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The patterns and predictors of knee osteoarthritis pain flares

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Abstract

Osteoarthritis is the commonest joint disease in the world and is the main reason for activity limitation in adults. Notably, knee osteoarthritis (KOA) accounts for most of the global osteoarthritis burden and is especially prevalent in Asia, including Sri Lanka. Although KOA is now much better understood, it is still a disease without a cure and patients suffer profoundly from KOA pain. While it is generally accepted that intermittent KOA pain or knee osteoarthritis pain flares (KOAF) is symptomatic of early KOA, this phenomenon remains poorly understood. Therefore, more insights about the intermittent nature of knee pain can help to develop more effective methods to manage both the pain and progress of the disease.

Knee osteoarthritis pain flares, its associated risk factors, and progression are the focus of the research presented in this oration. This research investigated the multiple risk factors and potential predictors of KOAF using data from two cohorts, one in Australia and another in Sri Lanka. Thereafter, a multivariable model was estimated to predict KOAF in the following 30 days. Subsequently, short-term pain evolution in persons with KOA pain fluctuations was examined to identify distinct and disparate pain trajectories, to better understand the evolution of pain in early KOA.

This new information helps identify those at high risk of KOAF and has the potential to enhance patient education and resource allocation. Research findings about short-term pain trajectories, in particular, will ensure that patients at the highest risk of pain progression are targeted and treated in a timely manner.

Key words: knee osteoarthritis, pain flares

Introduction

Osteoarthritis (OA) is the most widely prevalent joint disease in the world and is a leading cause of disability in older persons.[1] Osteoarthritis of the knee (KOA) is particularly disabling, and accounts for approximately 80% of the global OA burden.[2] KOA is especially prevalent in Asia, including Sri Lanka,[3] and studies show that KOA burden is on the increase.[4] The concept that KOA is a disease of wear and tear is now disputed. Recent research has shown that KOA is the result of a disruption in joint-tissue metabolism caused by an imbalance between repair and destruction of joint tissues. Mechanical, inflammatory, and metabolic factors mediate cartilage degradation, osteophyte formation, bone remodelling, and joint inflammation,[5,6] which culminates in loss of joint function.[7]

Despite recent progress in understanding of the disease, KOA is still a disease without a cure. Current treatment focuses on non-pharmacological methods such as education, self-management of pain, exercise, and assistive devices. There is evidence that conservative treatment is at least as efficacious as surgery.[8] However, conservative management focuses on significant weight loss,[9] and regular physical activity,[10] both of which are not always achievable nor feasible in adults; particularly older adults, with reduced physical activity, slow metabolism; living in community-based settings. Consequently, there is still no definitive, effective therapeutic intervention for this disease and KOA progresses relentlessly, with no known remission. In addition, there is a discordance between radiological findings and pain, so the disease is difficult to characterise and study.[11,12] So, the prevalence of KOA continues to rise with increasing longevity, consuming increasing shares of dwindling resources for health care.

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A multitude of pathogenic risk factors, each with the potential impact on the joint individually or in combination, make KOA a disease which is difficult to understand. As Berenbaum (2019) says, "OA may actually be a nebula of several diseases" (p.3), which cannot be characterised due to lack of markers/ investigations to aid differentiation. So, identifying different KOA phenotypes can help select subgroups of patients for whom a particular treatment option would be effective. Understanding the "pain phenotype", is especially useful because of the significant discordance between radiographs and knee pain. Therefore, we need to develop a better understanding of KOA pain, and current efforts to reconceptualise KOA as an acute on chronic symptomatic pain disorder are timely. While it is generally accepted that KOA pain[9,10] can be constant or intermittent, the intermittent nature of early KOA pain, or knee osteoarthritis pain flares (KOAF) remains poorly understood. Therefore, more insights into the intermittent nature of knee pain holds the potential to develop more effective methods to manage both the pain and progression of the disease.

The research submitted for this oration aims to address this gap in knowledge on KOA. Its first component identifies multiple risk factors and potential predictors of KOAF in two disparate cohorts, one in Australia and another in Sri Lanka. The second component uses these risk factors to predict KOAF. The third component investigates whether pain in persons with previous pain fluctuations, or intermittent pain, has different pain trajectories in the short term. It is felt that studying intermittent pain and KOAF in two disparate populations will prove more instructive and provide useful comparative insights which can be used in clinical practice.

