PTOA Question 6: Is there an accepted timeline for the appearance of PTOA that would most clearly relate to the clinical scenario?

Annette M McCoy, Stuart B Goodman

RESPONSE/RECOMMENDATION: No
There is no consensus on the timeline for PTOA after injury, with significant variation noted between injury type and anatomical location. Age, sex, BMI, and other factors are known to play a role in the emergence of PTOA and should be accounted for. Depending on the outcomes of interest, there is value in short-term (<2 years), medium-term (2-10 years), and long-term (>10 years) follow-up after injury to evaluate PTOA. Patient-reported outcomes may not be the best proxy for structural PTOA. Comparisons across studies will be facilitated by a consensus definition for PTOA.

LEVEL OF EVIDENCE: Moderate to High
PTOA has been reported to develop within a few weeks of injury or decades after injury. No single preclinical animal model is likely to recapitulate all phases of disease, but they are more likely to be valuable for short- to medium-term outcomes than for long-term outcomes.

DELEGATE VOTE:

RATIONALE: Development of post-traumatic osteoarthritis (PTOA) after injury is a commonly reported outcome for studies evaluating methods of treatment (conservative or surgical repair), but there is no single accepted post-operative duration of follow-up for this outcome. To establish commonly accepted norms for short-term, mid-term, and long-term follow-up, a comprehensive literature search was conducted within PubMed using the search phrase “post-traumatic osteoarthritis incidence”, yielding 273 potentially relevant articles, of which 174 were published since 2018 and were therefore considered most likely to reflect current reporting practices. An additional 750 articles published in the past 2 years were retrieved from PubMed using the search phrase “osteoarthritis after injury” and screened for studies evaluating the development of PTOA after injury; studies evaluating outcomes after treatment of primary osteoarthritis or revision procedures were excluded. From the combined searches, 249 papers were selected for further evaluation.

There did not appear to be complete agreement on the definition of “long-term” outcome across studies, although this phrasing was most often applied to studies with follow-up of 10 years or greater [1-3]. In some studies, long-term outcomes were reported at less than 5 years post-injury/post-surgery [4-5], although this time frame may still encompass the preclinical phase of PTOA for many patients [6]. The terminology “mid-term” outcomes was most often applied to 2- to 5-year follow-up studies [7-9]. Studies including clinical data from time points ranging from 1 week to 1 year were generally classified as “short-term” outcomes [10-11] and were often combined with longer follow up to determine the predictive ability of early diagnostic indicators on longer term outcomes [12-13].

Some criticism has been levied against studies with short follow-up periods, based on evidence that PTOA may take 15 years or more to manifest clinically [14]. Indeed, a study leveraging the UK Biobank found that among 4233 individuals with knee injury, 25.9% developed PTOA over a median of 30.2 years. However it is notable that in this study, the

highest risk for OA development was within the first 5 years after injury (hazard ratio 3.26), although the increased risk for OA was sustained over a 40-year period [15]. In a study of nearly 50,000 Danish individuals sustaining knee fractures, 4% required total knee arthroplasty (TKA) over the 20-year follow-up period, compared to only 1% of the matched uninjured population, with the highest risk in the first 3 years after injury (hazard ratio 3.74) [16]. Similarly, in a study of 7701 Finnish patients with proximal tibial fractures, the risk of developing severe PTOA requiring TKA (4.3% of patients) was highest in the first 2 years following injury, with increased risk over the control population continuing throughout the follow-up period (5.1 ± 3.1 years) [17]. These large studies suggest that there is benefit to evaluation of outcomes in the medium-term, even if some PTOA will develop over a longer time frame. The same pattern is noted for patient reported outcomes. For example, a study utilizing the MOON cohort identified clinically significant knee pain in 23-26% of patients 2, 6, and 10 years post-ACL reconstruction [18]. The highest proportion of patients reporting pain was at 2 years post-operatively, and very few reported pain at multiple time points, suggesting that the course of pathology after reconstruction may differ widely between individuals. Age, sex, BMI, and other factors have been reported to influence the development of PTOA after injury [5, 15, 19]. A summary of recent studies reporting incidence of PTOA is shown in Table 1.

