

Depression and psychiatric disease associated with outcomes after anterior cruciate ligament reconstruction

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Abstract

While most patients with an anterior cruciate ligament (ACL) injury indicate satisfaction with surgical intervention, a significant proportion still do not return to pre-injury level of function or sport. Psychiatric comorbidities, such as depression, have recently been associated with poor clinical outcomes after ACL reconstruction (ACLR). To date, no article has yet examined how depression affects ACLR outcomes and how potential screening and intervention for psychological distress may affect postoperative activity level. The purpose of this review is to delineate potential relationships between depression and ACLR outcome, discuss clinical implications and identify future directions for research.

Key words: Depression; Preoperative evaluation; Anxiety; Anterior cruciate ligament reconstruction; Patient reported outcome; Orthopedic surgery

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Core tip: A difference exists between patients suffering

from psychiatric disease, such as depression, and those with psychological constructs, such as pain catastrophization, that hinder sport performance. The former may require clinical evaluation by a mental health professional. The latter may be dealt with through counseling and physical therapy. When assessing a patient with anterior cruciate ligament injury, it may be useful to screen for symptoms of hopelessness and anhedonia that have persisted for at least two weeks, two inquiries found on the Patient Health Questionnaire 2 (PHQ-2). Patients who respond positively to the PHQ-2 should be referred for further evaluation and counseled accordingly.

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INTRODUCTION

The anterior cruciate ligament (ACL) is the most commonly injured ligament of the knee^[1]. Although treatment with ACL reconstruction (ACLR) can restore stability and knee kinematics^[2], a significant proportion of ACLR patients still do not return to pre-injury level of activity or sport^[1,3-6]. In recreational and professional athletes, Ardern *et al.*^[1] found that as much as 40% do not return to pre-injury level of sport two years postoperatively. Investigating this discouraging result, recent literature has recognized an association between psychological factors and ACLR outcome^[2,7-25].

In the continuum of psychological factors, clinical depression has recently been suggested as one of the most debilitating^[26-29]. Garcia *et al.*^[26] found that preoperative depressive symptomatology is associated with significantly worse self-reported functional outcome at one year postoperatively for patients undergoing ACLR^[26]. In addition, as many as two out of every five ACLR candidates may exhibit significant depressive symptomatology preoperatively^[16,26], a fourfold higher rate than the national average^[30].

To date, no review article has examined the impact of psychiatric disease, such as depression, on ACLR outcome and clinical practice. Instead, most of the focus has been on other psychological factors, such as fear of reinjury, athletic identity, self-efficacy, and locus of control, which are not true clinical diagnoses^[2,10,14,15,20,22,25,28]. Although psychological impediments may interfere with ACLR rehabilitation, they rarely have implications outside of sport^[2,16,18]. In contrast, depression is associated with significant general comorbidities and is the major risk factor for suicide in ACLR patient age groups^[31-36]. While past ACLR literature has called for patients reporting depressive symptoms to seek care from a sports psychologist^[2], recent studies have advocated

for depression screening tools and referral to mental health professionals, where therapy and pharmacologic treatment may be necessary^[15,26].

The purpose of this review is to delineate potential associations between depression and ACLR outcome, discuss clinical implications and identify future directions for research.

DEPRESSION SYMPTOMATOLOGY AND ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

In the United States, the second-most likely cause of death for patients in the 15-34 age group is suicide^[31]. According to the American Psychiatric Association, major depressive disorder (MDD) is the most salient risk factor for suicide^[32,37] and is estimated to affect up to 10% of the adult United States population^[30]. Individuals can meet diagnostic criteria for MDD when they exhibit at least five out of nine depression symptoms, such as anhedonia or hopelessness, for a duration of at least two weeks without the influence of substances (Table 1). Depression accounts for \$43 billion in medical costs annually and by 2020 could be the second largest cause of disability^[38]. Given the prevalence and impact of depression, many primary care specialties recommend guidelines for screening, treatment and referral^[38].

