Factors Contributing to Function of the Knee Joint after Injury or Reconstruction of the Anterior Cruciate Ligament*†

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Restoration of musculoskeletal function is a fundamental goal of orthopaedic treatment. Until now, clinical orthopaedic concepts of injury, repair, and restoration of function of musculoskeletal systems have been described and understood primarily in structural and biomechanical terms. This perception probably evolved because the structural characteristics are the most readily visualized factors, both in the clinical setting (for example, pathological laxity due to a ruptured ligament or a fracture) and through the preponderance of structural and pathoanatomical data offered by most current imaging modalities. Structural characteristics are also the factors most directly altered by operative intervention, such as stability following repair or reconstruction of a ligament or fixation of a fracture. It is a common belief that the restoration of measurable structural and biomechanical parameters to an injured joint, such as the knee, indicates the restoration of function to that system. We do not share this view.

In the past few years, emerging clinical and basic-science findings have indicated a much greater degree of underlying biological complexity. Evidence suggests that the correction of identifiable structural abnormalities is often not sufficient to restore a joint to its full preinjury level of physiological function. For example, replacement of a ruptured anterior cruciate ligament with a graft does not necessarily prevent pain, swelling, or degenerative changes in the knee, even if the increased anterior-posterior laxity that had been present before the procedure is restored to normal. This observation indicates that factors other than anatomical and structural ones probably contribute to the restoration of joint function after injury. We believe that, although these other factors are less easily visualized, they play an important role in the ultimate functional status of an injured musculoskeletal system, such as the knee. The purpose of this Instructional Course Lecture is to discuss the concept of musculoskeletal function and to consider the various factors that contribute to the restoration of knee function after injury or reconstruction of the anterior cruciate ligament.

Restoration of Knee Function after Injury or Reconstruction of the Anterior Cruciate Ligament

Reconstruction of the anterior cruciate ligament is one of the most commonly performed orthopaedic procedures in the technologically advanced countries of the world. The primary goal of the reconstruction is to restore stability to the knee and thereby, presumably, to restore its function and allow the patient to return to normal activities, including sports. Another goal is to prevent early degenerative changes. In order to achieve these goals, the immediate objective of the operation is to reduce abnormal laxity by substituting the injured anterior cruciate ligament with a graft. Current methods for the objective assessment of the success of such reconstructive procedures most often involve evaluation of structural and biomechanical parameters, such as knee laxity as measured with instrumented testing and degenerative changes as estimated on plain radiographs.

Daniel et al.[10] used a metabolic study (technetium

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bone scintigraphy) as well as a structural study (plain radiography) to assess the development of degenerative changes in patients who had sustained an acute traumatic hemarthrosis of the knee. Although it was non-randomized, their prospective study included a large number of patients who had an injury of the anterior cruciate ligament and had been managed non-operatively or with early or delayed operative reconstruction. The study also included patients in whom the knee was stable on instrumented testing and who were thus presumed to have a normal anterior cruciate ligament or only a partial tear. A disturbing finding of that study was that reconstruction of the anterior cruciate ligament did not prevent the development of early degenerative changes in the knee despite the fact that ligamentous stability had been restored. In fact, five years after the injury the reconstructed knees showed markedly greater degenerative changes on technetium scintiscans and standard radiographs than did those that had been treated non-operatively.

Follow-up studies by Daniel and coworkers[9,25] revealed that, an average of ten years after the injury, the reconstructed knees continued to show greater degenerative changes on plain radiographs than did those that had been treated non-operatively. This was attributed, in part, to the higher prevalence of operations involving the meniscus among patients who had a reconstruction. However, even when the knees that had had a meniscal procedure were excluded, more degenerative changes were seen in the reconstructed knees than in the knees that had been treated non-operatively. It should be noted that the reconstructive procedures were of an earlier era and included open techniques followed by a period of immobilization. Nevertheless, the results indicate that an operative procedure, which may restore mechanical normalcy, does not necessarily resolve all of the problems caused by associated pathological changes resulting from the original or subsequent trauma and, indeed, can represent an additional insult to the knee.

The main focus of ongoing work directed by one of us (D. C. F.) has been the analysis of patients with unstable knees who decide not to have operative treatment of the anterior cruciate ligament[25]. In that study, the anterior-posterior laxity of the knee, which was used as an indicator of the structural integrity of the anterior cruciate ligament, was measured with the KT-1000 device developed by Daniel et al.[10]. The early laxity grade was found to be predictive of the later laxity grade in knees that were not reconstructed[25]. Of fifty-three patients in whom the knee was classified as stable initially, forty-eight (91 per cent) had a stable knee ten years later. Of 111 patients in whom the knee was classified as unstable initially and who did not have a reconstruction, ninety-three (84 per cent) had an unstable knee ten years later. Despite the instability, less degenerative change was evident on the follow-up radiographs and bone scintiscans of these patients than on those of eighty-four patients in whom the ligament had been reconstructed. The activity level at the time of follow-up was similar for the patients who had had a reconstruction and those who had not had a reconstruction, and it was decreased in both groups compared with the level before the injury. The patients who had had a reconstruction had the greatest percentage reduction in the total number of hours of participation in sports. The changes in activity level, however, may have been made according to lifestyle choices that were unrelated to the functional capacity of the knee. The findings of the studies by Fithian[25] and by Daniel et al.[10] confirm that knees may remain free of degenerative changes in the presence of abnormal laxity secondary to injury of the anterior cruciate ligament and that the restoration of certain mechanical characteristics is not sufficient to restore the preinjury level of physiological function.

In a review of the literature regarding reconstruction of the anterior cruciate ligament[38], one of us (J. G.) noted a trend toward a high prevalence of good or excellent results ranging from 66 per cent (forty-five of sixty-eight) to 90 per cent (thirty-seven of forty-one)[1,3,5,9,10,28,46,50,54,64,66,71,74]. However, none of the investigators, with the exception of Daniel et al.[10], analyzed the outcomes of operative treatment relative to the results of non-operative treatment with a metabolic study in a large number of knees that had an injured anterior cruciate ligament. Gillquist also observed that perhaps the only effect of reconstruction of the anterior cruciate ligament in some individuals was to “give the patient enough security to go back to strenuous sports, and then [ruin] the knee.” The results of the study by Daniel et al. and the observations by Gillquist, along with the experience of many orthopaedic surgeons, belie a current recommendation in the international sports-medicine community that patients who have reconstruction of the anterior cruciate ligament should be encouraged to return to sports, particularly the sport during which the index injury occurred. Frank and Jackson[27], in a comprehensive review of the current state of reconstruction of the anterior cruciate ligament, observed that few reconstructed knees are returned to normal and that no normal ligaments are being created operatively.

