Preoperative Patient Optimization Before Hip or Knee Arthroplasty: Part 2

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ABSTRACT
Hip and knee arthroplasty are effective procedures for treating degenerative joint diseases when conservative treatments have failed. The purpose of this article is to further analyze modifiable risk factors in patients prior to surgery, with the aim of reducing postoperative complications. These factors include obesity, malnutrition, smoking, diabetes, anemia, opioid use, vitamin D deficiency, chronic renal failure, colonization by methicillin-resistant Staphylococcus, and inflammatory arthropathies. By addressing and optimizing these factors, surgeons can significantly reduce the risk of complications.
Keywords: Optimization; hip and knee arthroplasty; risk factors.
Level of Evidence: IV

Optimización preoperatoria del paciente para una artroplastia de cadera o rodilla: parte 2

RESUMEN
Las artroplastias de cadera y rodilla son procedimientos eficaces para el tratamiento de la enfermedad articular degenerativa cuando el abordaje conservador ha fracasado. El propósito de este artículo es continuar analizando los factores de riesgo modificables en un paciente antes de la cirugía, con el objetivo de disminuir las complicaciones posquirúrgicas. Estos factores incluyen obesidad, malnutrición, tabaquismo, diabetes, anemia, consumo de opioides, deficiencia de vitamina D, insuficiencia renal crónica, colonización por *S. aureus* resistente a la meticilina y artropatías inflamatorias. Si los cirujanos conseguimos mejoras o contrarrestar estos factores podremos reducir el riesgo de complicaciones.
Palabras clave: Optimización; artroplastias de cadera y rodilla; factores de riesgo.
Nivel de Evidencia: IV

INTRODUCTION

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are effective surgeries for improving the quality of life in patients with degenerative joint disease. However, complications arising from these surgeries can be catastrophic.[1] Some studies[2-4] report that modifiable risk factors can increase the likelihood of such complications. These include obesity, malnutrition, smoking, diabetes, anemia, opioid use, vitamin D deficiency, chronic renal failure, methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, and inflammatory arthropathies.

In 2022, we published the first part of this update, which analyzed the first five risk factors mentioned above.[5]

The purpose of this second part is to address the remaining risk factors and potential countermeasures. It should be noted that these measures have varying levels of supporting evidence, with some still inconclusive, but each will be analyzed in detail.

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OPIOID USE

Opioids are powerful analgesic drugs used to relieve severe acute pain, such as pain associated with major trauma or surgery. Their use has been increasing, as have the negative consequences associated with them.

Overuse of this class of drugs has reached epidemic levels in the United States. According to the *Centers for Disease Control and Prevention*, nearly 218,000 people died from overdoses related to prescription opioids between 1999 and 2017.[6]

Multiple studies have shown more complex postoperative outcomes in individuals who use opioids prior to THA or TKA. For example, Rozell et al. examined 802 patients who underwent THA and TKA and observed that the more opioids a patient used before surgery, the more likely they were to require opioids postoperatively. This increased the likelihood of complications such as hypotension, decreased urine output, the need for supplemental oxygen, prolonged hospital stays, and a higher risk of systemic infections caused by multidrug-resistant pathogens. Additionally, these patients were 2.5 times more likely to continue using opioids for 3 months post-surgery.[7] Zywiel et al. evaluated 49 patients who regularly used opioids for pain control prior to TKA and compared them to a group of non-opioid users. They reported more cases of arthroscopic revision for unexplained pain (5 vs. 0), more referrals to pain management specialists (10 vs. 0), and longer hospital stays (4.3 vs. 3.4 days).[8] Goesling et al. also confirmed the greater likelihood of postoperative opioid use in patients who had used opioids preoperatively. [9]

Moreover, the *Second International Consensus on Musculoskeletal Infections* (ICM) identified a link between opioid use and an increased risk of periprosthetic joint infection. In vitro studies and animal models have shown that opioids exert immunosuppressive effects, modulating both the adaptive and innate immune systems.

The *American Association of Hip and Knee Surgeons* recommends restricting the use of opioids for the treatment of hip and knee osteoarthritis to exceptional cases. They explicitly state that opioids should not be the first-line treatment for acute or chronic symptoms of osteoarthritis and should only be considered when other therapies have failed and surgery is not an option.

