

# Incidence of chronic kidney disease in patients undergoing arthroplasty: A systematic review of the literature

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## Abstract

Patients undergoing arthroplasty are exposed to different interventions that can lead to renal dysfunction. There is abundant evidence of the incidence and factors associated with acute kidney injury (AKI); however, the incidence and the factors associated with chronic kidney disease (CKD) are not clear. The objective of this study is to determine the incidence and associated factors in arthroplasty patients. A systematic review of the literature was carried out following the recommendations of PRISMA and the Cochrane Collaboration (PROSPERO Protocol CRD42018075929). The search was carried out in Medline, Embase, Cochrane and LILACS. No language or date limits were set. Observational studies were included: cases and controls, and cohorts. The revision of titles and abstracts and the reading of the full texts was performed in a paired manner. The quality of the evidence was evaluated with the Newcastle-Ottawa tool. The initial search found 1279 titles and abstracts. We excluded 115 duplicates, and 1153 in the reading of titles and abstracts. Three articles met the inclusion criteria and were of acceptable quality. The incidence of severe CKD after hip or knee arthroplasty was 1.2% at 1 year up to 6.5% at 9 years. The evidence of the incidence and risk factors associated with CKD in patients undergoing arthroplasty is very scarce and het-

erogeneous. Further primary studies are required in order to have more valid and trustable results.

## Introduction

Acute kidney injury (AKI) is part of the spectrum of kidney disease, and is characterized by an abrupt decrease in kidney function. AKI is a common, reversible and potentially preventable entity that increases the risk of cardiovascular events, death and chronic kidney disease (CKD).<sup>1</sup> It may appear *de novo* or superimposed on CKD, it is associated with a longer hospital stay and admission to intensive care, and leads to costs for health systems.<sup>1</sup> AKI appears as a perioperative complication in up to 50% of surgical patients.<sup>2</sup> There is abundant evidence of the relationship between surgical interventions and the development of AKI, especially for cardiovascular, major gastrointestinal, trauma and orthopedic surgery.<sup>3-6</sup> Knee and hip arthroplasties are among the most frequent surgeries in the United States, and the indications are Osteoarthritis, rheumatoid arthritis and trauma fractures.<sup>7-9</sup> AKI as a consequence of joint replacement surgery has been widely characterized in several studies. Its incidence exceeds 5%, and is more frequent in patients with underlying CKD.<sup>10-12</sup>

CKD, on the other hand, is a public health problem worldwide, defined as a glomerular filtration rate (GFR) lower than 60 mL/min/1.73 m<sup>2</sup> of body surface area for more than 3 months. The main risk factors are advanced age, hypertension, diabetes mellitus (DM), obesity and obstructive uropathy.<sup>13,14</sup> For 2016, the prevalence was calculated at 13.4% for all stages, and at 10.6% for stages 3 to 5.<sup>15</sup>

Research on perioperative outcomes in arthroplasties usually focuses on AKI and its risk factors, but not on CKD, despite its morbidity, mortality and socioeconomic impact.<sup>14,16,17</sup> Given the aforementioned facts, this study aims to determine the incidence and risk factors for the development of CKD in patients who undergo joint replacement.

## Materials and Methods

### Type of study

A systematic review of the literature was performed in the electronic databases MEDLINE, EMBASE, the Cochrane Library and LILACS. The initial search strategy was performed on October 26,

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Contributions: KC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: KC, GB. Acquisition of data: MBG, JPV, RBG, OAM, CMC. Analysis and interpretation of data: GB, MBG, JPV, RBG. Drafting of the manuscript: OAM, CMC. Critical revision of the manuscript for important intellectual content: KC, GB. Statistical analysis: GB. Supervision: RBG.

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2017 with the MeSH terms (“Chronic kidney disease” AND “Arthroplasty”), and was updated on October 28, 2018, just before the final analysis. The detailed search strategy is presented in Appendix 1.

### PICO strategy and eligibility criteria

The population under study was defined as those patients older than 18 years, irrespective of sex or race, from any country in the world who had undergone joint replacement surgery and who did not have CKD prior to surgery. Regarding this population we searched sociodemographic risk factors, comorbidities, surgery-related and anesthesia-related factors leading to the development of CKD after arthroplasty.