The remainder of the projects included in this manuscript ultilised two data sets. The first, a Sri Lankan study, longitudinally followed up persons with KOA pain fluctuations over a 90-day period. Data collection was done by telephone in the Sri Lankan cohort, as this was the best method of contacting the participants in real time. Trained investigators contacted participants every 10 days (control time point). Further, participants were asked to contact investigators whenever they experienced a KOAF. As a contingency, the participants were contacted every 5 days, and any unreported flare data were collected within 48 hours of onset. The second, the Australian cohort was longitudinally followed up over 90 days utilising a secure, dedicated website. These participants logged in at the time of KOAF (case time point) or every 10 days (control time point). Ethics clearance was obtained for both studies (Faculty of Medicine, Colombo (EC-16-177). University of Sydney (No. 14435) / University of Melbourne (HREC-0709220). The associations between risk factors and KOAF in both studies were examined using conditional logistic regression in Stata version 17. The analysis omitted persons whose KOAF failed to settle within 2 control periods. The findings of these projects are elaborated in three sections for reasons of clarity. The three components used different methodologies.

What risk factors are associated with knee osteoarthritis pain flares?

An in-depth understanding of the risk factors for KOAF is critical in understanding the pathogenesis of KOAF. Therefore, the first component of this oration describes two case-crossover studies which were used to identify risk factors associated with the outcome of acute onset, short-lived KOAF in the two cohorts.

Methods: This novel study design was particularly useful in identifying the effects of transient exposures which trigger acute disease exacerbations.[14,15] In both cohorts, persons with a diagnosis of KOA (based on the American College of Rheumatologists (ACR) criteria), who reported previous KOAF, were followed up for 90 days. Exposures to risk factors were assessed every 10 days (control time point) and whenever the participants experienced a KOAF (case time point). The hazard windows for different exposures were selected based on previous literature (Figures 1 and 2).

Results: The Sri Lankan study consisted of 260 persons (90% females), 77 (29.6%) persons did not continue follow-up. Only 120 persons had both valid control and case periods as persons with only case periods (1 participant), and only control periods (62 participants (34%)). There was no significant difference in the demographic characteristics between those with case-control periods, those lost to follow up, and those with control periods only. The Australian study had 313 participants (60.9% females) with a mean age and body mass index of 62.3 (SD=8.2) years and 29.6 kg/ m^2 (SD=6.5), respectively. Nearly 94% of these persons continued longitudinal follow-up for 90 days. During the follow-up period, 157 (48.3%) experienced at least one KOAF.

Both case-crossover studies identified numerous risk factors associated with KOAF. The Sri Lankan study independently demonstrated that knee buckling was associated with an increased risk of KOAF (Odds Ratio (OR) 5.1 (95% CI3.0-8.6),[16] as was shown in Australia.[17] There are multiple explanations as to why knee buckling triggers KOAF. A knee pushed beyond

its physiological range injures adjacent soft tissue/ bone causing inflammation with the release of nociceptive chemical mediators.[18,19] As the majority of periarticular structures are densely innervated, buckling/ injury will trigger pain.[20,21] Since knee buckling is potentially modifiable by physiotherapy, muscle strengthening, and bracing, identifying this risk factor is useful in clinical practice.

The Sri Lankan study did not demonstrate any association between squatting/kneeling and KOAF (OR 0.84 (95% CI 8.0-25.2)) (OR 0.66 (95% CI 0.22-2.0)) ($p<0.05$).[16] It was expected that kneeling/squatting would be associated with KOAF notwithstanding expectations to the contrary as kneeling/squatting generates adverse and high joint forces on the knee. These forces cause pain by forming pain-inducing inflammatory cytokines and causing microfractures in the subchondral bone.[21,22,23] But this lack of association can be explained. First, squatting was mostly performed for toileting and for veneration, all short-lived insults and potentially modifiable (i.e. half squat/half bend instead of fully squatting/kneeling). Further, many years of using these postures could have promoted habituation/adaptation of the lower-limb mechanics.[22] In addition, numbers engaging in these activities were small, possibly due to fear of triggering pain, a phenomenon called "adverse selection of the sample". Therefore, these numbers and duration of squatting/ kneeling may not have been adequate to demonstrate effective associations.[23] Squatting/kneeling was not assessed in the Australian study due to these habits being uncommon in Western cultures.