Patients requiring opioids should also be informed about the associated risks, have their doses and prescription duration limited, and be referred to pain specialists if prolonged use is necessary.[10]

VITAMIN D DEFICIENCY

Vitamin D promotes proper bone metabolism by maintaining parathyroid hormone at physiologically appropriate levels, stimulating osteoblastic activity, and promoting bone mineralization. It also exerts multiple effects on muscle activity. The active form, $1,25(OH)_2D$, can be produced locally in muscle cells, where it modulates myocyte function by regulating gene transcription and promoting the synthesis of new proteins, thereby strengthening each muscle fiber. This mechanism is associated with a reduced risk of falls and, consequently, a decreased incidence of fractures.[11] Another important function of vitamin D is its activation of the innate immune system, which helps fight bacterial infections through the intracrine regulation of monocytes, the activation of macrophages, and the modulation of antimicrobial peptides and cytokine production. It also activates the adaptive immune response through paracrine regulation in dendritic cells, T-helper lymphocytes, and B cells. Therefore, vitamin D plays a significant role in preventing periprosthetic infections.

The primary metabolite of vitamin D, 25(OH)D, is measured to assess vitamin D status in patients, with classifications and values shown in Table 1.

Vitamin D toxicity typically does not occur until 25(OH)D levels exceed 150 ng/mL.[12] Vitamin D deficiency has been associated with poor outcomes after THA or TKA, such as periprosthetic infection and longer hospital stays.[13] In a study by Sigurdardottir et al. involving 738 patients undergoing THA and TKA, the risk of surgical site infection was 0.85 times higher in patients with vitamin D levels ≤50 mmol/L, and 16% of patients had insufficient preoperative vitamin D levels.[14] Brambilla et al. conducted a systematic review of eight articles that examined the association between prosthetic surgery, vitamin D, and postsurgical outcomes. The review included six prospective observational studies and two retrospective case series, all of which reported preoperative vitamin D deficiency in patients undergoing THA or TKA, with prevalence rates ranging from 7.5% to 62.9%. Hypovitaminosis D was associated with at least one negative short-term outcome in 62% of the studies.[15] Weintraub et al. evaluated the

administration of 50,000 IU of vitamin D to 107 patients on the day of TKA to assess function, postsurgical outcomes, and complications. However, the study did not demonstrate statistically significant differences compared to patients receiving a placebo.[16] Mouli et al. compared two vitamin D administration protocols in 174 patients with vitamin D deficiency (25(OH)D <30 ng/mL) prior to TKA. The first protocol involved daily supplementation with D3 on a sliding scale from 1,000 to 6,000 IU, while the second protocol included a loading dose of 50,000 IU weekly for 4 weeks, followed by 2,000 IU daily. Vitamin D deficiency was corrected in 73.3% of the loading dose group (second protocol) and in 42.4% of the low daily dose group (first protocol) (p<0.001).[17] Morrison et al. found an association between vitamin D supplementation and reduced levels of interleukin 6 and interleukin 10 on the first and second days post-surgery. However, their results were based solely on patients undergoing TKA, so they could not definitively determine whether vitamin D insufficiency was a modifiable factor that could improve outcomes in hip or knee prosthetic surgeries.[18]

Table 1. Classification according to vitamin D values

Ranking	Value
Normal	40-60 ng/ml
Enough	25(OH)D >30 ng/ml
Insufficient	25(OH)D 21-29 ng/ml
Deficient	25(OH)D <20 ng/ml

Although we do not yet have compelling evidence to establish precise guidelines for preoperative vitamin D management, the ICM suggests that vitamin D deficiency may increase the risk of surgical site infections and periprosthetic joint infections in patients undergoing orthopedic procedures by impairing vitamin D-mediated innate and adaptive immune responses. Supplementation prior to surgery may enhance immune system function and potentially reduce the incidence of periprosthetic joint infections.

CHRONIC KIDNEY DISEASE (CKD)

CKD is defined by the presence of renal damage or decreased renal function for a period of three or more months, regardless of the underlying cause. Glomerular filtration rate (GFR), with a normal value of 125 ml/min/1.73 m², is the best indicator of renal function. Table 2 presents the classification of CKD based on GFR values.[19,20]

Table 2. Classification of chronic kidney disease according to glomerular filtration rate.

Grade	Value
Mild insufficiency	89-60 ml/min/1.73 m^2
Moderate insufficiency	59-30 ml/min/1.73 m^2
Severe insufficiency	29-15 ml/min/1.73 m^2
Dialysis	<15 ml/min/1.73 m^2

Between 10% and 20% of patients undergoing elective THA and TKA have moderate CKD.[21] In a Finnish study involving 18,575 patients undergoing THA and TKA, the mean survival time of each patient, based on CKD severity, was 11 years for mild cases, 9 years for moderate cases, and 6 years for severe cases (p = 0.001). The risk of death increased 1.9, 3.8, and 8.1 times, respectively, for each level of CKD severity.

