Relation of Anterior Cruciate Ligament Tears to Potential Chronic Cardiovascular diseases

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We have enrolled a cohort of former National Football League players (n = 3,506) who played since 1960 to assess potential long term health consequences associated with participating in the sport. Each participant has completed a self-administered questionnaire including reporting of physician-diagnosed health conditions. One of the early assessments was to evaluate whether anterior cruciate ligament (ACL) tears were associated with later life co-morbidities, including cardiovascular effects. We used Cox proportional hazards to estimate hazard ratios (HR) for joint replacement surgeries, myocardial infarction, sleep apnea, arthritis, dementia, and stroke by history of ACL tear during their professional career. For additional outcomes without date of occurrence reported we used logistic regression to estimate odds ratios adjusted for potential confounding variables in all models. After adjusting for covariates, former National Football League players who tore their ACL had approximately a twofold increase in muscular skeletal co-morbidities, including knee joint replacement and arthritis, compared with those without ACL tears. In addition, those with a history of ACL tears also had more than a 50% increased risk of myocardial infarction (HR 1.52; 95% confidence interval 0.97 to 2.38) and a slight increase in sleep apnea (HR 1.15; 95% confidence interval 0.96 to 1.38). ACL tears sustained by athletes may increase the risk of co-morbidities beyond the musculoskeletal system. As there are more than 100,000 ACL reconstructions annually in the United States, our findings could have widespread public health importance if these findings generalize to a population beyond professional football players. In conclusion, enhanced screening for other risk factors for these conditions in patients who have torn their ACL might identify those who could most benefit from prevention strategies. **(Am J Cardiol 2018;122:1879−1884)**

More than 100,000 people in the United States undergo Anterior Cruciate Ligament (ACL) reconstructions annually.[1] ACL tears are often sustained by athletes, and most studies of the effectiveness of ACL reconstruction use arthrometry, return-to-play, and career length as their main outcome measures.[2−7] Although these short-term successes are important for athletes whose livelihood depends on their ability to play, ACL tears may be associated with longer term health consequences, despite reconstructive surgery. One well-known long-term consequence is the subsequent occurrence of osteoarthritis.[8,9] Historically, ACL injuries have been treated as isolated damage to the musculoskeletal

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system. Few investigators have explored later life health outcomes beyond the musculoskeletal system. However, biological systems may impact one another and influence behavior, such that an injury to 1 system could have repercussions on other systems. Identification of such cross-system effects that contribute to later life morbidity could help develop strategies to mitigate or prevent long-term complications of ACL injuries. As part of a larger study we assessed the associations between ACL tears and long-term health related outcomes in former National Football League (NFL) players, a group at risk for ACL injuries.[28]

Methods

Starting in January of 2015, as part of an effort to establish a cohort of former NFL players, we attempted to contact all living former players who participated in the NFL since 1960. This year was chosen as there were substantial changes to the rules and equipment used by players that occurred over the earlier years of the game.

Records supplied by the NFL Former Players Association, supplemented by public online sources,[10] allowed us to identify approximately 16,000 former players who verifiably participated in the NFL. Of these, approximately 1,100 played before 1960, were deceased, or were otherwise unreachable at the time of our first contact. Potential contact information (email or home address) was obtained for 14,906; however, attempts to reach them failed for 2,549 (17%) as invalid or no longer correct. Of the remaining 12,357 players, only 140 (1.1%) actively declined to participate in the study. At the time of this analysis 3,506 (28.4%) had completed the survey. The study was approved by the Human Studies Committee of the Beth Israel Deaconess Medical Center, an affiliate of Harvard Medical School.