Although the Academy of American Orthopaedic Surgeons (AAOS) and American Orthopaedic Society for Sports Medicine (AOSSM) do not have guidelines in place for when to screen orthopaedic patients for symptoms of depression, recent literature suggests that depression can significantly affect orthopaedic patients and outcomes^[15]. For instance, the incidence for depression can be as high as 45% in orthopaedic trauma patients^[39], 42% in ACLR patients^[26], and above national average level for patients undergoing joint replacement^[40] and rotator cuff repair^[41]. In addition, depression has been found to be a risk factor for poor functional outcome for orthopaedic procedures with lengthy rehabilitation periods, such as joint replacement and vertebral disc replacement^[40,42]. Common symptoms of depression, such as fatigue, psychomotor agitation, and inability to concentrate, may interfere with rehabilitation^[32], particularly if recovery takes at least one year^[2].

Given the patient demographic and length of rehabilitation, ACLR and its association with depression has drawn recent interest. It is known that 15-25 year-olds have the highest incidence of ACL injury, which make patients of this age group common ACLR candidates^[12]. However, this is the same age-group vulnerable to the sequelae of depression, as suicide remains the second most common cause of death^[37]. In addition, rehabilitation after ACLR has long been recognized as an important aspect to recovery and return to sport^[6]. Compliance with rehab, however, can be especially difficult for those afflicted with depression due to the

Table 1 Diagnostic criteria of major depressive disorder¹

DSM-V	Diagnostic Criteria
Major depressive disorder	<p>Patient reports at least five of nine of the following depressive symptoms most of the day or almost every day for at least two weeks:</p> <p>(1) Depressed mood that may be characterized by sadness, emptiness or hopelessness; (2) Markedly diminished interest or pleasure in all or almost all activities; (3) Significant unexpected weight loss; (4) Inability to sleep or oversleeping; (5) Psychomotor agitation or retardation; (6) Fatigue or loss of energy; (7) Feelings of worthlessness or inappropriate guilt; (8) Diminished ability to think, concentrate or make decisions; (9) Recurrent thoughts of death, suicidal ideation without a specific plan or a specific suicide attempt or specific plan for committing suicide</p> <p>Symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning</p> <p>The episode is not due to the effects of substance or to a medical condition</p> <p>The occurrence is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders</p> <p>There has never been a manic episode or a hypomanic episode</p>

¹Adapted from the DSM-V guidelines.

length and intensity of exercise^[6].

RECOVERY FROM ACLR: A LENGTHY REHAB PROCESS

A number of postoperative rehabilitation protocols exist for ACL reconstruction patients, and many are physically demanding; however, there is minimal consensus as to which programs are most effective^[43]. In general, programs can incorporate early weight bearing and motion, closed kinetic chain exercises, cryotherapy and exercises to enhance balance, proprioception, and core strength^[44-48]. These are implemented at various stages in a tiered fashion beginning with controlling inflammation and restoring gait which later progresses to normalizing range of motion, strength, and activity^[46,49]. Other components of a physical therapy regimen such as neuromuscular electrical stimulation (electrotherapy), gait training, hydrotherapy, stair climber, and slide board programs have also been found to be safe and beneficial to some^[45-48]. In contrast, there is little evidence to support the use of a knee brace, continuous passive motion, or creatine supplements to enhance recovery^[47,48].

While most protocols are similar in the activities that are prescribed, they vary greatly on the time frame in which increasing levels of activity are permitted. Traditional rehabilitation programs tend to be more conservative in the level of activity permitted at each phase of treatment and typically require approximately one year to complete^[50]. Recently, aggressive protocols have become popular and have reduced the length down to 6 mo before return to full active function^[48,50-52]. These more progressive regimes typically allow full range of motion at 10 wk and return to sports if strength is greater than 80% as early as 16 wk^[43,46-48,50,52]. The number of physical therapy sessions in these accelerated programs varies greatly but generally averages around 20 sessions, most of which occur in the first three month^[49,53]. Home based programs, which average around 4 sessions within the same timeframe, have been found to be equally effective for motivated patients^[47,53-57].

