

# Proprioception Analysis following Anterior Cruciate Ligament Reconstruction using Stabilometry: A Prospective, Longitudinal Study

# Análise de propriocepção por estabilometria após a reconstrução do ligamento cruzado anterior: Um estudo prospectivo e longitudinal

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Abstract C

**Objective** Commonly used methods for measuring proprioception have resulted in conflicting reports regarding knee proprioception with anterior cruciate ligament (ACL) rupture and the influence of ACL reconstruction.

**Methods** One hundred subjects (50 patients with radiologically and arthroscopically confirmed unilateral ACL rupture and 50 normal controls) were assessed with regards to proprioception using dynamic single-leg stance postural stabilometry. Instrumented knee ligament laxity and knee outcome scores were also measured. Of the 50 patients in the ACL group, 34 underwent reconstruction and were reassessed postoperatively. **Results** There was a significant proprioceptive deficiency in the ACL group compared with their contralateral knee (p < 0.001) and to the control group (p = 0.01). There was a significant improvement in knee proprioception following ACL reconstruction compared to preoperative findings (p = 0.003). There was no correlation between ligament laxity measurements and outcome scores. A significant correlation was found preoperatively between outcome scores and proprioception testing had a significant correlation (r = 0.46) with post-operative proprioception (p = 0.006).

#### **Keywords**

- anterior cruciate
   ligament
- mechanoreceptors
- ► proprioception
- stabilometry
- ► knee ligament laxity
- knee outcome scores

Commonly used methods for measuring procarionte have resulted in conflicting reports regarding knee proprioception with anterior

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**Conclusion** Patients with an ACL rupture had a proprioceptive deficit which improved following ligament reconstruction. Knee outcome scores had a better correlation with proprioception than ligament laxity. Proprioception may be a superior objective measure than ligament laxity in quantifying functional knee deficits and outcomes in patients with ACL ruptures.

Level of Evidence III Therapeutic Study; Prospective Longitudinal Case-Control Study.

ResumoObjetivoO objetivo deste estudo foi avaliar a propriocepção do joelho por meio de<br/>estabilometria em pacientes com ruptura do ligamento cruzado anterior (LCA) antes e<br/>depois da reconstrução e correlacionar esses achados a resultados de testes instru-<br/>mentados de lassidão ligamentar e desfechos clínicos.

**Métodos** A propriocepção de 100 indivíduos (50 pacientes com ruptura unilateral do LCA confirmada à radiologia e artroscopia e 50 controles normais) foi avaliada por estabilometria postural dinâmica em apoio unipodal. A lassidão ligamentar do joelho instrumentado e suas pontuações de desfechos também foram medidas. Dos 50 pacientes do grupo LCA, 34 foram submetidos à reconstrução e reavaliados no período pós-operatório.

**Resultados** O grupo LCA apresentou deficiência proprioceptiva significativa em relação ao joelho contralateral (p < 0,001) e ao grupo controle (p = 0,01). A propriocepção do joelho melhorou de maneira significativa após a reconstrução do LCA em relação aos achados pré-operatórios (p = 0,003). Não houve correlação entre as medidas de lassidão ligamentar e as pontuações de desfechos. Além disso, observamos uma correlação significativa entre as pontuações de desfechos e as medidas de propriocepção antes da cirurgia. Essa correlação não foi detectada no período pósoperatório. O teste pré-operatório de propriocepção teve correlação significativa (r = 0,46) com a propriocepção pós-operatória (p = 0,006).

**Conclusão** Os pacientes com ruptura do LCA apresentaram déficit proprioceptivo que melhorou após a reconstrução ligamentar. As pontuações de desfecho do joelho tiveram melhor correlação à propriocepção do que a lassidão ligamentar. A propriocepção pode ser uma medida objetiva superior à lassidão ligamentar na quantificação de déficits funcionais e desfechos do joelho em pacientes com ruptura do LCA

## Palavras-chave

- ligamento cruzado anterior
- mecanorreceptores
- ► propriocepção

de déficits funcionais e desfechos do joelho em pacientes com ruptura do LCA. Nível de Evidência III Estudo Terapêutico; Estudo de Caso-Controle Longitudinal Prospectivo.