Our main predictor variable of interest was history of ACL tear during active playing years. As there are many knee injuries that can be sustained during athletics, involving several ligaments with similar sounding abbreviations, we attempted to avoid conflation of injuries by asking whether or not they had undergone reconstruction surgery, rather than simply asking whether or not they tore their ACL, since return to play without reconstruction is unlikely and thus a significantly memorable event. The outcomes explored included self-reported knee joint replacement, hip joint replacement, and a number of long-term co-morbidities, including outcomes related not only to the musculoskeletal system but also cardiovascular, endocrine, neurologic, psychological, and social domains.

Although reported health conditions were not independently validated,[11] we attempted to minimize misclassification by asking players whether or not they were ever prescribed a medication or underwent surgery for a given medical condition, and the year they were first diagnosed or treated. For conditions such as myocardial infarction (MI), stroke, players were asked, “Has a health care provider ever told you that you have any of the following diagnoses or health outcomes?” and if they did, the year of diagnosis. For other treated conditions (chronic pain, depression, anxiety, hypertension, and hypercholesterolemia) timing information was not collected. We measured potential covariables that might also affect our outcomes, including age, race, and body mass index (BMI) at the time they stopped being an active player, seasons of professional football played, position played, and history of cigarette smoking. Position played was grouped by category as previously described by Baron et al[12]: category I included defensive backs, punters, kickers, quarterbacks, and wide receivers; category II included linebackers, running backs and tight ends; and category III included defensive and offensive linemen. For participants who neglected to fill in their age, age was determined from a publicly available resource.[10]

We screened age, race, position played, BMI at the time of active play, number of seasons played, and ever smoking for the potential to introduce confounding to our analyses by examining age-adjusted differences by history of ACL tear during active playing years. This was done using logistic regression with ACL tear as the outcome in separate models for each variable with age included in each as a predictor. Variables that predicted history of ACL tear with a $p < 0.20$ when adjusted for age were included in our main analyses of later life health outcomes. For those outcomes for which we had time of first event data, we used Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI). Follow-up began the year the player last played professional football, and ended at the time of the outcome or the date of return of the questionnaire for those who did not have a given outcome. We used age in years as the time scale of follow-up (time-metameter) to have optimal control for age in the analyses, given the strong age-dependence of our outcomes. Additional covariates were added to the model as separate terms. For outcomes without time of event data, we used logistic regression to estimate odds ratios (OR) and 95% CI adjusted for age and other covariates. We considered statistical significance at the 95% level of confidence. Analyses were performed using STATA 14.

Results

As of March, 2017 we had 3,506 former NFL football players who completed our initial questionnaire. The mean age of the respondents was 53 ± 14 years. Most respondents (59%) were white, 37% were black, and 4% listed themselves as “other.” Respondents played a mean of 6.8 ± 3.7years in the NFL with less than 2% with 15 years or more. Percentages in different position categories were nearly equal ranging from 31% to 34%. Of the 3,277 respondents who answered the question regarding surgeries they had during their playing years, 692 (21.1%) had undergone ACL reconstruction. Those former players who had torn their ACL were similar in BMI, race, and had similar smoking histories to those who had not torn their ACL. However, former players with a history of ACL tear were older, had slightly longer careers, and were more likely to have played linemen (Table 1).

In our main analyses, former players who had torn their ACL had a significant twofold elevated rate of subsequent knee joint replacement and a 50% excess rate of arthritis. We also found a 50% increase in the rate of MI in those who had torn their ACL, although this did not quite reach

Table 1
Characteristics of respondents (n = 3,506)

	ACL reconstruction		
	Yes n/N (%)	No n/N (%)	p value*
Age (years)			
<35	71/692 (10%)	354/2584 (13%)	0.001
35-54	263/692 (38%)	1085/2584 (42%)	
>54	358/692 (52%)	1145/2584 (44%)	
Race†			
White	409/683 (60%)	1506/2562 (60%)	–
Black	242/683 (35%)	940/2562 (35%)	0.78
Other‡	32/683 (5%)	116/2562 (5%)	0.58
Position category§			
I	208/686 (30%)	908/2559 (35%)	–
II	231/686 (34%)	800/2559 (32%)	0.02
III	247/686 (36%)	851/2559 (33%)	0.02
Body mass index (BMI), mean (SD), (kg/m^2)¶	30.5 (3.9 s.d.)	30.4(4.2 s.d.)	0.14
Number of seasons played	7.0 (3.5 s.d.)	6.7 (3.8 s.d.)	0.19
Ever smoked cigarettes**	125/684 (18%)	414/2567 (16%)	0.78

* p value for age was from a chi-square test. For other variables they are from logistic regression models adjusting for age.