Concept of Joint Function

This apparent lack of full functional restoration after injury of the anterior cruciate ligament is a cause for concern. Much of what may be considered important regarding the lack of restoration of joint function is derived from one’s concept of the meaning of the term joint function. Function can be defined as the purpose for which an entity is specially fit[79]. A concept of joint function proposed by the senior one of us (S. F. D.)[15] in 1996 is that joints are systems that are designed to transmit mechanical loads between components and yet, by virtue of the fact that they are living structures, to main-

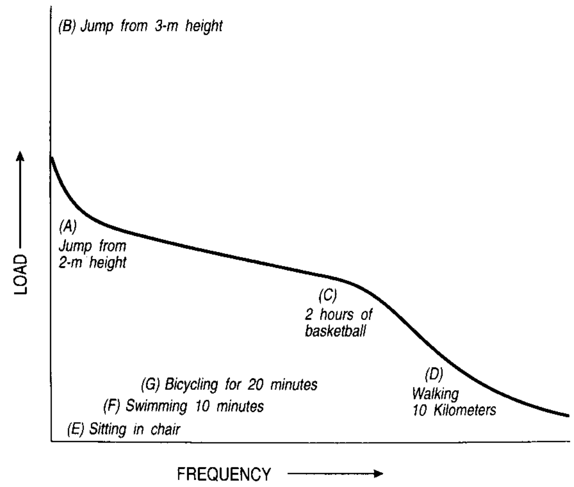

FIG. 1

Graph representing the envelope of function[15] for an athletically active young adult. The letters represent the loads associated with different activities. All of the loading examples, except *B*, are within the envelope for this particular knee. The shape of the envelope of function represented here is an idealized theoretical model. The actual loads transmitted across an individual knee under these different conditions are variable and are due to multiple complex factors, including the dynamic center of gravity, the rate of load application, and the angles of flexion and rotation. The limits of the envelope of function for the joint of an actual patient are probably more complex. (Reprinted, with permission, from: Dye, S. F.: The knee as a biologic transmission with an envelope of function. A theory. Clin. Orthop., 325: 12, 1996.)

tain tissue homeostasis over a broad range of physical demands. In mechanical engineering, systems that are designed to transfer loads differentially between components are called transmissions. The knee can thus be viewed as a kind of living, metabolically active, biological transmission whose function is to accept and redirect loads between and among the femur, tibia, patella, and fibula[15]. The cruciate ligaments in this analogy can be seen as non-rigid, sensate adaptive linkages within the transmission. The articular cartilages can be viewed as bearings and the menisci, as mobile sensate bearings[22] within the transmission. The muscles act not only as cellular engines that provide motive forces across the knee in concentric contraction but also as brakes and dampening systems that absorb shock loads in eccentric contraction[15]. Winter[80] revealed that the muscles about the knee actually absorb more than three times the energy that is generated in motive forces. The various components of a living joint are constantly metabolically active, with complex molecular and cellular mechanisms that are designed to maintain and restore tissue homeostasis under normal and injurious biomechanical conditions[45]. In our view, the concept of musculoskeletal function includes the capacity not only to generate, transmit, absorb, and dissipate loads but also to maintain tissue homeostasis while doing so.

Envelope of Function

The envelope of function[15] is a concept that was developed by the senior one of us as a simple method that incorporates and connects the concepts of load transference and tissue homeostasis in order to visually represent the functional capacity of the knee. It defines a range of loading that is compatible with, and probably inductive of, the overall tissue homeostasis of a given joint or musculoskeletal system. The concept, in its simplest form, is a load and frequency distribution that defines a safe range of loading (the envelope of function) for a given joint[15] (Fig. 1). The upper limit of the envelope represents a threshold between loads that are compatible with tissue homeostasis and loads that initiate the complex biological cascade of trauma-induced inflammation and repair (Fig. 2). The area within the envelope is the zone of homeostasis or the zone of homeostatic loading. Loads that are beyond the threshold of the envelope but are lower than those that induce macrostructural failure of a component are in the area that can be termed the zone of supraphysiological overload. Loading in this region can cause, for example, the painful osseous remodeling associated with the initial stages of a stress fracture, which is evident as increased activity on technetium scintiscans before any structural changes are noted on radiographs. These sites of increased osseous metabolic activity may return to homeostasis, as documented by normal scintigraphic activity, following non-operative treatment primarily involving a reduction of loading. If more energy is placed across a joint, a second threshold is reached: the lower limit of the zone of structural failure. Such high loads result in overt macrostructural failure of at least one component of a joint

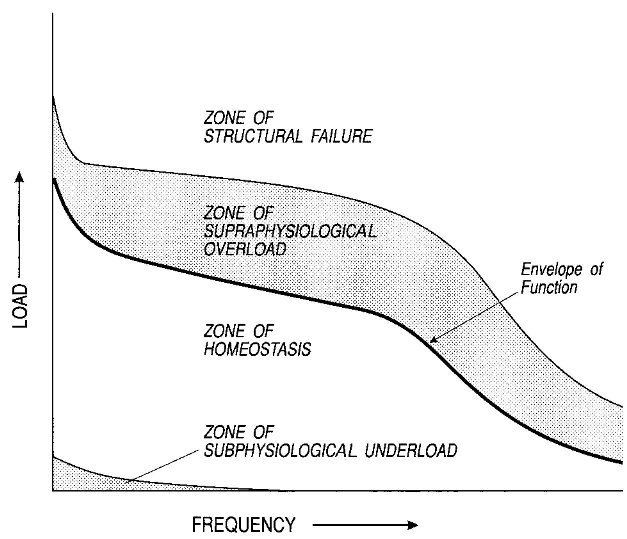

FIG. 2

Graph showing the four different zones of loading across a joint. The area within the envelope of function is the zone of homeostasis. The region of loading greater than that within the envelope of function but insufficient to cause macrostructural damage is the zone of supraphysiological overload. The region of loading great enough to cause macrostructural damage is the zone of structural failure. The region of decreased loading over time resulting in a loss of tissue homeostasis is the zone of subphysiological underload. (Adapted from: Dye, S. F.: The knee as a biologic transmission with an envelope of function. A theory. Clin. Orthop., 325: 13, 1996. Reprinted with permission.)

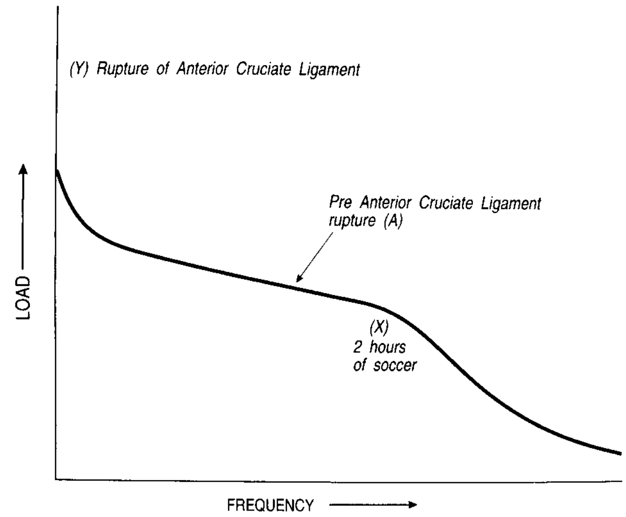

FIG. 3-A

Figs. 3-A through 3-D: Graphs demonstrating the dynamic character of the envelope of function of a knee with a rupture of the anterior cruciate ligament. (Reprinted, with permission, from: Dye, S. F.: The knee as a biologic transmission with an envelope of function. A theory. Clin. Orthop., 325: 14, 1996.)

Fig. 3-A: The preinjury envelope of function. Loading event X represents two hours of soccer and is within the preinjury envelope. Loading event Y represents a single load that is great enough to cause an acute rupture of the anterior cruciate ligament.