Table 1: Summary of PTOA incidence across locations and injury type, grouped by length of follow-up. “Short” follow-up is defined as < 2 years, “medium” as 2-10 years, and “long” as >10 years.

Joint	**Injury**	**Follow-up**	**Incidence of PTOA (%)**	**Citations**
Ankle	Fracture	Short	8.2-21.2	20, 21
		Medium	9.7-50	22-29
	Sprain	Long	3.9	30
Elbow	Fracture	Medium	45.3-72	31-31
Hip	Fracture	Medium	15.7-33	9, 23-24, 33-36
	Dislocation	Medium	5	37
		Long	33	38
Knee	ACL	Short	2.3-57	39-43
		Medium	10.4-50	8, 18-19, 41-44
		Long	4.5-70	1-4, 18, 45-53
	Meniscal injury		6	54
			13.9-17.9	55-56
	Fracture	Medium	3.04-8.2	17, 57-59
		Long	4-50	16, 58, 60
	Nonspecific injury	Medium	9.6-33	15, 61-62
		Long	34	63
Shoulder	Instability	Long	84	64
	Fracture	Medium	10.3	65
Wrist	Fracture	Medium	23.3-27	66-67

A challenge lies in inconsistency of reported outcomes across studies. Most report one or more patient outcome parameters (PROMs), including return to sport (RTS) and variants of the Knee Osteoarthritis and Outcome Score (KOOS) subscales and other quality of life measures. However, these outcomes are focused on clinical/functional outcomes (e.g., pain) and are not always explicitly identified as PTOA. Notably, there is there is evidence that patient perceived outcomes do not always accurately reflect the degree of recovery using more objective assessments such as radiographic changes, joint effusion, range of motion, etc. [68]. When reported, a diagnosis of PTOA was most often based on imaging changes (e.g., Kellgren-Lawrence (KL) scores). However, many of the studies with the lowest reported rates of PTOA used joint replacement as a surrogate for this outcome rather than radiography or other imaging findings [17, 57-59]. This may have resulted in an artificially low percentage of individuals reported to have OA after injury. Studies evaluating specific surgical treatments – particularly comparisons of different treatment approaches to the same injury – often reported revision or failure rates within a set amount of time post-operatively (e.g., 2 or 5 years) [57, 69-71], but it was not always clear if follow-up surgical procedures were due to persistent/recurrent clinical signs, radiographic progression of disease, or a combination of these or other factors.

Preclinical animal models that have a short time-course are favored for benefits related to cost and convenience, but they may not be an accurate reflection of clinical progression in human PTOA which limits their translational relevance. Induced small animal models of PTOA (mouse, rat, rabbit) are rarely evaluated over longer than 12 weeks, with endpoints more commonly in the 4- to 8-week range [72-80]. Larger models, such as the minipig or horse, can be extended to 4-6 months or longer in some studies [81-82]. When considered as a proportion of the expected lifespan of the animal, 4 to 12 weeks in a rat or mouse or 6 months in a minipig could be considered roughly equivalent to 5 to 7 years in a human, which would suggest that these studies are more likely to mimic short- to medium-term follow-up than long-term follow-up. However, this is almost certainly an oversimplification of the differences in pathophysiology between species and inciting injuries.

Conclusions: Comparisons across studies reporting outcomes after musculoskeletal injury are hampered by varying definitions of PTOA, differences between patient perception and clinical and/or radiographic assessment of disease progression, and incomplete understanding of the pathophysiology of PTOA after various injuries. There is likely value to evaluations performed over different time frames (short-term, medium-term, long-term), with the outcome of interest the key driver of which duration of follow-up is most appropriate for a given study. Existing preclinical animal models of PTOA (induced trauma) are unlikely to provide insight into long-term PTOA outcomes in humans.

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