Further, the Sri Lankan study demonstrated an increased risk of KOAF with any moderate physical activity (PhysA) in the week immediately before the KOAF. It is the first in medical literature to do so. It is possible that increased loading, in the short term, results in pain, particularly in the elderly and those overweight/obese or with maladjusted gait. This intense pain is related to knee adduction moment and external knee flexion moment.[24] The pathogenesis of pain with exercise is indirectly supported by imaging evidence which showed increased bone marrow lesions (associated with fluctuations of knee pain) with greater medial loads on the knee.[25] Interestingly, it has been demonstrated that following PhysA guidelines long-term does not cause an increased risk of incident radiographic or symptomatic KOA. This reduced risk of KOA, in the long term, was attributed to the fact that low-impact activities cause joint loading/ compression which in turn improves the cartilage matrix and chondrocyte activity. But in the short term, it has been postulated that "perturbations in local joint stress" could cause KOAF.[26] In fact, we have demonstrated short-term exacerbations of KOA pain with PhysA with or without knee buckling.[16,27] Therefore, this study further reinforces the fact that physical activity may trigger KOAF in the short-term. If long-term recommendations for regular exercise are to be implemented, it is imperative that this dimension of post-physical activity KOAF be tackled effectively. If not, persons may be discouraged from further exercise and would lose the long-term benefits of physical activity on KOA progression and other health outcomes. Therefore, persons should be encouraged to pace physical activity and engage in muscle strengthening and biomechanical corrections to minimise joint load.

The Sri Lankan study also demonstrated the novel finding that increased duration of wearing footwear was associated with a significant risk of KOAF (OR 4.3 (2.5-7.3)) while an increased duration of being barefoot was associated with a reduced risk of KOAF (Table1).[27] This pioneering study corroborated gait laboratory study findings which demonstrated that the mechanical advantages of walking barefoot are manifold. Gait analyses performed in patients with medial KOA previously demonstrated that barefoot walking significantly reduces peak knee joint loads and knee adduction moment. 3-Dimensional assessments have demonstrated adverse torque on the knee with higher hip internal rotation, knee flexion and varus torque with running shoes compared to barefoot.[28] In addition, barefoot walking improves the sensitivity of sensory perception of foot and activates the lower leg and foot muscles. So, proprioceptive input from the skin touching the ground is possibly beneficial.[29] This evidence strengthens the findings of our research by explaining some of the mechanisms by which being barefoot is associated with lower mechanical loads on the knee and reduces risk of KOAF. All types of shoes exert adverse torque forces on lower limbs compared to walking barefoot with the extent of knee loading being affected by footwear design and higher heel heights.[28,29] In contrast, the Australian study did not demonstrate any association between KOAF, PhysA, stability, and heel height of shoes.[30] These findings were attributed to only 34% of participants self-reporting their PhysA/shoe data. This was attributed to the lengthy questionnaire on PA/shoes causing lower response rates.

The Sri Lankan study showed that being distressed, nervous, upset, and jittery was associated with a significantly increased risk of KOAF, which was associated with a significantly increased risk of KOAF, with extremely severe mood being associated with increasing odds of KOAF (Table 2).[31] This was similar to previous Australian findings,[32] and also resonate with previous research, which found that pain causes stress,

Table 1. Association between KOAF, physical activity and being barefoot (duration in hours)

Flare	*Case Periods*	*Control Periods*	*Univariable Ratios (95% CI)*	*P*	*Case Periods*	*Control Periods*	*Multivariable OR (95% CI)*	*P*
Model examining association between KOAF, barefoot and physical activity categories (1 day before flare)								
Duration of being barefoot day before flare (hours)	224	725	0.85[a] (0.79-0.90)	<0.0001	224	725	0.85[a] (0.80-0.90)	<0.0001
Physical Activity Performed 1 day prior								
Mild Physical Activity Only	145	608	Reference		143	585	Reference	
Any Moderate	80	144	3.81 (2.35-6.19)	<0.0001	77	131	4.29[a] (2.52-7.30)	<0.0001
Any Vigorous	4	9	2.01 (0.53-7.63)	0.303	4	9	1.14[a] (0.28-4.59)	0.857
Model examining association between KOAF, barefoot and intensity of physical activity categories (2 days before flare)								
Duration of being barefoot 2 days before flare (hours)	224	725	0.85[a] (0.80-0.90)	<0.0001	224	725	0.84[b] (0.79-0.90)	<0.0001
Physical Activity Performed 2 days before								
Mild Physical Activity Only	145	608	Reference		143	585	Reference	
Any Moderate	80	144	3.73 (2.34-5.97)	<0.0001	77	131	4.27[b] (2.56-7.13)	<0.0001
Any Vigorous	4	9	0.49 (0.05-4.69)	0.537	4	9	0.26 (0.03-2.52)	0.246