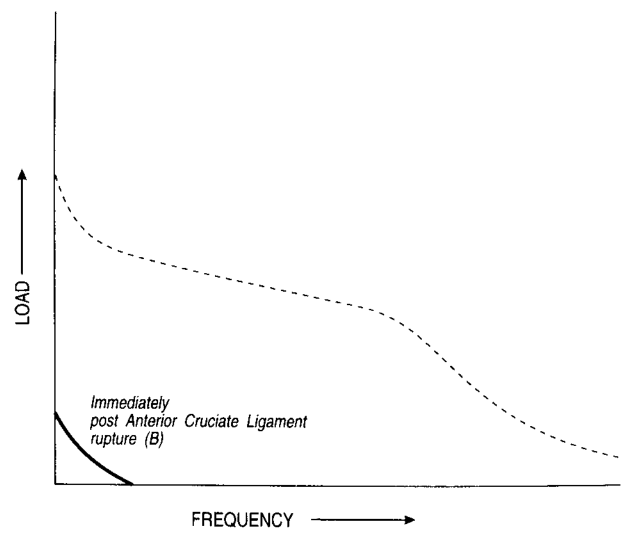

FIG. 3-B

The envelope of function immediately after rupture of the anterior cruciate ligament.

or musculoskeletal system, such as a rupture of the anterior cruciate ligament or a fracture of the tibial plateau. A lengthy period of decreased loading, such as may be associated with prolonged bed rest or extended space travel in a microgravity environment, can result in a loss of homeostasis as evidenced by osteopenia and muscle atrophy. This lower-threshold limit demarcates the zone of subphysiological underload. We believe that most, if not all, musculoskeletal systems respond to differential loading as depicted in these four regions.

Frost's extensive work[29-36] regarding homeostatic properties and principles of musculoskeletal tissues, particularly bone, independently corroborates and complements the concept of the envelope of function. Frost's view of excessive microdamage corresponds to the loading of tissues within the zone of supraphysiological overload. Too little loading over time, which results in disuse osteopenia, is reflected in his concept of minimum effective strain, or minimum effective signal, as a lower-threshold limit.

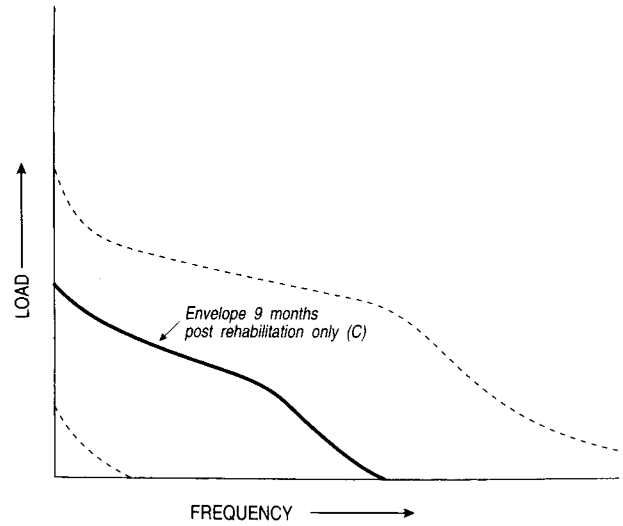

FIG. 3-C

The envelope of function nine months after treatment with a rehabilitation program alone. The envelope has broadened sufficiently to include most activities of daily living and certain low-impact sports, such as bicycling.

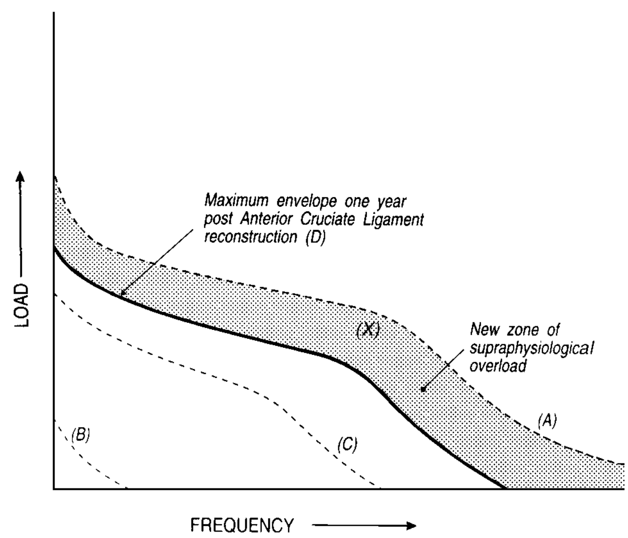

FIG. 3-D

The envelope of function one year after reconstruction of the anterior cruciate ligament and postoperative rehabilitation. The envelope has not been fully restored to the preinjury status. The area between the postoperative and preinjury envelopes represents a new zone of supraphysiological overload, which potentially extends to a zone of structural failure. If a patient returns to previous high-impact loading (X), which is now outside the postoperative envelope of function, the knee will be at risk for early degenerative changes and structural failure of the graft.

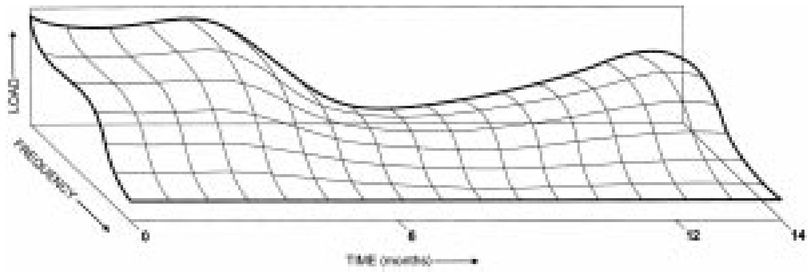

FIG. 4

A three-dimensional representation of the dynamic changes in the envelope of function of an idealized injured joint with time. The variable of time, from zero to fourteen months, has been added on a third, Z, axis. The downward slope of the undulations in the envelope represents diminished load-acceptance capacity after injury, while the upward slope of the undulations represents increased capacity due to healing of joint and neuromuscular tissues. In this case, the maximum capacity has not returned to normal by fourteen months.

The capacity of a knee to transfer loads safely can vary greatly after injury of the anterior cruciate ligament. Different envelope shapes can represent these changing capacities. An idealized preinjury normal envelope of function for a soccer player, for example, can be represented graphically (Fig. 3-A). A single high-load event, such as one causing acute rupture of the anterior cruciate ligament, can result in marked and immediate diminution of the envelope of that knee (Fig. 3-B). With time and rehabilitation alone, the function of many knees may be partially restored to a level that is sufficient for the patient to participate in activities of daily living, swimming, and bicycling and that may be compatible with tissue homeostasis (Fig. 3-C). We believe that this restoration is probably to a large degree a result of the effect of complex neuromuscular mechanisms providing improved dynamic control of the injured knee, which can be achieved through training and conditioning, despite the absence of the linkage provided by the anterior cruciate ligament. However, it is possible that only a certain additional percentage of the preinjury envelope of function can be restored by reconstruction in such a patient because the reconstruction may not correct all of the pathological changes in the joint (Fig. 3-D). These changes often include damage of subchondral bone, articular cartilage, and menisci; synovitis; and injury of the components of the neuromuscular system and other static restraints. Thus, if the patient is encouraged to resume high-stress sports activity, the injured knee may be forced into its new lower zone of supraphysiological overload. Such loading could result in increased subchondral microosseous remodeling that is detectable scintigraphically in the presence of normal radiographic findings. If left unchecked, this process may eventually lead to overt degenerative changes. This sequence of changes in the functional envelope of an idealized knee after injury of the anterior cruciate ligament provides a rational explanation for the findings of Daniel et al.[10] and Gillquist[38] as well as the observations of many practicing orthopaedic surgeons that are not explained from a purely structural and biomechanical perspective.