## Introduction

The central nervous system receives a collective neural input from peripheral receptors found within joints, ligaments, tendons, muscles, and skin.<sup>1–4</sup> The anterior cruciate ligament (ACL) contains mechanoreceptors and free nerve endings. The latter are more abundant and function as nociceptors, reacting to joint inflammation and pain stimuli. The mechanoreceptors found in the ACL include Pacinian corpuscles (quick adapting receptors activated by compression and mediate kinesthesia), Ruffini endings, and Golgi tendon organs (slow adapting receptors activated by stretch and mediate joint position sense).<sup>4–6</sup> These receptors signal potentially harmful deformations of the ligaments and knee joint via proprioceptive feedback which constitutes the afferent arc input. Protective reflexes intended to resist the injurious movements, such as reflex muscular stabilization, are initiated via efferent responses (Hilton's law).<sup>6</sup>

In addition to its proprioceptive role, the ACL is the primary restraint to anterior tibial translation and a major secondary restraint to internal rotation, thereby contributing to the normal kinematics of the knee.<sup>7–10</sup> Rupture of the ACL can lead to mechanical instability resulting in pathological displacement of the tibia relative to the femur. This may give rise to progressive instability, which can result in meniscal tears and early arthritis.<sup>11–13</sup> ACL reconstruction can be performed in order to restore mechanical knee stability. Following reconstruction, there are some patients who have a persistent laxity on clinical examination but, nonetheless, return to their preinjury level of activities.

	ACL group	Control group	
	(n = 50)	(n = 50)	
Mean age (yrs) (SD)	30 (9)	25 (5)	
Male: female	36:14	35:15	
Injured knee (right: left)	24:26	-	
Mean height (m) (SD)	1.72 (0.1)	1.75 (0.1)	
Mean weight (kg) (SD)	78.1 (14.4)	76.1 (14.4)	
Mean BMI <sup>*</sup> (kg/m <sup>2</sup> ) (SD)	26.2 (3.8)	24.6 (3.4)	

#### Table 1 Demographics of subjects

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; SD, standard deviation.

There are also some patients who have a clinically stable knee postoperatively but remain unsatisfied and continue to perceive a feeling of instability in their knee. Proprioception testing may be a superior end-point of quantifying a successful outcome following ACL reconstruction than clinically observed ligament laxity testing.

We conducted a prospective longitudinal study analyzing knee proprioception using dynamic single-leg stance postural stabilometry. The primary aim of the study was to evaluate if a proprioceptive deficit exists in patients with ACL ruptures, either compared to their contralateral knee or to normal controls. The secondary aim of the study was to investigate if there was an improvement following ACL reconstruction if a preoperative proprioceptive deficit was present. The tertiary aim of the study was to assess if a correlation existed between proprioceptive function, instrumented ligament laxity testing, and clinical outcome measures.

### **Materials and Methods**

Full approval was received for the study from the Research Ethics Committee and the Research Governance Committee. All subjects signed informed consent forms to participate. This therapeutic study is a prospective longitudinal casecontrol study which formed part of the first author's doctorate thesis.

There was a total of 100 subjects recruited to the study. **-Table 1** shows their demographic details. The mean time from injury to clinic review for the ACL group was 63 weeks (SD = 59).  $\succ$  Fig. 1 shows the mechanism of injury of the ACL group. An ACL rupture was diagnosed by clinical history and examination as well as magnetic resonance imaging (MRI) scan of the injured knee for all patients in the ACL group. The diagnosis was confirmed at the time of knee arthroscopy. The patients in the ACL group had a normal contralateral knee confirmed by clinical history and examination. Fig. 2 illustrates the flow of the patients in the ACL group through the study. Four patients with delayed surgical intervention postponed their operation for personal reasons (i.e., work or university commitments). One patient was recruited to the ACL group and underwent all the assessments except for the proprioception analysis as the equipment was unavailable at the time of the patient's attendance. However, the data for the remaining assessments that they did undergo are still included in the relevant