Table 2. Association between KOAF and domains in negative mood subscale of the Positive Negative Affect Score

KOAF			*Extent to which mood was experienced in the previous 10 days*							
	Case Period	*Control Period*	*A Little*		*Moderately*		*Quite a Bit*		*Extremely*	
			Univariable OR (95% CI)	*p*	*Univariable OR (95% CI)*	*p*	*Univariable OR (95% CI)*	*p*	*Univariable OR (95% CI)*	*p*
Negative Mood Score Domains										
Distressed	209	585	1.56 (0.92-2.64)	0.100	3.32 (1.88-5.86)	<0.0001	7.53 (3.02-18.77)	<0.0001	8.57 (1.52-48.47)	0.015
Nervous	209	585	2.51 (1.44-4.37)	0.001	3.05 (1.44-6.48)	0.004	4.62 (1.45-4.78)	0.01	16.66 (2.42-14.70)	0.004
Upset	209	697	1.51 (0.94-2.44)	0.089	2.5 (1.52-4.12)	<0.001	3.03 (1.42-6.46)	0.004	4.45 (1.30-15.20)	0.017
Jittery	210	593	3.47 (2.05-5.86)	<0.0001	7.08 (3.82-13.11)	<0.001	6.45 (2.51-19.34)	0.001	84.59 (7.51-1001.5)	<0.001
Irritable	210	593	2.09 (1.19-3.68)	0.010	1.27 (0.58-2.80)	0.550		1.81 (0.17-3.83)		0.788
Afraid	210	701	2.1 (1.26-3.49)	0.004	1.58 (0.73-3.41)	0.246	3.03 (0.99-9.32)	0.052	1.19 (0.11-12.71)	0.549
Guilty	210	705	1.19 (0.62-2.28)	0.598	2.3 (0.53-9.98)	0.265		0.47 (0.05-4.61)		0.518
Scared	257	697	2.08 (1.27-3.39)	0.003	2.49 (1.16-5.36)	0.019		2.12 (0.71-6.31)		0.178
Hostile	260	704	1.35 (0.69-2.64)	0.382	4.88 (1.17-20.4)	0.030		0.60 (0.50-6.72)		0.682
Ashamed	260	590	2.17 (1.02-4.65)	0.045	4.91 (0.77-31.52)	0.093		-		- 0.093

* The association between KOAF and each individual negative mood score domain was examined by univariable regression. Reference was class 0 (None et al)

which in turn leads to depression, poorer mood, and negative affect. Negative affect has been associated with clinically perceived pain in OA.[32,33] In addition, negative affect is believed to be a robust predictor of clinical OA pain.[33] Further, the poor mood may lower pain threshold and negatively affect pain perception.[34,35]. Though sleep was not examined in the Sri Lankan study, the Australian study showed that increased duration of weekday/weekend sleep was associated with significantly reduced odds of KOAF (0.61 (0.51-073) and 0.74 (0.64-0.86) (P<0.001). This was in keeping with previous studies, which showed that sleep, or the lack of it, could potentially impact the perception of pain. Population-based longitudinal studies have demonstrated that there is a strong dose-dependent relationship between sleep impairment and chronic musculoskeletal pain. Moreover, sleep quality has been linked to worsening knee pain in those with widespread pain and KOA.[36,37] This relationship between sleep and KOAF is very likely to work both ways because poor pain can reduce sleep and vice versa. This is particularly important as mood and sleep disturbances are amenable to behavioural and therapeutic interventions.

Additional associations between Knee Osteo-arthritis Outcomes Score (KOOS), Intermittent Constant Osteoarthritis Pain score (ICOAP) and KOAF were examined in the Australian data. As expected, the ICOAP (constant/intermittent) was significantly associated with KOAF[38] as were the KOOS subscales (P<0.0001). The KOOS is intended to evaluate the short-term outcomes in KOA,[39] and the ICOAP to evaluate the intermittent/and constant pain in KOA.[40] Therefore, the presence of these associations lends further validity to the case-crossover design. Further, our study demonstrated that traditional risk factors for KOA are not associated with KOAF.[41] Traditional risk factors of KOA may not be associated with short-term variability in pain though they are associated with long-term outcomes of KOA. It is postulated that as knee pain is already present, the impact of the risk factors which contributed to the original symptom causation, may not be large enough to be associated with acute on chronic manifestations. This statistical phenomenon has been described as biased due to conditioning on a collider.[42]

Can knee osteoarthritis pain flares be predicted?