† Subjects had the option to select more than 1 category;

‡ Other includes American Indian/Alaskan Native, Native Hawaiian/Pacific Islander, Asian and other;

§ Category I (defensive back, wide receiver, kicker/punter, and Quarterback), category II (linebacker, running back, tight end), and category III (offensive line, defensive line);

¶ kilograms/meter^2;

** 110 former players reported currently smoking.

statistical significance. The rate of sleep apnea was also slightly elevated, but not significantly so. Hip joint replacement, diagnosed dementia, and stroke were not significantly associated with ACL tears (Table 2). We considered whether the association between ACL tear and MI was the result of effects of ACL tear on knee replacement or arthritis that then in turn increase the risk of MI. If so, then all players with knee replacement or arthritis should have the same risk of MI regardless of previous ACL tear history and we should not see an association between ACL injury and MI in this group. However, we found a similar association with ACL tear in analyses restricted to only those former players who were status post knee replacement or who had arthritis (n = 1,885; 464 ACL tears; 85 MI; HR 1.56; 95% CI 0.94, 2.56). Similarly, there was not much difference in the association between ACL injury and sleep apnea in those with knee replacement or arthritis (HR 1.11; 95% CI 0.90, 1.37) in main analysis models. ACL tears, and knee replacement, and/or arthritis were related to reporting of chronic pain medication use and physical activity at the time of the questionnaire. Those who had knee replacement surgery or arthritis were on average approximately 10 years older than those without knee replacement or arthritis, and reported more pain medication use, less physical activity, and slightly higher BMI than those without, regardless of ACL injury status (Table 3). In those with a history of knee replacement or arthritis there was no age difference by history of ACL injury. In those without knee replacement or arthritis, players with a previous ACL injury reported somewhat more pain medication use and less physical activity, but no difference in BMI, compared with those without ACL injury. Overall, former players who had torn their ACL were significantly more likely to have chronic pain and be treated for hypertension (Table 4). None of the other outcomes tested were significantly associated with ACL tears.

Discussion

We found an expected increased rate of arthritis and knee replacement surgery after ACL injury, an expected outcome that is consistent with previous studies.[8,9,13–15] Furthermore, the diagnosis of chronic pain in former NFL players with a history of ACL tear is not surprising and is likely secondary, in part, to osteoarthritis. More surprising, was the more than 50% increased rate of MI in players with ACL tear. Although this did not quite reach statistical significance, there were almost 4 times fewer MI cases than knee replacement cases, and more than 10 times fewer than arthritis cases, which results in less power to detect a significant association. Similarly, we found a slightly elevated rate of sleep apnea in those with an ACL injury that did not quite reach statistical significance. To our knowledge such associations have not been previously reported.

Other investigators have found significant associations between osteoarthritis and hypertension, diabetes, and depression.[8] Thus, the association between ACL injuries and MI could relate to effects of ACL on subsequent knee replacement or arthritis. However, we saw a similar,

Table 2
Hazard ratio (HR) for later life diagnoses or surgery in NFL former players who ruptured their ACL during their active playing careers compared with those who did not