The envelope of function[15] can also be represented in three mathematical dimensions or more by the addition of other variables, such as time or the degree of flexion (Fig. 4).

Factors Contributing to Joint Function

In addition to the general factors of age, gender, and nutrition, we believe that several categories of factors contribute to the functional capacity of any joint. Although many different methods could be devised to organize all of the possible factors and there may be factors that have not yet been determined, we have found it logical and useful, especially from a clinical perspective, to consider four categories of factors: anatomical, kinematic, physiological, and treatment.

Anatomical Factors

Anatomical factors in joint function include the macromorphology and micromorphology, the resultant structural integrity, and the biomechanical characteristics of all components. In the knee, these include the ligaments, tendons, retinacula, muscles, menisci, articular cartilage, nerves, vessels, and bone. The alignment of the limb and the height and weight of the individual must also be considered. It is clear, from a review of the literature regarding the current state of anatomical restoration of the anterior cruciate ligament after injury, that normal morphology is not being regained despite the use of various operative techniques[27]. No current method of reconstruction recreates the complex fan morphology of the insertion of a normal anterior cruciate ligament on the femur and tibia. Most reconstructions of the anterior cruciate ligament are designed to mimic the anteromedial bundle of the ligament. The microanatomy of the anterior cruciate ligament is complex. Electron microscopy studies[63,65,72] have shown that the normal pattern of mixed large and small fibrils is not achieved with current reconstructive procedures (Fig. 5). In addition, the normal complex insertion of the ligament through transition zones of fibrocartilage and calcified cartilage is not reproduced with current techniques.

Ligaments not only act as structural checkreins that restrict the movement of joints but also serve as sources of sensation for more proximal neural elements[22,39,47,48,69].

To our knowledge, restoration of normal neuromorphology and distribution has not been documented in the current literature on reconstructions of anterior cruciate ligaments in humans, although Barrack et al.[6] recently demonstrated partial restoration of histological neuromorphology as well as limited restoration of sensory evoked potentials in canines. The increased laxity found in many knees after reconstruction of the anterior cruciate ligament demonstrates that the strength of the ligamentous substitute is insufficient for the loads that are applied. As far as we know, no animal model has demonstrated restoration of normal anatomical or biomechanical characteristics after reconstruction of the anterior cruciate ligament. As noted by one of us (J. G.)[38] and by van Rens et al.[77], even reconstructions that have appeared to be excellent have failed at relatively low loads.

Kinematic Factors

Kinematic factors can be defined as those that determine the motion of a given joint or musculoskeletal segment under load. In the knee, these factors include the pattern of sequential tightening of the fibers of the anterior cruciate ligament and the dynamic function of all of the complex neuromuscular control mechanisms, including neuroproprioceptive output characteristics from the limb as well as cerebral and cerebellar sequencing of motor unit contractions, spinal reflex mechanisms, dynamic muscle strength, and endurance[42,58,67,68].

The neuromuscular capability of the lower extremity after operative or non-operative treatment of a ruptured anterior cruciate ligament can be an important prognosticator of function of the knee[82]. The results of research have indicated the importance of eccentric muscle function in increased stiffness across the knee joint as well as the absorption of impact loads transmitted across the knee joint[80]. The importance of muscle tone for the protection of the static soft-tissue restraints of the knee has been demonstrated by a number of investigators. Wang and Walker[78] showed that a compressive force equal to approximately the body weight could decrease

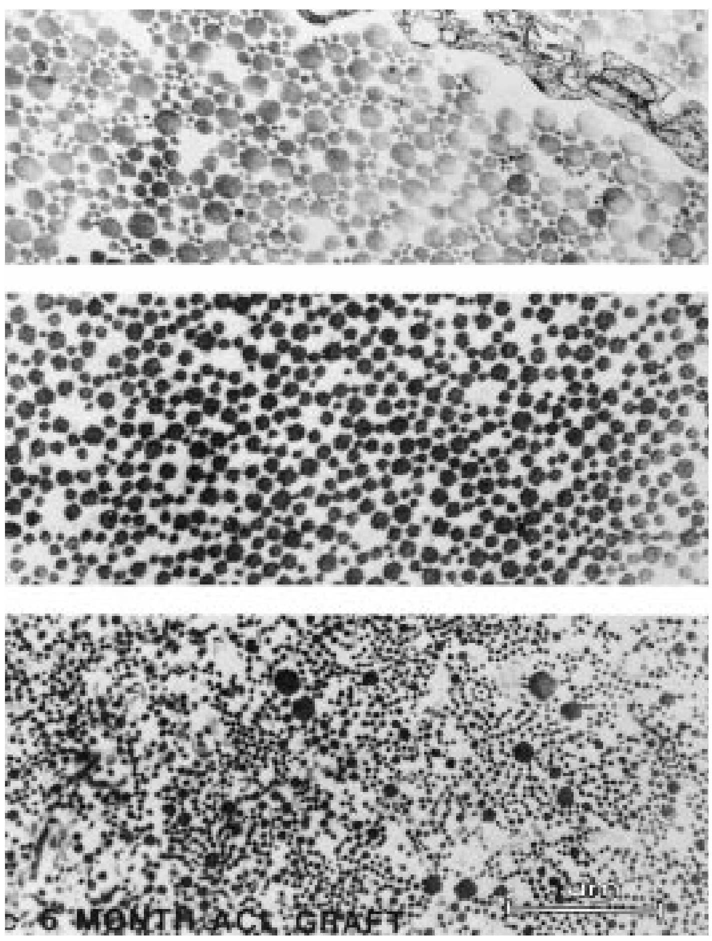

FIG. 5

Transverse-section electron microscopy studies. A normal patellar ligament from a human subject who was less than thirty years old (top) has a mix of large and small-diameter fibrils. A normal anterior cruciate ligament from a human subject who was less than thirty years old (middle) has fibrils that are smaller than those in the patellar ligament. An anterior cruciate ligament-patellar ligament autogenous graft that had been *in situ* for six months after implantation in a human (bottom) shows a predominance of small fibrils and the remains of the larger fibrils from the donor patellar ligament (original magnifications, × 34,000). (Reprinted, with permission, from: Oakes, B. W.: Collagen ultrastructure in the normal ACL and in ACL graft. In The Anterior Cruciate Ligament. Current and Future Concepts, p. 214. Edited by D. W. Jackson. New York, Raven Press, 1993.)