The second component explores the possibility of predicting KOAF. As KOAF are both unpredictable and distressing, identifying those at high risk of KOAF will enable patient education and allocation of health care; and selection of participants for flare-design related endpoints. Though some might argue that risk factors and predictors are similar, association and prediction are two different constructs, and association does not equal causality.[43] Therefore, the second section of this oration described the development of a multivariable prediction model to predict KOAF in the following 30 days.

Methods: The outcome was the occurrence of a KOAF in the following 30 days. A KOAF was defined as current pain with a ≥2-point increase (on a 0-10-point numeric rating scale (NRS)) from background level of pain intensity in the index knee at Day 0, provided pain episode lasted ≥4 hours and settled within 2 control periods (20 days). The predictor variables were selected based on result of previous studies which examined associations with KOAF or KOA pain. Following recommendations in the literature, this study utilized only predictor assessment at baseline (even though predictors were assessed repeatedly during follow-up). All predictors available in the dataset, which were feasible to use in routine clinical practice, were included in the base model. Records with missing data on parameters of interest was omitted from the analysis , by record wise deletion. A receiver operating characteristics (ROC) curve-based elimination method was used to reduce the number of predictors. Feature selection using a multiple bootstrap method was used to eliminate highly correlated variables and retain only important predictor. Specifically, 10-fold cross-validation was done by random seed generation, and the sample was split into 10 groups, holding nine groups for model development with the remaining one used for model validation. ROC curves were constructed based on the scores obtained from this 10-fold cross-validation method.[44]

Results: The Australian cohort consisted of 313 persons with complete data on variables of interest were included. The most parsimonious KOAF risk prediction model, with the best predictive capacity, developed from the Australian cohort was the model which had a ROC curve (area under the curve (AUC) of 0.73 (95% CI 0.66-0.80)). This model contained demographic variables (age, years of OA, BMI, and sex) with higher baseline pain scores, presence of knee buckling/injury, higher ICOAP (constant and intermittent subscales) and use of unstable shoes and higher heel heights. Cross-validation was repeated 300 times and average AUCs calculated. Variables were removed one at a time and AUC of ROC curve was estimated, using AUCs as a measure of overall model performance selection using a multiple bootstrap method was used to eliminate highly correlated variables and retain only important variables. The internally validated model had a ROC AUC of 0.66 (0.62-0.70).[45]

Discussion: As Parry et al (2017) point out, "flares are best thought of as multi-dimensional constructs".[46] Correspondingly, the final multivariable KOAF prediction model contained a combination baseline parameters including age, sex, BMI pain scores, parameters which reflect poor mood or function, and occurrence of knee insults. This prediction model was significantly impacted by factors which affect the mechanical stability of the joint (i.e. injuries, knee buckling etc) and factors which affect the perception of pain.[45]

Previous research has shown that joint loading is affected by being overweight/obese or female and that it confers an increased risk of KOA.[47] Knee insults and unstable shoes or higher heel heights cause adverse joint mechanics and increase knee joint torques.[48,49] These mechanical insults may trigger inflammation with release of tissue cytokines and metalloproteinase that result in pain. The pain in KOA, is affected by mood, pain perception and related psychological factors, as pain perception is, in part, driven by many factors including central mechanisms.[50] Higher levels of pain sensitisation may cause progression from a no knee pain state to intermittent pain and finally to constant pain. Determinants of pain in KOA, though multifactorial and multifaceted, are possibly unique and constant for the given person. So greater variability in pain is affected by poor mood, frustration, and reduced happiness, even when assessed at baseline. This would explain why pain scores, positive/negative affect scales and ICOAP were included in the model.

It is envisaged that revision of this model, with newer predictors, including novel imaging predictors, will further improve the predictive capacity of the model. This would be useful to improve clinical practice, research on and care of persons with KOAF. Another factor that would improve the understanding of KOA pain is to identify persons whose pain evolves in a pattern or trajectory different from others. Therefore, the third aspect discussed here is the identification of pain trajectories in persons with a history of previous pain fluctuations.

Does knee pain in patients with knee osteoarthritis flares follow distinct trajectories?