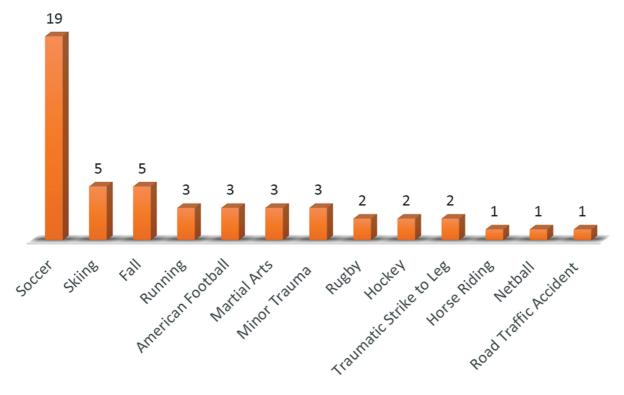


Fig. 1 Mechanism of injury ACL group (n = 50),

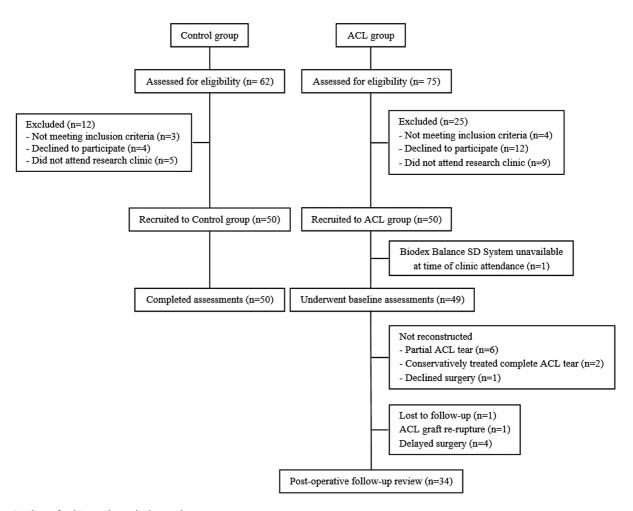


Fig. 2 Flow of subjects through the study.

sections. Of the 34 patients who underwent ACL reconstruction, 25 had an ipsilateral middle third bone-patella tendonbone autograft, and 9 had an ipsilateral quadrupled hamstring autograft. At the time of surgery in the ACL group, 11 patients were found to have a concomitant medial meniscal tear, 8 patients had a lateral meniscal tear, and 11 subjects had both a medial and a lateral meniscal tear. All patients with concurrent meniscal tears also underwent a partial meniscectomy. None of the patients had significant associated articular cartilage lesions. The mean time to follow-up was 14 weeks (SD = 4) following surgery.

**- Fig. 2** illustrates the flow of the subjects in the control group through the study. All the participants in the control group had normal knees confirmed by clinical history and examination of both knees as well as an MRI scan of one knee. The control group data was also used as the normal controls in other published studies.<sup>14,15</sup>

Subjects who were 16 to 45 years of age were included. Participants were excluded from the study if there was a concomitant posterior cruciate ligament (PCL), medial collateral ligament (MCL) or lateral collateral ligament (LCL) tear of the knee, significant history of ankle or hip pathology, lumbar spine symptoms (including radiculopathy in either limb), neurological or vestibular disease, diabetes, or regular

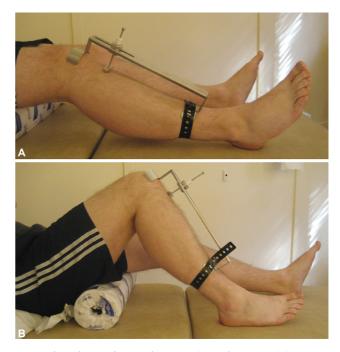


Fig. 3 The Rolimeter knee arthrometer (A) Lachman test (B) Anterior drawer test.



Fig. 4 Single-leg stance postural stability testing using the Biodex Balance SD System.

use of opiate analgesics. In addition, subjects were excluded from the control group if there was a significant history of any knee pathology.

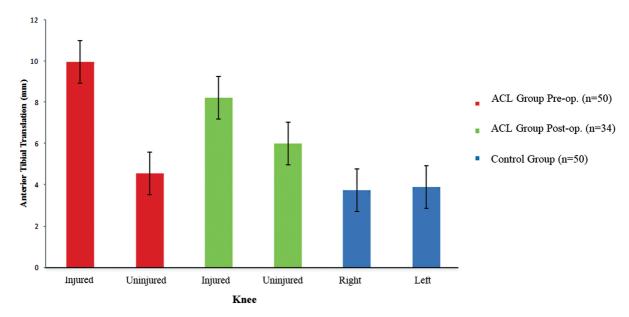
The Rolimeter knee arthrometer (Aircast Incorporated, Summit, NJ, USA) was used to measure quantitatively the anterior displacement of the tibia relative to the femur of both knees in both groups. The maximum manual instrumented test was used to measure ligament laxity in both the Lachman test (20° knee flexion) and the anterior drawer test (90° knee flexion) (**~ Fig. 3**). The registered anterior displacement (in mm) was used for statistical analysis.