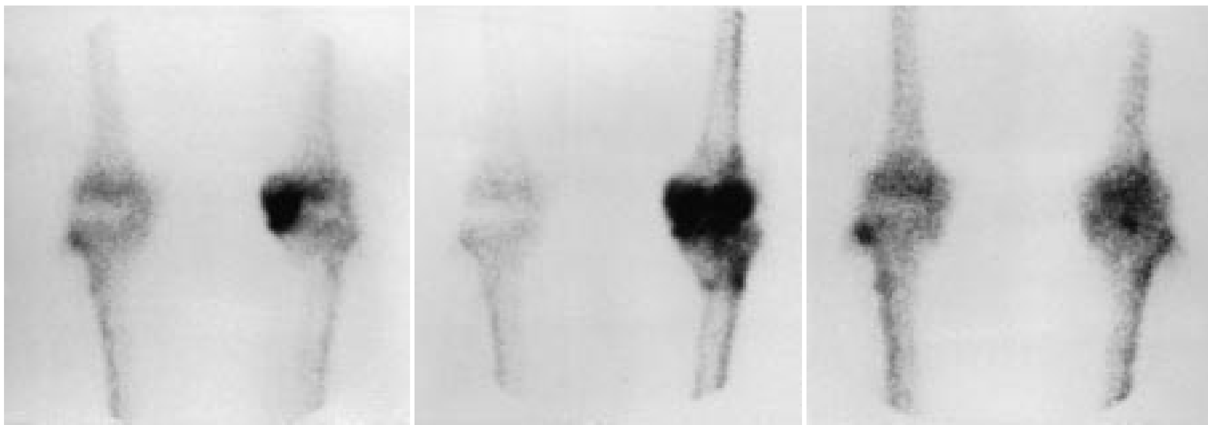

FIG. 6-A FIG. 6-B FIG. 6-C

Figs. 6-A, 6-B, and 6-C: Anteroposterior technetium scintiscans of the knees of a thirty-two-year-old man, demonstrating restoration of osseous homeostasis after reconstruction of the ligament. (Reprinted, with permission, from: Dye, S. F., and Chew, M. H.: Restoration of osseous homeostasis after anterior cruciate ligament reconstruction. Am. J. Sports Med., 21: 749-750, 1993.)

Fig. 6-A: Preoperatively, there is intense uptake in the medial compartment of the left knee.

Fig. 6-B: Four months after the reconstruction and a partial medial meniscectomy, there is marked uptake in three compartments.

Fig. 6-C: Twenty-one months postoperatively, normal scintigraphic activity has been restored in the medial compartment, with mild residual uptake in the proximal part of the tibial tunnel.

rotatory laxity by 80 per cent. Markolf et al.[55] demonstrated the substantial protective effect of well conditioned muscles in the lower extremities of athletes. Those authors showed a tenfold increase in the stiffness of the knee joint with contraction of the muscles compared with the stiffness with the muscles in a relaxed state. Recent work has indicated that weakness of the quadriceps after reconstruction of the anterior cruciate ligament primarily reflects a deficit in neural activator drive from the central nervous system rather than a pure muscle weakness[24]. In addition, several authors[40,82] have emphasized the importance of specific and exact temporal activation of muscle, as reflected by muscle reaction time and time to peak torque. Research by Wojtys and Huston[81], who studied the effects of injury of the anterior cruciate ligament and reconstruction of the patellar ligament with an autogenous graft as well as neuromuscular performance, indicated that patients who were managed operatively did not regain the same functional performance as demonstrated by a group of age-matched controls. Those authors indicated that formal rehabilitation of the knee improved muscle strength, endurance, time to peak torque, and muscle reaction time but did not restore normal levels of performance. During isokinetic testing, the hamstrings reached peak torque before the quadriceps in the control subjects. However, the pattern was reversed in the patients who had been managed operatively; the hamstrings reached peak torque after the quadriceps even at eighteen months postoperatively. Of interest is the fact that the untreated, contralateral limb of the patients who had had a reconstruction also showed the same abnormal recruitment pattern.

The importance of proprioceptive neuromuscular conditioning to the function of the knee was demonstrated by Caraffa et al.[8] in a prospective, controlled study of 600 soccer players on forty teams. During three full seasons, the prevalence of injury of the anterior cruciate ligament in 300 soccer players who participated in proprioceptive training was substantially lower (a mean of 0.15 injury per team) than that in a similar group of 300 players who did not participate in proprioceptive training (a mean of 1.15 injuries per team). The evidence strongly suggests that it is possible to prevent certain injuries of the anterior cruciate ligament with simple enhancements of the neuromuscular control mechanisms[8].

Physiological Factors

Physiological factors can be defined as the biochemical and metabolic processes that maintain and restore tissue homeostasis in joints and musculoskeletal components. The complex physiological factors that determine homeostasis of musculoskeletal systems under normal conditions and after injury are becoming the focus of orthopaedic research worldwide[37]. The recent emphasis on these factors is shown by the distribution of the types of research presented at the meetings of the Orthopaedic Research Society. During the last decade, the emphasis has shifted from biomechanical and structural studies to the assessment of metabolic variables.

The loss of tissue homeostasis is often undetectable with the use of structural imaging studies, such as plain radiography and magnetic resonance imaging. This loss, which is demonstrated in bone by persistently abnormal technetium scintiscans after the injury, can be a prelude to the eventual development and progression of irreversible degenerative changes[11,14,18,21,23]. The capability of a scintiscan to demonstrate regions of eventual overt degenerative changes in a knee before radiographic changes are evident was validated in an animal model by McBride et al.[53]. Those authors created a posttraumatic osteoarthrosis model by sectioning the anterior cruciate ligaments of rabbits. With use of sequential radiographs, technetium scintiscans, and histological analysis, the authors found that the scintiscans showed increased osseous metabolic activity by two weeks, whereas radiographic changes could not be detected until the eighth week. Recent studies[18,19] have shown that the restoration of osseous homeostasis, as documented by normal findings on technetium scintiscans, is possible after reconstruction of the anterior cruciate ligament with a bone-patellar ligament-bone autogenous graft followed by incremental rehabilitation (Figs. 6-A, 6-B, and 6-C). Of interest is the finding that, four months after the reconstruction, the scintiscans demonstrated much greater activity, reflecting the fact that a major operation represents a serious yet reversible metabolic disturbance in the knee. Aglietti et al.[2] showed that some residual abnormal scintigraphic activity after reconstruction of the anterior cruciate ligament, with uninjured or repaired menisci, is compatible with the absence of overt degenerative changes as many as five years postoperatively.

Compared with technetium scintigraphy, positron emission tomography with use of $fluorine_{18}$ is capable of much higher resolution of radiographically undetectable increased osseous metabolic activity in a chronically symptomatic knee after injury of the anterior cruciate ligament[17]. This technique involves the production of short-half-life positron emitters, such as $fluorine_{18}$, generated in a cyclotron by the addition of a proton to the nuclei of a stable precursor. The added proton converts to a neutron by emitting a positron (an anti-particle of the electron). When a positron comes into contact with a nearby electron, a matter-antimatter annihilation event occurs, with the production of gamma radiation detectable with scintillation devices[61,62]. $Fluorine_{18}$ combines to sites of active turnover of bone, thereby localizing the process. This scintigraphic method is fundamentally different from the standard technetium scintiscan, which relies on the carrier molecule methylene diphosphonate. In one study[18], a thirty-four-year-old man with a unilateral chronically symptomatic injury of the anterior cruciate ligament had increased osseous metabolic activity in three compartments on technetium bone scintigraphy. The positron emission tomography scan confirmed the intraosseous location of the increased osseous metabolic activity at high resolution (Fig. 7). With the use of different tracers and metabolites, positron emission tomography may be able to geographically demonstrate homeostatic characteristics of musculoskeletal soft tissue with high resolution.