Regardless of the exact regimen followed, the road to recovery requires myriad hours of physical therapy to return to pre-injury level of activity. In addition, return to full, pre-injury state function does not always occur. For instance, Schenck *et al.*^[54] found that patients returned to good function on average at 21.6 mo (range: 12-48). In a meta-analysis conducted by Arden *et al.*^[6], only 63% of patients were able to return to their pre-injury sport; 44% returned to competition. The average time between surgery and the resumption of any type or level of sports was 7.3 (range 2-24) mo, and those that returned to competition required on average 36.7 mo postoperatively^[3].

The psychosocial impact of such a long recovery process can be particularly devastating. A lack of mobility may result in social isolation and lowered self-efficacy or a loss of self-worth as a result of not being able to perform pre-injury state functions^[15]. The latter is particularly applicable for collegiate or professional athletes who gain a strong sense of self-worth from their physical performance capabilities^[58]. For instance, collegiate athletes who sustained ACL injuries demonstrated seven times more depression relative to baseline and exhibited mood disturbances, anger, depression, and lowered self-esteem^[10,17,27,59]. Those who suffered career ending injuries reported much lower life satisfaction scores compared to their non-injured counterparts^[27]. Those that require knee stability as part of their occupation, such as military personnel and manual laborers, are also severely affected by the long recovery process. A study conducted by the Australian Army found that only 71% of personnel who underwent ACLR returned to active duty after 3 years^[60,61]. Particular emphasis must be placed on these patient populations to minimize psychosocial health deterioration during the rehabilitation process^[62].

THE MECHANISM OF DEPRESSION AND IMPLICATIONS FOR RECOVERY

Although it has been shown that depressed patients undergoing ACLR report lower self-reported outcome

Table 2 Systemic effects of clinical depression on immune system and hypothalamic-pituitary-adrenal axis

Target system	Effect
Immunologic system	Increased interleukin-1 Increased interleukin-6 Increased tumor necrosis factor- α
Musculoskeletal system	Decreased bone formation Increased bone resorption (likely 2/2 increased interleukin-1 and subsequent osteoclast activity)
Hypothalamic-pituitary-adrenal axis	Increased cortisol

scores, it is unclear why. Since no randomized controlled studies have been conducted, causation has yet to be determined. ACL injury alone may lead to depressed mood and depressed mood may lead to poor self-reported functional outcome. Adherence to rehabilitation protocol after ACL reconstruction has been shown to strongly correlate with surgical outcome^[18]. Thus, one possible explanation for compromised subjective outcomes in depressed patients is that those who experience greater symptoms of depression are less likely to adhere to the necessary rigorous ACL rehabilitation, leading to poorer clinical outcomes. Other literature propose fear of reinjury, pain catastrophizing and a lower internal Health Locus of Control - defined as the perception of one's ability to control life events - as other possible mechanisms^[63]. It is plausible that ACL patients who are depressed are more likely to have these aforementioned psychosocial impediments that can disrupt the recovery process. Indeed, successful recovery from surgical intervention has been suggested to require a dynamic biopsychosocial cycle consisting of a patient's affect, cognition and behavior^[22]. Thus, it is also possible that clinical depression is just one in a continuum of psychosocial and musculoskeletal factors that contribute to surgical outcome^[18,22,63].

In addition, it has been suggested that depression is a systemic disorder with increased inflammatory markers that contribute to worse medical outcome^[33,64,65] (Table 2). In addition to decreased serotonin levels, depressed patients have been found to have elevated levels of interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)- α , decreased cell-mediated immunity and increased cytokine response compared to non-depressed HIV and cardiovascular disease patients^[33,64,65]. These cytokines are particularly significant to musculoskeletal injury since IL-1 activates osteoclasts, thereby decreasing bone formation and density, while IL-6 and TNF- α are acute phase reactants that are implicated in fever and inflammation^[33]. While depression may certainly exacerbate psychological impediments to recovery, there may be an immunologic basis as well, a concept that warrants future investigation.