All subjects of both groups were assessed using the Tegner activity score<sup>16</sup> and the Lysholm knee score.<sup>16</sup>

The Biodex Balance SD System (Biodex Medical Systems Incorporated, Shirley, NY, USA) was used to quantitatively measure postural stability (**~Fig. 4**). It has been validated for its use in assessing dynamic single-leg postural stability.<sup>17–19</sup> Stabilometry is an accepted method of measuring proprioception in the ACL deficient knee.<sup>20,21</sup> The Biodex Balance SD System consists of a multiaxial moveable platform which computes an output in the form of an overall stability index (OSI). A low score indicates that the subject has good postural stability (and, therefore, good proprioception), and a high score reflects poorer stability and proprioception. Each leg in all the participants (in bare feet) was assessed 3 times for a duration of 20 seconds for each test period. The computer output for each leg was calculated from the average of the three tests. The mean OSI result was used as the quantitative measure of proprioception for the purpose of statistical analyses.

## **Statistical Analysis**

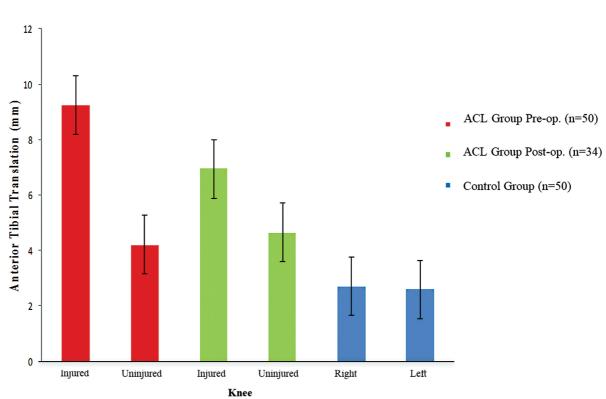
A *post-hoc* power calculation for this study was derived from the results of the longitudinal within-group analysis of the ACL group injured knee log (OSI) (primary outcome) as detailed in **~Table 4**. The sample size of 34 subjects based on a conventional type I error of 5% with a within-group mean difference of 0.23 and a within-group standard deviation of 0.40 yielded a statistical power calculation of 90.2% for this study. All data variables for both groups displayed a normal distribution (verified by both plotted histograms and the Shapiro-Wilks test) except for the OSI measurements (negatively skewed distribution). Data transformation was



Lachman Test

Fig. 5 Instrumented ligament laxity measurement for the Lachman test displaying means and standard errors.

implemented using the natural logarithm following which the log (OSI) data demonstrated a normal distribution and was used for the purposes of statistical calculations using the appropriate parametric tests. The level of statistical significance was set at p < 0.05. Statistical analysis was performed using the SPSS for Windows, version 25.0 (IBM Corp.,



**Anterior Drawer Test** 

Fig. 6 Instrumented ligament laxity measurement for the anterior drawer test displaying means and standard errors.

	Uninjured knee <sup>a</sup>	Control group <sup>b</sup>	Injured knee postop <sup>a</sup>	
	p-value (95%CI)	p-value (95%CI)	p-value (95%CI)	
Lachman				
Injured knee preop.	< 0.001* (4.6, 6.2)	< 0.001* (5.2, 7.3)	< 0.001* (1.0, 2.5)	
Injured knee postop.	< 0.001* (1.4, 3.1)	< 0.001* (3.7, 5.4)	-	
Anterior Drawer				
Injured knee preop.	< 0.001* (4.3, 5.8)	< 0.001* (5.4, 7.8)	0.001* (0.9, 3.3)	
Injured knee postop.	< 0.001* (1.5, 3.1)	< 0.001* (3.4, 5.2)	_	

 Table 2
 Statistical analysis of instrumented ligament laxity measurements

Abbreviation: 95% CI, 95% confidence interval.