Marks et al.[57] demonstrated the association between acute rupture of the anterior cruciate ligament and impaction injuries of the anterior aspect of the lateral femoral condyle and the posterior aspect of the lateral tibial plateau with the use of technetium bone scintigraphy and magnetic resonance imaging. The impaction injuries occurred secondary to failure of the ligament with transient rotatory subluxation of the lateral compartment (Figs. 8-A, 8-B, and 8-C). The specific sites of these osseous injuries are commonly associated with acute rupture of the anterior cruciate ligament[75]. Johnson et al.[50] noted metabolic and structural damage of articular cartilage on the anterior aspect of the lateral femoral condyle overlying a region of subchondral injury, as evidenced by death of chondrocytes in some patients after injury of the anterior cruciate ligament (Fig. 9). It is likely that the capacity of such knees to transfer loads would be diminished compared with the

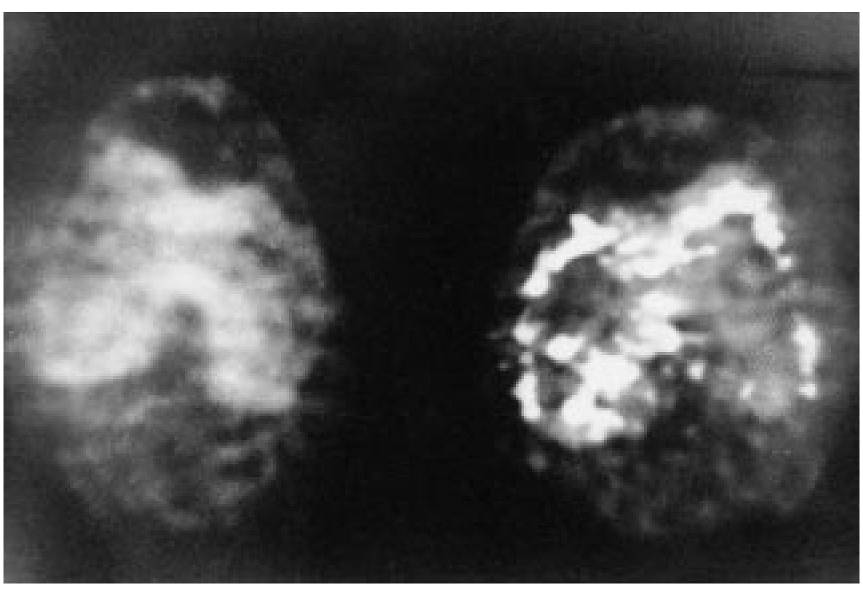

FIG. 7

$Fluorine_{18}$ positron emission tomography scan of the knees of a thirty-four-year-old man who had an eight-year history of chronic injury of the anterior cruciate ligament of the right knee. The white areas indicate increased osseous metabolic activity in the distal aspect of the right femur. No $fluorine_{18}$ activity is noted in the left femur.

FIG. 8-A

Figs. 8-A, 8-B, and 8-C: Images of the knees of patients who had an acute rupture of the anterior cruciate ligament. (Figs. 8-B and 8-C are reprinted, with permission, from: Dye, S. F.: The use of technetium scintigraphy in the assessment of musculoskeletal trauma. In Recent Advances in Operative Orthopedics. Vol. 3, p. 204. St. Louis, Mosby-Year Book, 1995.)

Fig. 8-A: Lateral radiograph showing the impact of the anterior aspect of the lateral femoral condyle on the posterior aspect of the lateral tibial plateau that occurs with acute rupture of the anterior cruciate ligament. (Courtesy of Paul H. Marks, M.D.)

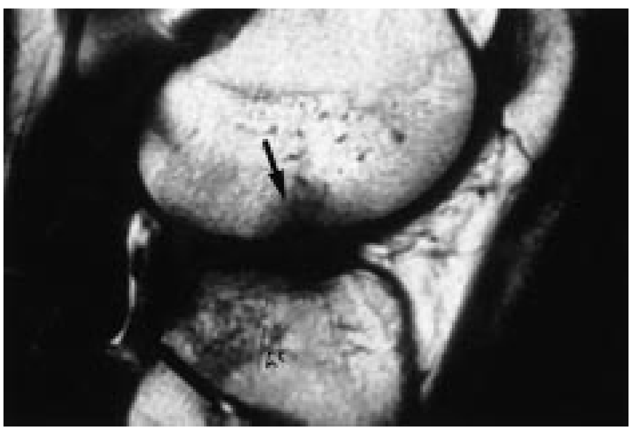

FIG. 8-B

T1-weighted magnetic resonance image showing sites of osseous injury of the anterior aspect of the lateral femoral condyle (closed arrow) and the posterior aspect of the lateral tibial plateau (open arrow).

capacity of knees with normal tissues.

In contradistinction to knees with the acute pattern of injury, chronically symptomatic knees with an injured anterior cruciate ligament have demonstrated loss of osseous homeostasis primarily in the medial compartment, which is rarely involved in the index injury[12,20]. This chronic pattern of increased scintigraphic activity in the medial compartment probably reflects a different underlying pathokinematic genesis than that involved in the acute pattern seen in the lateral compartment with an impaction injury. The medial compartment is anatomically more constrained than the lateral compartment[70,76]; therefore, it is probably subjected to greater forces with the increases in translation associated with the absence of a functional anterior cruciate ligament. These greater forces can induce increased osseous metabolic activity, as shown on technetium scintigraphy (Fig. 6-A).

Recent basic-science research[26] has established that the mechanical environment affects, in addition to the homeostasis of bone, the homeostasis of soft tissues, including cartilage, ligaments, and tendons. For example, chondrocytes remodel the extracellular matrix in response to changes in cellular deformation secondary to load[7,41,43], as demonstrated by increases in proteoglycans, interstitial ion concentration, and pH. Micromanipulation of individual cartilage cells *in vitro* has been shown to increase the cytosolic calcium level[44], which plays a role in the synthesis of DNA, the synthesis of extracellular matrix, and cellular differentiation[73].

The *in vivo* response of articular cartilage to differential loading was demonstrated by Kiviranta et al.[51] in a canine model. Those authors showed that moderate loading across the knee joint (as produced by the dogs running four kilometers a day for fifteen weeks) induced an increase in the thickness of the articular cartilage and an increase in the proteoglycan content, whereas excessive loading (as produced by the dogs running twenty kilometers a day up a 15-degree grade for forty weeks) resulted in quantitative decreases in the thickness of the cartilage and in the production of proteoglycans.