Articles that met the following eligibility criteria were chosen: 1) randomized, prospective and retrospective observational controlled clinical trials and cross-sectional studies, without restriction as to the date of publication, language of publication or place of realization, 2) follow-up of at least 6 months after surgery, 3) studies whose outcome was the development of CKD, 4)

studies that used the KDIGO definition of CKD (abnormalities of renal structure or function, present for  $\geq 3$  months, with implications for health).<sup>14</sup> The research protocol of this systematic review was registered in PROSPERO with the identification number CDR42018075929, and is available at: [http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42018075929](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018075929)

### Study selection

Two independent reviewers carried out a two-step selection process that consisted of: 1) discarding the studies that did not meet the eligibility criteria through reading titles and abstracts, 2) for potentially eligible articles, full compliance with the criteria was evaluated through reading the full text. In addition, a secondary search was conducted using the references of each included article, according to the eligibility criteria, to include additional relevant studies. Disagreements between reviewers were resolved by consulting a third reviewer.

### Data extraction

An adapted data extraction form was used, which included, but not limited to, the following variables: name, objective and type of study, study population, risk factors for developing CKD (e.g. type of anaesthesia, sociodemographic factors), type of joint replacement, and definition of CKD. Before the final version of the form, a pilot test was carried out.

### Bias evaluation

To evaluate the quality and risk of bias of the included studies, the Newcastle-Ottawa Scale (NOS) was used for each study, because this is a reliable instrument.<sup>18,19</sup> For the evaluation of cohort studies, three parameters were taken into account: the selection of the cohort, comparability between exposed and unexposed, and the results obtained. A study was considered of high quality when it obtained 9 points. With values  $\leq 7$ , the study was considered to have a high risk of bias.

## Results

The MEDLINE search yielded a total of 1101 articles, EMBASE 167 articles, CENTRAL 9 articles and LILACS 2 articles, for a total of 1279 articles (Figure 1). Both hip and knee arthroplasties were taken into account. From the total search result, 115 articles were excluded because they were duplicates, for a total of 1164 articles; after the analysis of titles and abstracts, 1153 articles were excluded. After the second review

of the 11 selected articles, 5 articles were excluded in which the patients had CKD prior to surgery.<sup>20-24</sup> One case report was excluded, one that did not meet the definition of CKD,<sup>25</sup> and another because it was a narrative review.<sup>26</sup> Finally, only 3 articles met the eligibility criteria and were included in this review.

### Study characteristics

The retrospective study by Chandran and Giori included patients from the *Veterans Affairs Medical Center* database. The study covered the period between October 1999 and September 2000, on 1940 patients undergoing total hip replacement with metal-metal prostheses.<sup>27</sup> They excluded 198 patients who had a previous diagnosis of total or partial hip replacement or revision of the replacement. Of the remaining 1742, 33 had a previous diagnosis of CKD, which left a cohort of 1709 patients as the final study population. The patients included in the study had an average age of 76.1 years at the time of the intervention, and 97.6% were men. Nine years after the surgery, 240 patients had been diagnosed with CKD, that is, a 9-year incidence of 14% (Table 1).

The study by Hassan,<sup>28</sup> published in 2015, included patients who had primary osteoarthritis, post-traumatic osteoarthritis or rheumatoid arthritis and underwent total knee replacement, with a sample of 678 patients that added 702 total knee replacements. In the initial cohort 647 arthroplasties were included that had complete records. The study included patients who underwent surgery between January 2009 and December 2012. The patients were followed up for a year after the intervention by measuring their serum creatinine levels until their normalization or until the patient being referred to a renal unit. The results of the study showed that 8 patients developed severe CKD, for an incidence of 1.2%.

In the same year, Hassan published a retrospective study evaluating the incidence of kidney disease and its risk factors after total hip replacement in patients with primary osteoarthritis, femoral neck fractures and post-operative complications of osteosynthesis of hip fracture.<sup>29</sup> The patients included in this study were between 37 and 93 years old (average of 69 years). The sample included 599 patients, but the final cohort was 586 patients who had complete records. Patients who underwent surgery between January 2011 and December 2013 were included, and follow-up lasted at least 9 months after surgery, at which time it was concluded that 10 patients, 1.7%, had developed severe CKD.

Table 1. Characteristics of the studies included in the review.