<sup>a</sup>Within-group comparison; paired Student t-test

<sup>b</sup>Between-group comparison; independent-sample Student *t*-test

\*Statistically significant at <0.05 level

Table 3 ACL group knee outcome scores

	Preoperative	Postoperative	p-value <sup>a</sup> (95% CI)	
	Mean (SD)	Mean (SD)		
Lysholm	71.7 (12.8)	85.3 (10.5)	< 0.001 (8,18–19,18)	
Tegner	3.3 (1.2)	4.1 (0.2)	0.006 (0,23–1,28)	
	Preinjury	Postoperative		
Tegner	6.7 (1.3)	4.1 (0.2)	< 0.001 (2,11–3,31)	

Abbreviations: 95% CI, 95% confidence interval; SD, standard deviation. <sup>a</sup>Within-group comparison; paired Student *t*-test

\*Statistically significant at p < 0.05 level

Armonk, NY, USA). The power calculation was performed using the Minitab statistical software version 19 (Minitab LLC, State College, PA, USA).

### Results

► Figs. 5 and 6 illustrate the findings of the instrumented ligament laxity measurements of both the Lachman test and the anterior drawer test respectively, and ► Table 2 shows the results of their statistical analyses. There was no significant difference between the right and left knees of the control group for either the Lachman test (p = 0.53; 95% CI -0.50, 0.26) or the anterior drawer test (p = 0.32; 95% CI -0.10, 0.30). There was a significant difference of both tests when comparing the injured knee of the ACL group preoperatively to their uninjured knee of the ACL group showed a significant improvement compared to preoperative findings but still had a significant difference compared to their uninjured knee and the control group.

**- Table 3** shows the results of the knee outcome scores for the ACL group. There was a significant improvement post-operatively of both the Tegner activity score and the Lysholm score. A significant difference persisted between the preinjury and postoperative Tegner activity scores.

► **Table 4** shows the proprioception measurements for the ACL and the control groups. The results of their statistical analyses are shown in **► Table 5**. There was no significant difference found between the right and left knees of the control group (p = 0.42; 95% CI -0.04, 0.10). There was no significant difference found of the uninjured knee in the ACL group between preoperative and postoperative results (p = 0.28; 95% CI -0.05, 0.19). There was a statistically

**Table 4** Means and standard deviations of stabilometry measurements (log [OSI])

Group	Mean (SD)	
ACL group preoperatively ( $n = 49$ )		
Injured knee	0.70 (0.45)	
Uninjured knee	0.46 (0.35)	
ACL Group postoperatively (n $=$ 34)		
Injured knee	0.47 (0.40)	
Uninjured knee	0.42 (0.39)	
Control group (n = 50)		
Right knee	0.49 (0.35)	
Left knee	0.52 (0.34)	

Abbreviations: OSI, overall stability index; SD, standard deviation.

	Uninjured knee <sup>a</sup>	Control group <sup>b</sup>	Injured knee postop <sup>a</sup>	
	p-value (95%CI)	p-value (95%CI)	p-value (95%CI)	
Injured knee preop.	< 0.001* (0.14, 0.34)	0.01* (0.05, 0.38)	0.003* (0.10, 0.42)	
Uninjured knee	_	0.73 (-0.16, 0.12)	—	
Injured knee postop.	0.25 (-0.03, 0.13)	0.85 (-0.18, 0.15)	—	

Table 5 Statistical analysis of stabilometry measurements (log [OSI])

Abbreviations: 95% CI, 95% confidence interval; OSI, overall stability index.

<sup>a</sup>Within-group comparison; paired Student t-test

<sup>b</sup>Between-group comparison; independent-sample Student *t*-test

\*Statistically significant at p < 0.05 level

**Table 6** Correlations between knee outcome scores, stabilometry and instrumented ligament laxity measurements of the injured knee of the ACL group

	<i>Pre</i> operative			Postoperative		
	Log (OSI)	Lachman	Anterior drawer	log (OSI)	Lachman	Anterior drawer
	r / p-value <sup>a</sup>	r / <i>p</i> -value <sup>a</sup>	r / p-value <sup>a</sup>	r / p-value <sup>a</sup>	r / <i>p</i> -value <sup>a</sup>	r / p-value <sup>a</sup>
	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI
Lachman	0.07 / 0.630			-0.24 / 0.180		
	(-0.22, 0.34)			(-0.53, 0.11)		
Anterior drawer	-0.07 / 0.640			0.09 / 0.620		
	(-0.34, 0.22)			(-0.26, 0.42)		
Tegner	-0.42 / 0.003*	0.02 / 0.890	0.13 / 0.370	-0.12 / 0.500	-0.19 / 0.2900	-0.15 / 0.4200
	(-0.63, -0.16)	(-0.27, 0.30)	(-0.16, 0.40)	(-0.44, 0.23)	(-0.50, 0.16)	(-0.46, 0.20)
Lysholm	-0.35 / 0.016*	-0.25 / 0.090	-0.20 / 0.180	-0.09 / 0.610	-0.22 / 0.230	-0.02 / 0.920
	(-0.58, -0.07)	(-0.50, 0.04)	(-0.46, 0.09)	(-0.42, 0.26)	(-0.52, 0.13)	(-0.36, 0.32)

Abbreviations: 95% CI, 95% confidence interval; OSI, overall stability index.