Tendons also appear to be quite sensitive to a differential range of loading. Arnoczky et al.[4] and Shirakura et al.[73] demonstrated that the cells within a tendon deform in response to tensile load, thus leading to a differential manifestation of metabolic characteristics. With use of confocal laser microscopy, both groups of authors determined that the deformation was non-linear in response to load. They suggested that cell membranes do not deform beyond a certain degree because of the physical limitations imposed by the cell membrane or the local matrix. Like the deformation of cartilage cells, increased cytosolic calcium concentrations have been

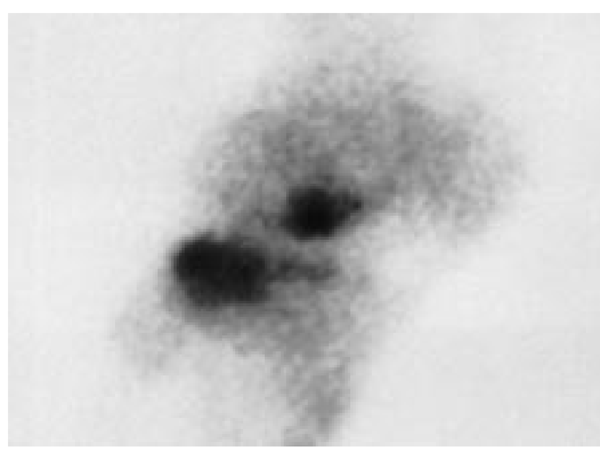

FIG. 8-C

Technetium-99m methylene diphosphonate scintiscan showing regions of increased osseous metabolic activity at the sites of osseous impaction on the anterior aspect of the lateral femoral condyle and the posterior aspect of the lateral tibial plateau.

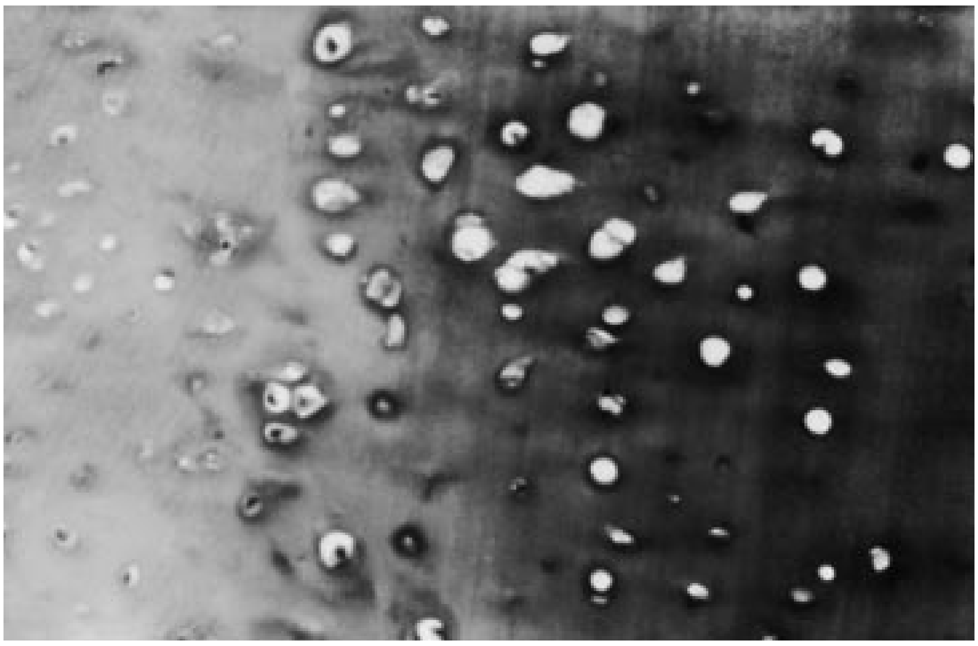

FIG. 9

Micrograph of articular cartilage from the anterior aspect of the lateral femoral condyle, three weeks after acute injury of the anterior cruciate ligament, revealing death of chondrocytes as evidenced by the absence of nuclear material in the empty lacunae. The more superficial layers of the articular cartilage are to the right, and the deeper layers are to the left (hematoxylin and eosin; original magnification, × 20). (Courtesy of Darren L. Johnson, M.D.)

found in response to strain, which suggests a common pathway regulating the response of *in situ* cellular deformations of tenocytes[73]. For example, Shirakura et al. showed that there was minimum cytosolic calcium concentration at 0 per cent strain, the calcium concentration was increased at 2 per cent strain, it was maximum at 4 per cent strain, and it started to decrease at 6 per cent strain (Fig. 10).

The basic-science studies that we noted are beginning to define the upper-threshold limits of the enve-

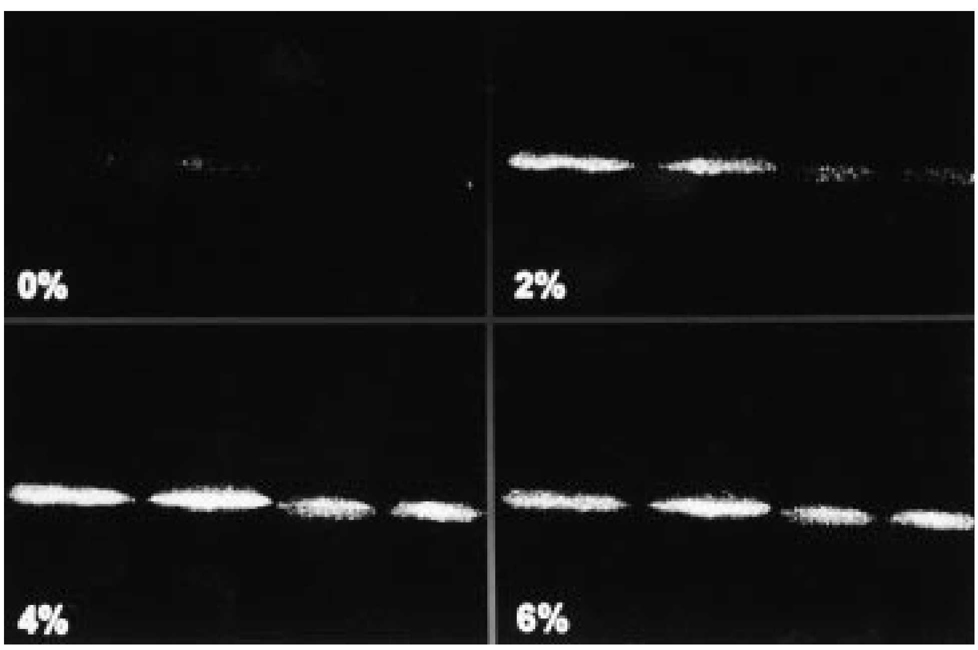

FIG. 10

Sequential images of living tenocytes, made with the use of confocal laser microscopy. A section of living tendon was put under 0, 2, 4, and 6 per cent strain, and the intracellular cytosolic calcium concentration was assessed qualitatively. At 0 per cent strain there was minimum cytosolic calcium concentration, at 2 per cent strain there was increased calcium concentration, at 4 per cent strain there was maximum calcium concentration, and at 6 per cent strain there was decreased calcium concentration. (Reprinted from: Shirakura, K.; Ciarelli, M.; Arnoczky, S.; and Whallon, J. H.: Deformation induced calcium signalling in tenocytes in situ. In Transactions of the Combined Orthopedic Research Societies of the United States of America, Japan, Canada, and Europe, p. 94. San Diego, California, Nov. 5, 1995.)

