade III |
| Kjaersgard-Andersen et al[26] | 13 grade I, 7 grade II, and 6 grade III |
| Sperling et al[29] | 44 grade I, 12 grade II, and 2 grade III |
| Custom classifications | — |
| Ko et al[27] | 52 type I and 49 type II |
| Verhofste et al[30] | 11 grade Ia, 8 grade Ib, 6 grade Ic, and 14 grade II |

**Table 4.** Summary of Heterotopic Ossification by Indication for Shoulder Arthroplasty

| Primary Diagnosis | No. of Operated Shoulders | No. of HO Shoulders (%) |
|---|---|---|
| Osteoarthritis | 339 | 73 (21.5) |
| Rheumatoid arthritis | 51 | 6 (11.8) |
| Posttraumatic arthritis | 13 | 0 (0.0) |
| Cuff tear arthropathy | 398 | 59 (14.8) |
| Osteonecrosis | 15 | 1 (6.7) |
| Fracture/dislocation | 48 | 7 (1.8) |

HO = heterotopic ossification



shoulder arthroplasty (26%), and nine of 58 shoulders after hemiarthroplasty (16%; Table 5).

## Range of Motion

Four of the six studies reported the mean elevation and external rotation in non-HO and HO shoulders after shoulder arthroplasty (n = 780 shoulders). Sperling et al[29] did not record forward elevation in patients, but the data are included for completeness of external rotation scores. If applicable, values were averaged between HO grades to get the final mean angles for HO shoulders. In summary, non-HO and HO shoulders had a mean elevation of 124° and 113°, respectively, and mean external rotation of 34° and 36°, respectively. No notable differences were found in the mean elevation and external rotation angles of non-HO and HO shoulders ($P$ = 0.7680 and 0.8545, respectively; Table 6).

## Biological Sex

Three of the five studies that separated HO outcomes in male and female shoulders (n = 354 shoulders) reported that a markedly greater proportion of men developed HO after shoulder arthroplasty. In this selected sample, HO developed in 65 of 103 male shoulders (63%) compared with 101 of 251 female shoulders (40%). However, when including all five studies (n = 980 shoulders), HO developed in 139 of 410 male shoulders (34%), with a mean incidence of 45% compared with 134 of 570 female shoulders (24%) with a mean incidence of 28% (Table 2).

## Symptoms

Several symptoms were reported in the included studies, including pain and ankylosis. Overall, 35 of 287 HO shoulders (12%) developed symptoms (Table 1). No studies classified the symptoms by demographics or preoperative risk factors, such as age, biological sex, primary diagnosis, and the like. It was difficult to assess the specific etiologies of the symptoms, and it was not clear that HO was directly related to the symptoms.

## Prophylactic Measures

Two of the included studies investigated prophylactic measures, specifically the preventive effect of NSAIDs on the formation of HO post shoulder arthroplasty (n = 93 patients). Both studies administered NSAIDs, such as naproxen or indomethacin, for the first few weeks after surgery. Given that there was limited quantitative data in the studies, HO incidence rates could not be compared, and only a brief discussion on preventive effects of NSAIDs is included. Both studies reported no benefit of the use of NSAIDs against the formation of HO after shoulder arthroplasty because no notable difference was found in the incidence of HO formation in cases with and without NSAID treatment.

**Table 5.** Summary of Heterotopic Ossification by Type of Shoulder Arthroplasty

| Surgical Technique | No. of Operated Shoulders | No. of HO Shoulders (%) |
|---|---|---|
| Total shoulder arthroplasty | 434 | 113 (26.0) |
| Reverse total shoulder arthroplasty | 505 | 137 (27.1) |
| Hemiarthroplasty | 58 | 9 (15.5) |
| Revision shoulder arthroplasty | 41 | 28 (68.3) |

HO = heterotopic ossification

**Table 6.** Range of Postoperative Motion in Nonheterotopic Ossification and Heterotopic Ossification Shoulders

| Author | Mean Elevation in Non-HO Shoulders (°) | Mean Elevation in HO Shoulders (°) | Mean External Rotation in Non-HO Shoulders (°) | Mean External Rotation HO Shoulders (°) |
|---|---|---|---|---|
| Kjaersgaard-Andersen et al[26] | 78 | 67.7 | 14.7 | 18 |
| Ko et al[27] | 133 | 121 | 19 | 25 |
| Olsen et al[28] | 160 | 150 | 45 | 45 |
| Sperling et al[29] | — | — | 56 | 57 |
| Overall | 123.7 | 112.9 | 33.7 | 36.3 |

HO = heterotopic ossification

## Discussion

Although there have been numerous studies that have evaluated HO after hip, elbow, and knee arthroplasties, these outcomes have not been well studied following shoulder arthroplasty. In this systematic review, the incidence of HO after shoulder arthroplasties was estimated to be approximately 28% after averaging data from six studies that included 1,028 patients undergoing shoulder arthroplasties along with 1,038 operated shoulders. This rate is lower than the incidence of HO after total hip arthroplasty (47%) but higher than the incidence of HO after total elbow arthroplasty (10%).[17,19] However, substantial variance was observed in the incidence of HO among the included studies, ranging from 15% to 62%. This lack of consistency can be attributed to different surgical techniques, indications, follow-up times, predisposing factors, and definitions of HO to meet criteria along with predisposing factors in patients.