Diagnoses/Surgery	n*	Age-adjusted only HR† (95% CI)	Main analysis HR‡ (95% CI)	p value
Knee joint replacement	430	2.20 (1.76 – 2.75)	2.07 (1.64 – 2.60)	<0.01
Arthritis	1783	1.54 (1.34 – 1.76)	1.53 (1.33 – 1.76)	<0.01
Myocardial infarction	118	1.46 (0.94 – 2.25)	1.52 (0.97 – 2.38)	0.07
Sleep apnea	777	1.18 (0.99 – 1.42)	1.15 (0.96 – 1.38)	0.13
Hip joint replacement	281	1.05 (0.77 – 1.42)	0.99 (0.73 – 1.36)	0.99
Dementia	123	1.10 (0.69 – 1.74)	1.08 (0.69 – 1.74)	0.76
Stroke	97	0.83 (0.48 – 1.42)	0.78 (0.44 – 1.38)	0.40

* Number of outcome cases out of a total of 3,506 former players.

† Adjusted for age only by including age as the time scale.

‡ Additionally adjusted for position, career length, and BMI during professional play.

Table 3
Current pain, exercise, BMI, and age for categories of ACL and knee joint replacement/arthritis

History of injury and surgery	n	Currently taking pain medications* n (%)	Current exercise (met-hrs/wk) median (25th, 75th %)	Current BMI mean (s.d.)	Age mean (s.d.)
Without knee replacement or arthritis					
No ACL injury	1,259	158/1231 (13%)	36 (16.8, 58.6)	30.7 (4.6)	47.7 (13.8)
ACL injury	217	36/205 (18%)	30.8 (11.5, 51.0)	30.8 (4.4)	47.1 (13.3)
With knee replacement or arthritis					
No ACL injury	1,278	516/1244 (41%)	25.8 (10.5, 43.8)	31.6 (5.2)	56.2 (13.3)
ACL injury	464	191/436 (44%)	25 (8.8, 40.3)	31.4 (5.0)	57.5 (12.9)

* Row percent compared with those not on pain medications for that category. Those not reporting medication use were excluded.

association between ACL and MI when analyzing only the group of players with knee replacement or arthritis (although with a wider confidence interval because of smaller numbers), which implies that there is an effect of ACL injury on MI that is independent of ACL injury effects on knee replacement or arthritis. Decreased exercise habits in players who tore their ACL could plausibly increase the risk of MI.[8,16] Exercise is associated with a reduced risk of depression and cardiovascular disease,[17,18] and a previous study in Swedish soccer players found decreased activity after ACL tears.[15] A true longitudinal follow-up study with physical activity collected over the course of follow-up will be needed to more completely address this issue. As there were no significant differences in current BMI by ACL tear history, it is unlikely that weight gain explains the increased risk of MI in those who tore their ACL. The increased prevalence of chronic pain, potentially resulting in increased inflammation, may contribute to the increase in nonmusculoskeletal co-morbidity. Former players with a history of ACL tears and resulting osteoarthritis and pain, may have a higher consumption of nonsteroidal anti-inflammatory drugs (NSAIDs). One NSAID in particular, rofecoxib, was reported to have been associated with increased risk of MI.[19,20] However, most of our respondents tore their ACLs well before rofecoxib was introduced in 1999. Furthermore, the drug was discontinued 10 years before our questionnaire being administered. In addition, other NSAIDs may in fact reduce the risk of MI particularly in patients with arthritis and inflammatory pain.[19,20] Therefore, while possible, the discovered association between past ACL tears and MI is unlikely accounted for solely by the use of NSAIDs. The association with arthritis, despite ACL reconstruction, may be due to several factors. While satisfactory biomechanical outcomes can be achieved through reconstructive surgery, there are likely differences between postoperative knee function and preinjury function. In addition, decreases in activity after injury may lead to physical deconditioning and weight gain, resulting in increased joint loading with weight bearing, 2 factors that are also associated with the development of osteoarthritis.[15,16] However, we did not see a significant difference in current BMI status in those with or without previous knee replacement or arthritis.