OTHER PSYCHIATRIC DISEASE AND ACLR

Other common psychiatric diseases, such as anxiety and

psychotic disorders, have not been studied with respect to recovery after ACLR, but have been implicated in orthopaedic disease. For instance, many studies have noted an elevated incidence of preoperative anxiety disorders in orthopaedic patients such as those with osteonecrosis of the femoral head^[66-68], which have led to worse patient reported outcomes for joint replacement patients^[69-72]. Others have noted that anxiety disorders, such as posttraumatic stress disorder have led to worse clinical outcome following lower extremity orthopedic surgery for patients^[73-76].

In addition, psychotic disorders such as schizophrenia and delirium have been implicated in worse postoperative outcome and leaving the hospital against medical advice^[77-80]. In orthopaedic patients, it has been suggested that patients with psychiatric disease may have increased hypothalamic-pituitary-adrenal (HPA) responses to the stress of surgery^[34]. As Kudoh *et al.*^[34] suggests, elevated cortisol may accelerate injury to vascular endothelial cells and promote the development of atherosclerosis or hypertension.

However, no studies have yet to look at anxiety and psychotic disorders and their association with ACLR outcome.

RECOMMENDATIONS FOR CLINICAL PRACTICE: EVALUATION OF ACLR CANDIDATE

Evaluation of ACL reconstruction candidates requires obtaining a pertinent history, performing a thorough physical exam, and utilizing diagnostic imaging. Classically, patients with ACL tears will complain of a "popping" sensation followed by acute swelling and a feeling that their knee is unstable. Other aspects of a clinical history to elicit include time and mechanism of injury, location of pain, and functional ability. On the physical exam, general evaluation for knee pain should be conducted which include inspection, palpation, and testing for mobility, strength, and stability. Specialized tests for ACL integrity include the Lachman, Pivot Shift, and Anterior Drawer^[81-83]. While all three should be performed, the Lachman has been shown to be the most useful^[83]. Sensitivity and specificity of the Lachman for ACL tears have been reported at 84% and 94%, respectively^[83]. Comparison with the contralateral knee is also important as many patients have increased laxity that may not be

Table 3 Patient Health Questionnaire 2¹

Over the past 2 wk, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
Litter interest or pleasure in doing things	0 ²	1 ²	2 ²	3 ²
Feeling down, depressed, or hopeless	0 ²	1 ²	2 ²	3 ²

¹Adapted from Arroll *et al*^[86]; ²Sum points from both questions (range 0-6). A score of 3 or higher is considered positive and should be further evaluated by Patient Health Questionnaire-9.

Table 4 Diagnostic criteria for major depressive disorder utilizing SIGECAPS mnemonic¹

Sleep	Insomnia or hypersomnia nearly every day
Interest	Markedly diminished interest or pleasure in nearly all activities most of the time
Guilt	Excessive or inappropriate feelings of guilt or worthlessness most of the time
Energy	Loss of energy or fatigue most of the time
Concentration	Diminished ability to think or concentrate; indecisiveness most of the time
Appetite	Increase or decrease in appetite
Psychomotor	Observed psychomotor agitation/retardation
Suicide	Recurrent thoughts of death/suicidal ideation

¹Adapted from the Diagnostic and Statistical Manual of Mental Disorder, 4th ed.

pathologic. Lastly, MRI imaging may be used to assist with diagnosis^[83]. Together, the constellation of signs and symptoms can be used to determine whether the patient is a candidate for ACLR.

Recommendations for managing an ACLR patient with depression center on three domains: Stratifying risk, screening for early signs of mental health deterioration, and implementing effective interventions. Risk stratification involves identifying patients who may have poor postoperative rehabilitation outcomes as a result of their mental health state. This can be performed both preoperatively and postoperatively. While depression is not an absolute contraindication for surgery, if it is identified at the preoperatively, consideration can be made to delay surgery so that the patient can seek mental health services^[15]. Postoperatively, those who are considered high-risk should be monitored more closely. Emphasis should be placed on demographic groups that have been shown to be the most affected by ACL injury and the lengthy recovery process including athletes, military personnel, and manual laborers^[59-62,84]. Those who exhibit high levels of psychological stress or low levels of self-efficacy should also be placed in the high-risk category given literature suggesting a connection between these two factors and poor recovery from injury or surgery^[15,85].