CKD associated with diabetes demonstrated a synergistic effect on mortality risk compared to CKD alone (odds ratio [OR] = 8.15).[22] Fox et al. compared complications in patients undergoing arthroplasty with and without CKD and found a higher incidence of hematoma, wound infection, and cardiac, urinary, and pulmonary complications (Table 3).[23]

Table 3. Complications in arthroplasty according to the presence or absence of chronic kidney disease (CKD).

	Arthroplasty with CKD	Arthroplasty without CKD	p
Hematoma	2.5%	0.8%	<0.0001
Wound infection	0.7%	0.4%	<0.0319
Cardiac complications	1.3%	0.6%	<0.0067
Urinary complications	3.9%	2%	<0.0001
Pulmonary complications	2.2%	0.5%	<0.0001

Few studies specifically analyze the relationship between CKD and implant survival. Jämsä et al. evaluated 18,979 patients and found no significant differences in all-cause or septic revision rates across different CKD stages. These findings remained unchanged when diabetes and body mass index were accounted for. Lee et al. conducted a study using data from the Taiwanese national healthcare system, examining complications in THA and TKA. They observed that CKD patients had a higher incidence of periprosthetic infections at 1, 3, and 6 months, as well as at 1 year post-surgery. Additionally, these patients were more likely to experience aseptic loosening within 1 year of follow-up. [24,25]

The ICM indicates that patients with CKD have an increased risk of surgical site infection but require stratification to adequately assess their risk. Current evidence suggests that CKD patients requiring hemodialysis have worse outcomes than those who do not require hemodialysis or renal transplantation.

Given the reduced risks of surgical site and periprosthetic joint infections after surgery, patients on hemodialysis should be evaluated for renal transplantation prior to undergoing total arthroplasty.

COLONIZATION BY METHICILLIN-RESISTANT *S. AUREUS*

Staphylococcus aureus is a common microorganism responsible for joint prosthesis infections, and there is an established biological correlation between preoperative colonization and infection.[26] Sousa et al. detected an *S. aureus* colonization rate of 22.2%with only 0.8% being methicillin-resistant *S. aureus* (MRSA). The rate of joint prosthesis infections was higher, though not significantly, in *S. aureus* carriers compared to non-carriers (3.9% vs. 2.0%).[27] Ashkenazi et al. retrospectively analyzed 711 patients undergoing total arthroplasties and found that patients with MRSA had longer hospital stays (p = 0.008), lower odds of discharge (p = 0.003), and higher levels of readmission at 30 days (p = 0.030) and 90 days (p = 0.033) compared to patients with methicillin-sensitive *S. aureus* (MSSA). However, major and minor complications at 90 days were comparable between the groups. Rates of septic revisions were higher in MRSA patients (p = 0.049).[28]

At the Cleveland Clinic, Santana et al. found that patients with MRSA had an increased hospital stay of more than one day (odds ratio [OR] = 1.88), and patients with a high body mass index were at a greater risk of colonization (OR = 1.36), with statistically significant results for both cohorts of total hip arthroplasty (THA) and total

knee arthroplasty (TKA).[29] It is unclear whether the increased risk of infection is related to the immune status of the MRSA-carrying patient or to their comorbidities, such as diabetes, chronic kidney disease (CKD), or immunosuppression. However, the presence of an endogenous pathway for the onset of surgical site infection is recognized. Notably, MRSA infections can also occur in non-carrier patients, potentially related to the healthcare institution where the patient is hospitalized and the geographical epidemiological context.[30]

Several methods for detecting MRSA carriers have been described, including standard culture techniques, but their sensitivity is highly variable and depends on the number of samples taken and the sampling methods employed. Detection from various body sites increases sensitivity in identifying carriers, and the use of nasal swabs as a substitute for colonization testing can identify two-thirds of MRSA carriers. Polymerase chain reaction techniques provide faster results but are more expensive, and their advantages over traditional cultures are inconsistent.[30] The most frequent site of colonization is the nostrils. Nasal decolonization has been shown to reduce the MRSA/MSSA bioburden, which could decrease the rate of periprosthetic infection; however, the evidence is limited to studies with low external validity.