Our findings should be considered in light of their limitations. Former NFL players are a highly select group of elite athletes. Thus, while these findings could be of importance to anyone with an ACL injury, it will be important to confirm them in a more general population sample. In addition, although our cohort of former professional football players is large, at the time of this analysis it represented only about 30% of potentially contactable former players. As a result, the prevalence of medical conditions in our respondents may differ from the entire population of former NFL players; our findings should not be considered accurate representations of the prevalence of these medical conditions in all former NFL players. However, it is unlikely that this would have accounted for our findings of associations between ACL injury and health outcomes, as that would only occur if participation in our study was driven by a combination of ACL injury and the health outcomes. It is possible that some players tore their ACLs, but elected not to undergo surgery. This seems unlikely, however, as one could not resume football or other sports activities without an intact ACL mechanism.

In addition, all of the data thus far obtained is self-reported by questionnaire. ACL tears have such an impact on playing career that we believe players are more likely to accurate recall them. With regard to outcomes, data from both general populations and in football players on reporting of chronic illnesses suggest reasonably accurate reporting for our conditions of interest.[21,22] Additional evidence to this point is that the total number of ACL repairs reported

Table 4
Odds Ratios (OR) of being prescribed or recommended medications in athletes who ruptured their ACL compared with those who did not

Medications (prescribed or recommended)	n*	Age adjusted OR (95% CI)	Main analysis OR† (95%CI)	p value
Chronic pain	1973	1.66 (1.39 − 1.99)	1.70 (1.41 − 2.04)	<0.01
Hypertension	1325	1.23 (1.03 − 1.48)	1.20 (0.99 − 1.44)	0.06
Depression	720	1.17 (0.93 − 1.42)	1.16 (0.94 − 1.44)	0.16
Diabetes mellitus	313	1.14 (0.86 − 1.52)	1.11 (0.83 − 1.49)	0.48
Anxiety	742	1.08 (0.88 − 1.32)	1.03 (0.83 − 1.28)	0.77
Hypercholesterolemia	1214	1.01 (0.95 − 1.21)	0.97 (0.80 − 1.17)	0.75

* Number of outcome cases out of a total of 3,506 former players.
† Adjusted for age, position, career length, and BMI during professional play.

compares favorably with the estimates of such injuries, accounting for the number of our respondents and years included, reported by NFL team doctors over the period 1985 to 2013.[27–29] If our findings hold true in further studies, interventions to prevent the risk of MI, and sleep apnea might be considered for people who have torn their ACLs. For example, introducing nonimpact, nonweight bearing aerobic activity, such as swimming or bicycling, might allow those with post-traumatic osteoarthritis to obtain the health benefits associated with regular exercise while minimizing the impact to the knee joint and the pain associated with arthritis. In addition, enhanced screening for other risk factors for MI and sleep apnea could potentially identify those at highest risk, leading to interventions to prevent these outcomes.

In conclusion, our findings suggest that ACL injuries are associated with negative long-term health outcomes that may go beyond the musculoskeletal system, including MI. Efforts to prevent the increased risk of these outcomes in athletes who tear their ACLs should be considered and prospectively studied. For American football players specifically, successful efforts to reduce the incidence of ACL tears sustained during play would not only reduce the number of surgeries and time away from sport, but might also reduce the risk of longer term medical conditions associated with ACL tears.[23] As it is unlikely 100% of ACL injuries will be prevented in the foreseeable future, improving the surgical techniques available might decrease the risk of long-term outcomes, including osteoarthritis, that are associated with ACL tears.[24] Better methods for the treatment of post-traumatic osteoarthritis might also improve the health outcomes of patients who have already developed this condition after sustaining an ACL tear.[25] Finally, if these findings prove generalizable beyond professional football players, the public health and clinical implications would be substantial. There are currently more than a million football players in the US high schools alone. And ACL tears are common in soccer, basketball, gymnastics, lacrosse, and many other sports, with an increased incidence observed in female athletes.[26,27] Thus, future studies in such other populations are of great importance.

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Dr. A. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

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