TABLE I

CATEGORIZATION OF FACTORS THAT CONTRIBUTE TO THE ENVELOPE OF FUNCTION IN KNEES WITH AN INJURY OF THE ANTERIOR CRUCIATE LIGAMENT

Factors	History	Physical Examination	Instrumented Testing	Imaging
Anatomical	Sense of looseness	Positive Lachman test	Abnormal instrumented laxity testing	Radiographs, magnetic resonance imaging
Kinematic	Giving-way	Positive pivot-shift test	Abnormal instrumented six-degrees-of-freedom testing	Cine computed tomography, cine magnetic resonance imaging
Physiological	Aching	Warmth and tenderness	Instrumented infrared temperature assessment	Technetium-99m methylene diphosphonate scintiscans, positron emission tomography

lope of function at the tissue and cellular levels. In other words, a certain degree of loading and resultant deformation is compatible with, and perhaps inductive of, homeostasis of musculoskeletal tissues. Forces beyond that degree of loading result in metabolic tissue failure, and sufficiently high or prolonged loads result in structural tissue failure. The studies that we discussed provide strong evidence linking differential loading and musculoskeletal tissue response.

Treatment Factors

Treatment factors include non-operative measures, such as restriction of load, neuromuscular training (muscle-strengthening and proprioceptive enhancements that result in increased force production, load absorption, coordination, and balance), bracing, and anti-inflammatory therapies (such as medication and tissue-cooling), as well as operative procedures, including those involving the menisci and the articular cartilage and various techniques of repair or reconstruction of the anterior cruciate ligament.

Indicators of Functional Restoration

Indicators that a joint is being loaded within its physiological capacity — that is, within its envelope of function — include the absence of discomfort, of warmth, of swelling, and of functional instability as well as the presence of normal findings on long-term radiographs and a technetium scintiscan. Indicators that a joint is being loaded outside of its functional envelope include discomfort, warmth, swelling, instability, abnormally increased activity on a technetium scintiscan, and eventual development of radiographic degenerative changes. The various factors that contribute to joint function can be categorized on the basis of the history, physical examination, instrumented testing, and imaging (Table I). In 1997, Marks[56] suggested the concept of the anterior cruciate ligament risk equation, with which he attempted to detail and differentially weight the various factors that pertain to the knee.

We believe that the effects of all of the extant factors, including treatment factors, that contribute to joint function are summated at the cellular and tissue levels by the presence or absence of homeostasis. As Daniel et al.[10] showed, the knees of patients who had a structurally inadequate anterior cruciate ligament demonstrated a positive Lachman test and an abnormal instrumented laxity test on clinical examination but still functioned well, without the development of degenerative changes. This may have been the result of changes in lifestyle to allow for limitation of loading as well as excellent dynamic muscle-sequencing and robust metabolic maintenance and repair mechanisms, resulting in overall joint homeostasis as demonstrated in bone by technetium scintigraphy[10].

Unlike most imaging studies that are currently available to orthopaedic surgeons, scintigraphic techniques allow for the geographic assessment of tissue homeostasis of osseous components about joints[13,18]. Magnetic resonance imaging, as currently configured, cannot reliably demonstrate sites of increased osseous metabolic activity[13] or even whether a given joint is in a living subject or from a cadaver[52]. Better methods of documenting and tracking the homeostatic characteristics of all musculoskeletal components, including soft tissues, may reveal a variety of underlying metabolic adaptive processes. These processes are at present mostly covert. Positron emission tomography[60,61] or other imaging technology, such as functional magnetic resonance imaging[59,62], may be able to provide this information in the future. Someday, orthopaedists and their patients may be able to view a three-dimensional hologram of the knee or other musculoskeletal systems, with the differential degree of healing of various tissues represented by different colors and intensities[16]. When these underlying metabolic adaptive mechanisms can be easily visualized and tracked over time, insights may be gained that could result in different concepts of musculoskeletal injury and response. These insights may lead to currently unexpected therapeutic advances.

Overview

A knee with an injured anterior cruciate ligament is an interesting representative of a damaged musculoskeletal system. The restoration of certain structural and biomechanical parameters alone does not ensure the restoration of physiological function. We believe that it is important to consider the range of factors that contribute to the functional capacity of the knee, including kinematic and physiological factors, when managing patients who have an injured anterior cruciate ligament. The conceptualization of tissue damage and response after such an injury should be broadened to include the often complex associated pathological changes noted in a variety of musculoskeletal components besides the anterior cruciate ligament. The combination of osseous and cartilaginous damage and the disturbance of the neuromuscular control mechanisms, in addition to the damage to the anterior cruciate ligament and other tissues, can result in diminution of the functional capacity of the entire joint to transmit load safely.

From our review of the current literature regarding reconstruction of the anterior cruciate ligament, it seems clear that perfection — that is, full restoration of the preinjury status — often is not achieved and the long-term results are not completely satisfactory. However, the function of knees that have been treated with modern reconstructive techniques along with incremental rehabilitation has been shown to approach normal, as documented on postoperative scintigraphic studies that showed no early degenerative changes[18,19].

The goal of therapy after injury of the anterior cruciate ligament should be the maximization of the load-transference capacity of the knee joint as safely and predictably as possible. Rehabilitative, non-operative management may be sufficient for many patients. Despite the best therapeutic efforts, however, it is likely that the full preinjury function of the joint will not be restored in most patients. The use of the envelope-of-function construct can thus be of value in educating patients by demonstrating, in simple graphic form, the estimated potential functional capacity of a joint at different stages in the treatment program. The envelope also demonstrates the activities that are more likely to be safe and therefore compatible with long-term function of the joint as well as the activities that may be associated with a risk of early degenerative changes.

We view with concern the continued presence of even mild discomfort, warmth, and swelling associated with certain loading activities in knees that have an injured or reconstructed anterior cruciate ligament. These findings are a direct clinical manifestation of a loss of joint homeostasis. Patients who have these findings should be counseled to decrease, at least temporarily, the loading across the symptomatic joint. This decrease in loading, in combination with other non-operative means, should reverse the clinical signs toward homeostasis.

By recommending that patients decrease loading across the joint to a safe level that is compatible with the maintenance of tissue homeostasis through avoidance of certain high-loading activities, we are not advocating a sedentary lifestyle. On the contrary, it is desirable that patients be as active as possible within the upper-threshold limits of their own specific functional envelope. Even a patient who has a severely damaged knee often can participate safely in an aerobic swimming or bicycling program that effectively maintains muscle strength and tone, flexibility of the joint, cardiovascular conditioning, and production of endorphins without supraphysiological overload of the joint as a whole[15].

Additional advances in the treatment of knees with injury of the anterior cruciate ligament are likely to result not only from better techniques for recreating an internal structural linkage but also from methods to improve the neuromuscular control mechanisms, such as prevention of muscle atrophy and restoration of proprioception. Advances are also likely to come from improvements in the metabolic healing properties of all injured musculoskeletal tissues, perhaps through such techniques as genetic engineering. Therapeutic methods that are designed to work symbiotically with the patient's unique set of musculoskeletal characteristics are likely to result in successful orthopaedic treatment.

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