<sup>a</sup>Pearson product moment correlation analyses.

\*Statistically significant at p < 0.05 level.

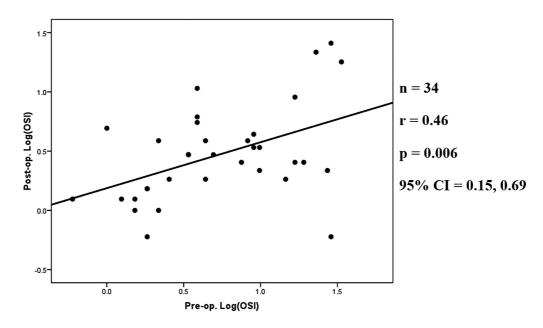
significant difference between the injured knee of the ACL group preoperatively when compared to their uninjured knee and also to the control group. There was no significant difference found between the uninjured knees of the ACL and the control groups. There was a statistically significant improvement in proprioception of the injured knee in the ACL group compared to preoperative findings following ACL reconstruction, to the extent that no significant difference was found between their operated knee and either their uninjured knee or the control group.

• **Table 6** shows the results of the Pearson correlation analyses between knee outcome scores, stabilometry and ligament laxity measurements of the injured knee of the ACL group. Preoperatively, proprioception measurements had a significant (inversely proportional) correlation with both knee outcome scores. A higher knee outcome score (i.e., better function) was associated with a lower log (OSI) score (i.e., good proprioception). There was no significant correlation between ligament laxity measurements and proprioception. Postoperatively, there were no statistically significant correlations between any of these variables. **- Fig. 7** illustrates the scatterplot of the Pearson correlation analyses comparing pre and postoperative proprioception measurements of the injured knee of the ACL group. A significant (directly proportional) correlation was found demonstrating that low preoperative log (OSI) scores were associated with low postoperative log (OSI) scores.

### Discussion

The results of this study found that there is a significant proprioceptive deficit as measured by dynamic single-leg postural stabilometry in patients with an ACL rupture as compared to their contralateral uninjured knee and to normal controls. ACL reconstruction significantly improved proprioception to the level of normal controls. We found no significant difference in proprioception between the uninjured knee of the ACL group and that of the control group. Clinical outcome measures were found to have a better correlation with proprioception than with instrumented ligament laxity testing.

Beard et al.<sup>22</sup> defined proprioception into three components; joint position sense (static awareness of joint position in space), kinesthesia (detection of joint movement and



**Fig. 7** Pearson product moment correlation analysis of proprioception measurements of the injured knee of the ACL group before and after reconstruction.

acceleration), and the efferent closed-loop reflex which regulates muscle stiffness. The complex interactions between the afferent sensory and the efferent motor pathways are collectively referred to as the sensorimotor system.<sup>20</sup> The present study measured proprioception using dynamic single-leg postural stabilometry, which assesses both the afferent and the efferent neuromuscular pathways.<sup>23</sup> This has the advantage of assessing proprioception whilst the subjects are balancing upright and is a more dynamic technique than the joint position sense (JPS) or threshold to detection of passive movement (TDPM) testing methods, in which the subjects are in the seated position.

The present study found a significant improvement of proprioceptive function at an average of 14 weeks (approximately 3 months) following surgery. In other studies, Iwasa et al.<sup>24</sup> showed that proprioception did not recover fully until 18 months after reconstruction, Fremerey et al.<sup>2</sup> showed that proprioceptive recovery occurred 6 months after surgery while Reider et al.<sup>4</sup> demonstrated an improvement of TDPM as compared to preoperative values as early as 6 weeks following reconstruction. Graft reinnervation alone is unlikely to explain a proprioceptive improvement as soon as 3 months after surgery in the present study. A more probable explanation would be that ACL reconstruction provides a static restraint and, thereby, improves the abnormal relationship between the femur and the tibia (i.e., abnormal knee kinematics) that exists in the ACL deficient knee. This, in turn, reduces the abnormal neural output from the joint capsule and the remaining ligaments and intraarticular structures of the knee.<sup>4,24</sup>