Study, location, type of study	Adjustments, Affected population	Interventions	Age of participants during the intervention	Sample	% of losses of the sample	Period within which the intervention was carried out	Duration of post-intervention follow-up	Results of CKD incidence	Definition of CKD
Chandran 2011 (-), California, USA. Retrospective cohort study (27).	Patients with total hip arthroplasty from the Veterans Affairs Hospital database	Primary total hip replacement (metal-metal)	Average age: 76.1 years	1709 patients	11.91%	October 1, 1999 to September 30, 2000	Nine years after primary total hip replacement	240 of 1709 patients, incidence = (14%)	ICD-9 Code
Hassan 2015 (-), Belgium. Retrospective cohort study (28).	Patients with primary osteoarthritis, post-traumatic osteoarthritis, rheumatoid arthritis	Primary knee replacement	Average age: 69 years (range 37-93)	647 patients	2%	January 2009 to December 2012	Up to one year depending on post-surgery creatinine levels	8 of 647 patients Accumulated incidence: 1.2%	RIFLE 1.5 (28)
Hassan 2015 (-), Belgium. Retrospective cohort study (29)	Patients with primary osteoarthritis, femoral neck fractures and complications after osteosynthesis of hip fractures	Primary total hip replacement	Average age: 69 years (range 37-93)	586 patients	8%	January 2011 to December 2013	At least 9 months after surgery	0 of 586 patients, 1 incidence = 1.7%	RIFLE 1.5 (29)

### Study quality

The study by Chandran and Giori scored 4 on the NOS. The group of patients was selected from the *Veterans Affairs Medical Center* database, and the information for the study was obtained from their medical records. Patients with pre-existing CKD were excluded; the study did not include a non-exposed cohort with which to make a comparative analysis. Patients were screened for a diagnosis of CKD after 9 years after undergoing arthroplasty. The reported losses were calculated at 11.91%.<sup>27</sup>

The study by Hassam scored 5 on the NOS. The subjects included were obtained from databases and medical records of the Department of Orthopedics of the *Nyokoebing Falster Hospital* in Denmark. It did not add the comparability parameter because it did not have a control group. Patients with baseline CKD were excluded. A 9-month follow-up was made after the arthroplasty, to measure the incidence of CKD. A total of 8% of losses was reported on the initially included sample.<sup>29</sup>

The study on knee arthroplasty as a risk factor for developing CKD scored 5 on the

NOS. The data were obtained from the databases and medical records of the Department of Orthopedics of the *Nyokoebing Falster Hospital* in Denmark. As with the previous study, this one did not include a non-exposed cohort with which to make a comparative analysis. The patients did not have any type of kidney injury prior to knee replacement. The renal function of the patients included in the study was assessed during one year after the arthroplasty. We estimated 2% of losses at the end of the study.<sup>28</sup>

### Results of individual studies

After a 9-year follow-up in the study by Chandran and Giori, 336 patients, corresponding to 20% of the sample, were diagnosed with some kind of kidney disease: 240 with CKD, 60 with AKI, and 36 in whom the chronicity was not specified. Of the CKD patients, 22 were classified as severe (requiring renal replacement therapy [RRT]), 75 in stage 4 or 5 non-dialysis and 143 in stages 2 and 3.<sup>27</sup>

The study by Hassan on hip arthroplasty included 586 patients. Of them, 81 had AKI

(13.8%) and 10 of these developed severe CKD, for an incidence of 1.7%. Some risk factors for developing this pathology were hypertension, advanced age, general anesthesia, intraoperative hypotension and the use of prophylactic dicloxacillin.<sup>29</sup>

In Hassan's study on knee arthroplasty, 9.7% patients developed postoperative AKI; 55 improved in the follow-up, but 8 required long-term dialysis, for a 1.2% incidence of severe CKD after a one-year follow-up. The risk factors for developing CKD were similar to those for hip arthroplasty.<sup>28</sup>

### Discussion and Conclusions

At the end of the systematic review, 3 articles were included. Chandran's study, with a 9-year follow-up, found that 6.5% of patients required RRT on a permanent basis, and 22% of the cohort had comorbid DM.<sup>27</sup> In his two publications, Hassan evaluated the incidence of postoperative AKI and made a 9 and 12 month follow up. Within the AKI group, the incidence of severe CKD was 1.2% for the knee replacement cohort, and 1.7% for the hip replacement cohort.<sup>28,29</sup>

The overall incidence of CKD in Chandran's study was 14%. In the studies by Hassan it was not possible to calculate the overall incidence of CKD (28,29). The differences found in these studies regarding the incidence of severe CKD can be explained by the duration of the follow-up; in the first study, it lasted 9 years, and in the other 2 it lasted 9 and 12 months, respectively. It is likely that one year is an insufficient time to evaluate this outcome.