Several options are available for decolonization, such as:

- Mupirocin ointment: This bactericidal agent has a prolonged action and is applied in the nostrils twice a day for 5 days before surgery. Its advantages include low cost and high efficacy, with a decolonization rate of 94% after one week. However, in 3.3% of cases, it can lead to residual antimicrobial resistance, and this rate increases ninefold with previous use. Another disadvantage is the requirement for application twice a day for five days, which may reduce compliance with therapy; nevertheless, it remains the most commonly used nasal decolonization strategy for MRSA/MSSA.[31,32]
- Povidone iodine: Applied to the nostrils in a 5% solution 1 hour before surgery, this agent aims to improve patient compliance and reduce bacterial resistance. Unlike mupirocin, povidone iodine provides bacterial suppression for up to 12 hours after application. Although it has been studied less than mupirocin, some studies have demonstrated that it achieves similar results in reducing acute infections.[33]
- Alcohol- and chlorhexidine-based solutions: Recently introduced, these agents aim to enhance patient compliance, combat the emergence of bacterial resistance, and can be administered in a single dose.[34]

Despite these findings, larger and better-designed studies are necessary to demonstrate that routine screening and decolonization are cost-effective and feasible.

In light of this information, the ICM has been unable to make a definitive recommendation regarding the routine implementation of preoperative protocols for the detection and decolonization of *S. aureus*, as the literature on this subject is contradictory. Furthermore, the ICM has not made a conclusive recommendation on individual versus universal treatment, although the universal treatment strategy appears to be the easiest to implement; consequently, the application of this prophylaxis remains somewhat empirical.

INFLAMMATORY ARTHROPATHIES

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are widely used procedures for patients with advanced-stage symptomatic arthritis. Inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and spondyloarthritis—including ankylosing spondylitis and psoriatic arthritis—expose patients to an increased risk of adverse events after surgery, including deep vein thrombosis, pulmonary thromboembolism, acute myocardial infarction, stroke, and infections. [35,36]

In addition to the inflammatory arthropathy itself, many patients are also treated with biologics, which further complicates their surgical risk profile. According to Galloway et al., the use of these agents increases the risk of infections, with the highest risk occurring at the onset of treatment, subsequently decreasing to levels comparable to those of patients with rheumatoid arthritis not treated with biologics.[37] In a Danish study, patients treated with biologics had a hazard ratio of 1.35 for infection and 4.82 for deep vein thrombosis compared to patients with rheumatoid arthritis receiving different treatment regimens. When compared to patients with rheumatoid arthritis who did not receive biologic therapy and patients without inflammatory diseases, no increased risk of acute myocardial infarction or postoperative stroke was observed.[36]

The risk of superficial or deep periprosthetic infection increases after surgery in individuals with inflammatory diseases. For example, patients with rheumatoid arthritis face a 50% higher risk of infection than those without this underlying condition. For this reason, preventing infection in these patients is a top priority.

Given these significant complications, in 2022, the *American College of Rheumatology*, together with the *American Association of Hip and Knee Surgeons*, updated the guidelines for the perioperative management of biologic agents in patients undergoing elective TKA and THA. It is essential for healthcare providers to be familiar with these management strategies. This update is summarized in Tables 4 and 5. Generally, the administration of biologic drugs should be interrupted one life cycle prior to surgery, depending on the specific drug, and can be resumed after uncomplicated wound healing, while non-biologic drugs can continue during the perioperative period.[38]

Table 4. Medications that can be administered in the perioperative period

Disease-modifying antirheumatic drugs	Dose interval	Time of surgery since last dose
Methotrexate	Weekly	At any time
Sulfasalazine	Once or twice/day	At any time
Hydroxychloroquine	Once or twice/day	At any time
Leflunomide	Daily	At any time
Doxycycline	Daily	At any time
Apremilast	Twice/day	At any time
Mycophenolate mofetil	Twice/day	At any time
Azathioprine	Once or twice/day	At any time
Cyclosporine	Twice/day	At any time
Tacrolimus	Twice/day	At any time
Rituximab	Intravenous, every 4-6 months	4-6 months
Belimumab	Weekly	At any time
Anifrolumab	Intravenous, every 4 weeks	4 weeks
Voclosporin	Twice/day	Ongoing

Table 5. Medications to be discontinued prior to surgery (only those available in Argentina)

Biological drugs	Dose interval	Recommended time of surgery since last dose of medication
Adalimumab (HUMIRA®)	Every 2 weeks	3 weeks
Etanercept (ENBREL®)	Every week	2 weeks

FINAL CONSIDERATIONS

In light of the aforementioned points, it is evident that there remains a lack of precise evidence regarding the management of some modifiable risk factors. We primarily rely on measures suggested by associations or consensus guidelines, which are often not supported by high-quality studies. Given the moderate or low level of evidence available, we believe it is the responsibility of each surgeon to stay informed and ensure the multidisciplinary management of each patient, involving the relevant specialties as appropriate for each case.

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