The third component of research presented in this oration identifies whether persons with previous pain fluctuations had distinct pain trajectories in the following 30 days.

Methods: This project longitudinally followed-up the KOOS pain scores (KOOS-p) every 10 days for 90 days. Latent growth curve models, specifically latent class growth analysis (LCGA) and growth mixture modelling (GMM), were applied to the data from the Australian cohort to explain the heterogeneity in KOOS-p scores over 90 days.[51] Once the best fitting model was selected according to accepted statistical criteria, baseline factors were included in the multinomial regression model to identify characteristics unique to the different clusters.

Results: The analysis revealed that clusters of persons with previous KOA pain fluctuations had unique KOOS-p trajectories over 90 days. Three distinct trajectory-clusters of pain were identified: Cluster 1: Low moderate pain at baseline with large improvement (n=11, probability=0.86); Cluster 2: Low-moderate pain at baseline with minimum change (n=254, probability= 0.90) and Cluster 3: Moderate-high pain at baseline worsening (n=46, probability=0.78). Significant differences were seen between classes on the following: pain, ICOAP (intermittent scale), perceived stress, negative affect score, and knee buckling ($p<0.05$). Cluster 3, the poorest pain trajectory cluster, was characterised by higher baseline pain, higher intermittent ICOAP pain subscales, negative affect scores, perceived stress, a recent knee injury and buckling, and being more obese/overweight compared to the other classes (Figure 3).[51]

Discussion: This study was the first to examine short-term pain trajectories in KOA, unlike previous studies which explored longer term pain trajectories.[52,53] As KOAF are phenomenon of early KOA, this study gives novel insight to pain evolution in early disease. The largest cluster had a stable pain trajectory. As early disease, is characterised by self-limiting inflammation, these findings are is in keeping with this postulate.[54] A smaller cluster had progressive pain. These persons had higher weight, on average. This is in keeping with previous studies where pain increased or decreased with body weight in a dose dependent fashion. Knee insults were also commoner in this cluster, keeping with postulate that KOAF are triggered by local perturbations in joint stress.[54,55] The poorer pain clusters had higher negative affect/pain scores confirming that poor mood/lower pain thresholds are associated with poorer pain progression.[56] These findings demonstrate that different risk factors influence pain trajectories in persons with KOA. Future research, imaging, genetic and molecular studies, are required to identify the multitude of mechanisms which cause these pain trajectories to diverge.

Conclusions

These research projects, in combination, independently identified several risk factors which are

both associated and predictive of KOAF. In addition, these same risk factors determine poorer pain progression, even over a short time frame, in persons with previous pain fluctuations, at highest risk of KOAF.

These findings suggest interesting research directions for the future. There is uncertainity as to whether KOAF need to be stopped or shortened, or whether they are a necessary part of healing within the joint. However, it has been observed that KOAF increase in frequency with time, taking more time for resolution, ultimately reducing the joint reserve. This will culminate in joint failure, as end-stage KOA. These research presented in this oration identified two categories of KOAF risk factors; those associated with joint loading and those associated with perception of pain. However, further research is needed to identify how these factors affect normal joints or how normal levels of these risk factors affect vulnerable joints.

The current state of knowledge accepts that symptoms or imaging alone do not give enough information about how the individual's disease-stage affects the course of disease. Some triggers seem to cause rapid progression. Therefore, identification of symptom trajectories in this project, will help in future longitudinal profiling of patients. The present research clearly demonstrated that distinct short-term pain trajectories are present in persons with pain fluctuations, and that baseline characteristics impact the evolution of pain. But, more research is necessary to identify how these short-term trajectories relate to long term pain trajectories in KOA.

Predicting those at greatest risk of KOAF can be the first step in the formulation of targeted treatment of persons with KOA. The "one size fits all" strategy currently used in many contexts is unlikely to be correct and is the likely reason for the lack of effect in clinical trials in KOA. The heterogeneous mix of KOA patients in clinical trials is possibly blunting the treatment effect seen in those for whom the treatment really works. Therefore, the KOAF prediction model, will help to prevent and manage the treatment of at least one aspect of KOA, which are KOAF. KOAF seem to be at the juncture between early and end-stage disease. Therefore, intervention at the KOAF stage has potential to transform the disease course and prevent progression to end-stage KOA. This in turn, will mitigate the looming health crisis of KOA, particularly with increasing age, joint trauma, and obesity, in Sri Lanka and elsewhere.

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