Of the 287 shoulders that developed HO, 12% were reported to be symptomatic, and only approximately 2% received revision surgery. This finding is important because it indicates that HO is an uncommon complication of shoulder arthroplasty with most patients being asymptomatic and not requiring revision surgery. Boehm et al[25] reported five revision in their review; however, none of these revision surgeries were for complications of HO. Instead, revision surgeries were performed due to rotator cuff disease developed in three patients and clavicle fractures in the other two patients. However, scant data were found in the included studies regarding surgical excision and resection of HO after shoulder arthroplasty; therefore, no inference can be drawn on surgical management. This review also garnered that no notable differences were found in the mean elevation and external rotation angles of non-HO and HO shoulders ($P$ = 0.7680 and 0.8545, respectively). Thus, HO shoulders do not seem to be limited in mobility and can function normally in basic tasks.

This review also investigated potential risk factors that can affect the incidence of HO post shoulder arthroplasty. Analysis of five studies (n = 980 shoulders) indicated that men may have a higher risk of developing HO. In this sample, HO developed in 34% of male shoulders compared with 24% of female shoulders. This finding is in agreement with total hip arthroplasty literature that have shown that men have a higher risk of developing HO than women.[31-33] With this increased incidence of HO in men, it can be recommended that physicians should consider HO risk especially in the revision arthroplasty setting.

Furthermore, this review also found that patients with osteoarthritis and cuff tear arthropathy seem to have the greatest relative risk of developing HO after shoulder arthroplasty with incidence rates of 22% and 15%, respectively (n = 894 shoulders). In evaluating the types of shoulder arthroplasties in the included studies (n = 1,038 shoulders), revision shoulder arthroplasty appears to be a notable risk for HO development with a mean incidence rate of 68% compared with reverse, total, and hemiarthroplasty (27%, 26%, and 16%, respectively). However, the revision shoulder arthroplasty sample size was drastically smaller (n = 41 shoulders) than the other types of shoulder arthroplasties in the included studies.

Limited data were available on prophylactic measures against HO after shoulder arthroplasty. In the sample size that was included (n = 93 patients), NSAIDs do not appear to have a protective effect on the development of HO post shoulder arthroplasty. This is because HO incidence rates were similar in patients who took NSAIDs and those who did not. Although there is a lack of data, it can be deduced from this review that NSAIDs

should not be considered a viable option for minimizing risk of HO post shoulder arthroplasty until further evidence is presented. Conversely, physician recommendation for NSAIDs treatment can be still considered to reduce other HO or postoperative symptoms, such as pain and inflammation.

This review was subjected to a thorough methodology, which played a role in its strength. All screening, data extraction, and quality assessment were completed by two independent reviewers with moderate agreement at all stages ($\kappa$ = 0.520 to 0.533). In total, our review included 1,028 patients with 1,038 operated shoulders who underwent shoulder arthroplasty, which is a substantial sample size for the evaluation of HO incidence, risk factors, and potential management. Our strict inclusion criteria also aided the reliability of the study by limiting the number of studies that did not directly focus on HO patients and outcomes of interest. This made it possible to separate outcomes regarding the HO patients from patients who did not develop HO after shoulder arthroplasty. All studies were also retrospective in nature, which made data comparison more appropriate.

This study was limited by the fact that a lot of heterogeneity was observed between the studies, such as the sample size, surgical technique, indications, and follow-up time. In addition, variable methods were found to classify HO and specify symptoms such as pain and ankylosis. This could create confounding variables that could potentially skew HO results like the incidence rates and severity of symptoms. In addition, the reporting of specific HO outcomes was not consistent in each study, such as risk factors, clinical symptoms, and prophylactic measures. Despite these inconsistencies, we included all these studies in this review given the scant literature on HO evaluation after shoulder arthroplasty.

## Conclusion

HO commonly occurs following shoulder arthroplasty; however, it asymptomatic in most patients. The most notable risk factors in our review were men and revision surgeries. It was also found that HO was most common in operated shoulders with osteoarthritis and cuff tear arthropathy. The type of shoulder arthroplasty does not seem to make a notable difference in HO development, yet revision surgeries appeared to have a higher incidence rate in a limited sample size. This review also indicates that NSAIDs do not prevent the risk of HO development after shoulder arthroplasty; yet, future studies are needed to verify this claim.

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