There was a significant improvement in ligament laxity measurements following ACL reconstruction, but a significant difference remained as compared to their contralateral uninjured knee and to normal controls. The present study found a significant improvement of both validated knee outcome scores when the ACL group were reassessed 3 months following surgery. Preoperatively, proprioception measurements were found to have a significant correlation with both knees' outcome scores. There was no significant correlation between the proprioception results and the instrumented ligament laxity measurements. Ligament laxity had no correlation with either of the knee outcome scores. This shows that proprioception is a better objective measure of knee impairment and perceived functional stability than ligament laxity testing. Barrett<sup>11</sup> demonstrated that proprioception measured using JPS testing methods correlated well with functional outcome and patient satisfaction and poorly with clinical ligament testing.

However, postoperatively, proprioception had no significant correlation with any of the outcome scores or ligament laxity measurements. An explanation for this is that the outcome scores ask questions relating not only to activities of daily living, which the patients may return to relatively early after surgery (such as walking and returning to work), but also to running, sprinting, activities which involve cutting movements, and return to competitive sport. Following an ACL reconstruction, patients undergo a structured rehabilitation program which involves a gradual increase in activity levels. Indeed, returning to full contact sport is prohibited until 9 months after surgery, in the study's host. These aspects will have a bearing on the answers that subjects can give to certain items in the outcome scores. Furthermore, a significant difference between the preinjury and postoperative Tegner activity score was noted. Therefore, a correlation may indeed exist between postoperative proprioception and the knee outcome scores, but the analyses may have been obscured by the activity limiting restrictions which were imposed on the patients at the early stages following their surgery. A correlation analysis performed 9 months or later after surgery may have yielded a different result.

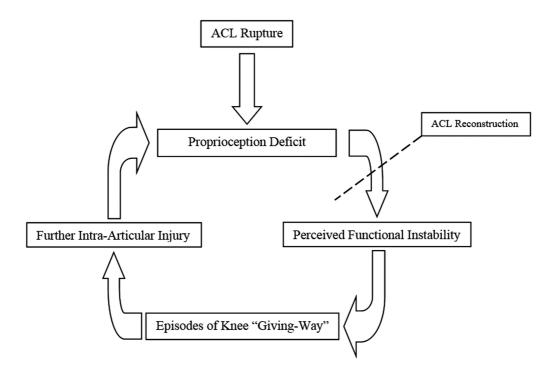


Fig. 8 The knee injury cycle. ACL reconstruction aims to improve proprioception and thereby interrupt the cycle.

There was a significant correlation between pre and postoperative proprioception measurements. This relationship can help inform the surgeon that patients with an ACL rupture and a good level of proprioceptive function prior to surgery are likely to have a good functional outcome following an ACL reconstruction. Conversely, a patient with a poor level of proprioceptive function prior to surgery is less likely to have as good a postoperative functional outcome. The contrary can also be argued, that patients who have a good level of proprioception following an ACL rupture maybe better candidates for conservative treatment. The secondary stabilizers in their knee maybe sufficient to allow satisfactory progress with a structured rehabilitation program back to a premorbid level of sporting activity. Similarly, patients who have poor preoperative proprioceptive acuity may require reconstructive surgery in order to protect the remaining intact structures of the knee which are providing a degree of proprioceptive input and prevent any further decline in this respect. - Fig. 8 summarizes the concept of proprioceptive deficits leading to further knee injuries and the impact that an ACL reconstruction has in preventing further functional decline.

The weaknesses of this study include the length of time for the follow-up review following surgery (approximately 3 months) and the number of subjects (16 patients) in the ACL group that did not return for their postoperative assessment. There is also the possibility that the structured rehabilitation program undertaken by the subjects postoperatively may have played a significant role in the proprioceptive improvement.

## Conclusion

The present study showed a significant proprioceptive deficit as measured by dynamic single-leg postural stabilometry in patients with an ACL rupture that improved following ligament reconstruction. The proprioceptive acuity of the uninjured contralateral knee was similar to that of normal controls and is, therefore, an adequate comparator for proprioception. Knee outcome scores had a better correlation with proprioception analysis than instrumented ligament laxity measurements.

#### **Financial Support**

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#### **Conflict of Interests**

The authors have no conflict of interests to declare.

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