Coca S, *et al.* made a systematic review in which they documented a *Hazard Ratio* (HR) of 8.8 (95% CI 3.1-25.5) for CKD after an AKI episode, and of 3.1 (95% CI 1.9-5.0) for severe CKD, confirming that AKI episodes are independent risk factors for CKD.<sup>30</sup>

Another contributing factor to the differences in incidence was comorbidity. While in Chandran's study, 22% had DM, in Hassan's studies, only 10% had DM.<sup>28,29</sup> The presence of DM is a variable that can cause confusion, given that some DM patients may have developed CKD due to diabetic nephropathy rather than for the fact of having undergone an arthroplasty, even when the pre-surgical renal function values were within normal ranges.

In a cohort of patients older than 65 years, in which the CKD prevalence was evaluated at the time of the arthroplasty and the incidence of postoperative AKI, 13.5%

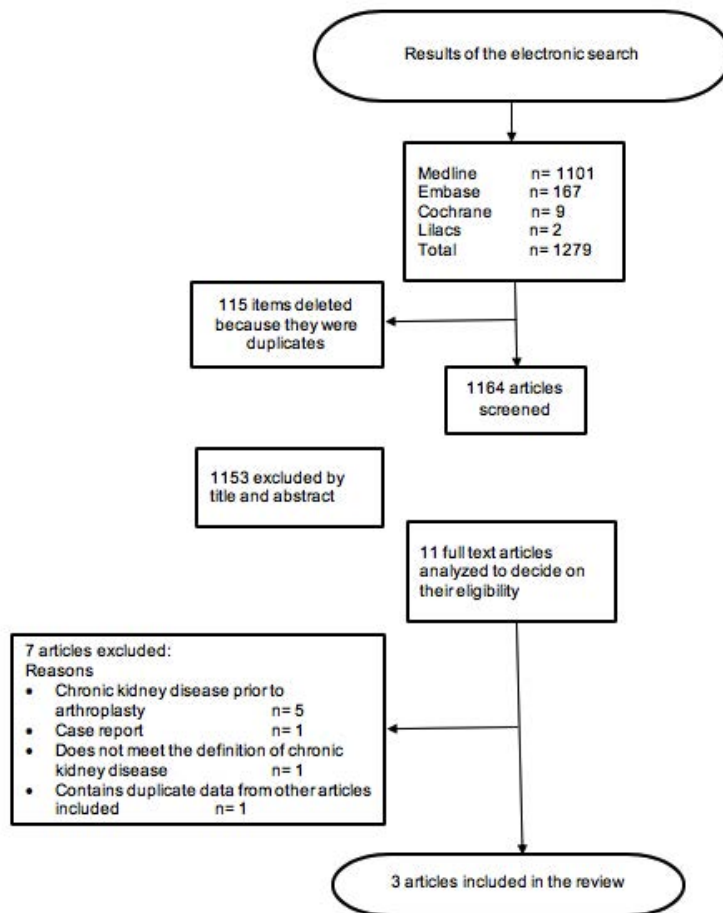


Figure 1. Flow chart of the number of articles screened and finally included.

of the patients were found to have baseline CKD with a GFR lower than 60 mL/min, and of these 26.6% had DM, 45% required emergency arthroplasty and 2.9% met the AKI criteria. Despite the comorbidity, only 59% of patients were monitored for creatinine levels in the postoperative period; assessing the incidence of postsurgical CKD was not one of the objectives of this study.<sup>31</sup> Failure to monitor creatinine levels contributes to the underdiagnosis of both AKI and CKD. None of the articles indicated or suggested intra- or postoperative surgery-related causes for the development of CKD. The articles by Hassan *et al.* found AKI-related risk factors, such as advanced age, hypertension, general anesthesia, dicloxacillin, and baseline low systolic and diastolic blood pressure. One of the limitations of our review is the low quantity and quality of the studies, all of which lacked a control group. In addition, confidence intervals are not mentioned. On the other hand, it was not possible to perform a meta-analysis in our study due to the heterogeneity of the articles.

Given the relationship between CKD and other chronic diseases, it is important to perform an adequate exclusion of independent variables to determine if the development of CKD is due to a comorbidity or is surgery related. In addition, it can be useful for monitoring patients who have AKI after an arthroplasty, given the high incidence associated with this type of interventions.

In conclusion, the information available on the incidence and the predisposing factors for developing CKD after an arthroplasty is scarce, inaccurate and of low quality. The results obtained are limited to retrospective studies conducted on older populations, which cannot provide significant reproducibility findings.

In order to achieve the objective set forth in this article, future research should focus on performing prospective cohort studies with adequate sample sizes, which allow us to accurately estimate CKD prevalence and incidence, as well as analyze the possible associated risk factors.

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