Most importantly, many questionnaires exist for screening depression, including the Patient Health Questionnaire (PHQ), Center for Epidemiologic Studies Depression Scale (CESDS), and Geriatric Depression Scale (GDS)^[15,38,86]. Among the validated tests, perhaps the one that is most applicable to the ACLR population is the PHQ which, due to a concise format that can be applied rapidly in an orthopedic setting^[86] (Table 3). It involves a short, two question survey (PHQ-2) to screen

for depressed mood and anhedonia over the past 2 wk. Those that screen positive are then evaluated by the longer PHQ-9, a nine-question survey. The PHQ-2 may rule out, but not definitively diagnose, depression, but is as effective as longer screening instruments, such as the Beck Depression Inventory. The PHQ-2, for instance, has been found to be up to 97% sensitive in adults. In addition to the PHQ-2, SIGECAPS is also a popular mnemonic that can be easily used by orthopedic surgeons or physical therapists to quickly screen for different manifestations of depression^[33] (Table 4).

A number of interventions have been recommended for ACLR patients with depression, although it is important to note that none have been studied with respect to ACLR outcomes. Most suggest referral to a primary care or mental health provider with the application of pharmacotherapy if indicated^[2,15]. Existing psychiatric literature suggests that pharmacologic intervention can improve medical outcome, such as decreasing mortality in HIV and cardiovascular patients^[33,65]. In the orthopaedic literature, referral to a sports psychologist, pain desensitization therapy, cognitive behavioral pain management, goal setting, and positive self-talk courses, books, or audiotapes^[15,48]. Specific interventions include attending preoperative education classes or developing a peer support network with previous patients or athletes who have recovered from injury. Given the link between physical therapy adherence and outcomes, it may also be beneficial to increase the number of in-office sessions for ACLR patients with depressed symptomatology especially in the later stages of treatment where more home sessions are typically prescribed. Indeed, patients with or without MDD who adhere to the same in-office schedule report similar outcomes in the early phase of treatment^[26]. Conversely, home based programs with

minimal supervision have only been shown to be effective in motivated individuals with high self-efficacy^[47,53], which would not be recommended to potentially depressed ACLR patients. Establishing a treatment pathway for preoperatively depressed ACLR patients could help improve rehabilitation adherence and potentially functional outcomes.

RECOMMENDATIONS FOR FUTURE RESEARCH

Review of the literature leads to three recommendations for future research regarding ACLR patients and their association with psychiatric disease. First, it is clear while recent literature suggests an association exists between depression and ACLR outcome, more work is needed to elicit the significance of the chronology of the mood disturbance and its effects. For instance, do only patients with preoperative depression symptomatology perform worse or do the symptoms primarily manifest in the recovery phase? In addition, up to how long postoperatively do patients classified as having MDD report worse outcomes than non-MDD counterparts? Currently, there is no literature on outcomes past one-year follow-up; second, research examining the importance of intervention for ACLR patients with depression symptomatology is needed. While many studies encourage providers to be aware of depression symptomatology, there has yet to be evidence that intervention, whether through referral, behavioral therapy, or pharmacotherapy, can improve outcomes; lastly, future studies should also examine other common psychiatric disorders, such as general anxiety disorder and PTSD, since these have been implicated in poor outcome for patients undergoing other orthopaedic procedures.

CONCLUSION

Existing literature suggests that patients who sustain ACL injury may report higher rates the national average of depression symptomatology and that these symptoms may be associated with worse postoperative outcome. Providers should therefore consider screening ACLR candidates for depression, perhaps with the PHQ-2. Future research should strive to delineate the timing of depression in ACLR patients, the effect of interventions and whether other psychiatric diseases are associated with ACLR outcomes.

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